National Institute for Health and Care Excellence

Draft for Consultation

# Prophylaxis against infective endocarditis

*Clinical Guideline 64.1*

*Methods, evidence and recommendations*

*May 2015*

*Draft for consultation*

*Developed by the National Institute for Health and Care Excellence*

**Disclaimer**
Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

# Contents

# Clinical guidelines update

The NICE Clinical Guidelines Update Team update discrete parts of published clinical guidelines as requested by NICE's Guidance Executive.

Suitable topics for update are identified through the new surveillance programme (see surveillance programme interim guide).

These guidelines are updated using a standing Committee of healthcare professionals, research methodologists and lay members from a range of disciplines and localities. For the duration of the update the core members of the Committee are joined by up to 5 additional members who are have specific expertise in the topic being updated, hereafter referred to as 'topic expert members'.

In this document where 'the Committee' is referred to, this means the entire Committee, both the core standing members and topic expert members.

Where 'standing committee members' is referred to, this means the core standing members of the Committee only.

Where 'topic expert members' is referred to this means the recruited group of members with topic expertise.

All of the core members and the topic expert members are fully voting members of the Committee.

Details of the Committee membership and the NICE team can be found in appendix A. The Committee members' declarations of interest can be found in appendix B.

# 1 Summary section

## 1.1 Update information

In 2008 NICE published a guideline (CG64) on prophylaxis against infective endocarditis. This 2015 guideline on the same topic updates and replaces the 2008 publication.

A UK study published in the BMJ in 2011 (Thornhill et al. 2011) looked at the impact of the NICE guideline and showed an 80% fall in antibiotic prescribing thereby indicating that the guideline had been effectively implemented. A longstanding increase in the incidence of IE was also noted but with no clear evidence of any additional increase following publication of the guideline. This increase in the incidence of IE was not well understood and there were a number of possible reasons for this.

The publication of further research by the same research group, covering the period 2000 to 2013 (Dayer et al. 2014), suggests that the incidence of IE continues to increase in both low and high risk groups above the baseline trend, in contrast to the 2011 study, following the publication of NICE's guidance in 2008. Given the uncertainty of the association as suggested by the research, this has triggered an exceptional update to assess all new evidence relevant to this guidance.

The objective of this update is to assess new evidence since 2008 for all review questions covered by the original Scope, except the review question on the information needs of patients regarding the benefits and risks of antimicrobial prophylaxis for IE.

**Strength of recommendations**

Some recommendations can be made with more certainty than others. The Committee makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the Committee is confident that, given the information it has looked at, most people would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

For all recommendations, NICE expects that there is discussion with the person about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help them to reach a fully informed decision (see also 'Patient-centred care').

**Recommendations that must (or must not) be followed**

We usually use 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally we use 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

**Recommendations that should (or should not) be followed– a 'strong' recommendation**

Recommendations that an intervention should be used are made when we are confident that for the vast majority of patients, an intervention will do more good than harm, and be cost effective. Similarly, we recommend that an intervention should not be used when we are confident that an intervention will not be of benefit for most patients.

## Recommendations that could be followed

Recommendations that an intervention could be used are made when we are confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

# 1.21 Recommendations

**Adults and children with structural cardiac defects at risk of developing infective endocarditis**

**1.1.1 Healthcare professionals should regard people with the following cardiac conditions as being at risk of developing infective endocarditis:**

- **acquired valvular heart disease with stenosis or regurgitation**
- **valve replacement**
- **structural congenital heart disease, including surgically corrected or palliated structural conditions, but excluding isolated atrial septal defect, fully repaired ventricular septal defect or fully repaired patent ductus arteriosus, and closure devices that are judged to be endothelialised**
- **previous infective endocarditis**
- **hypertrophic cardiomyopathy.**

**Patient advice**

**1.1.2 Healthcare professionals should offer people at risk of infective endocarditis clear and consistent information about prevention, including:**

- **the benefits and risks of antibiotic prophylaxis, and an explanation of why antibiotic prophylaxis is no longer routinely recommended**
- **the importance of maintaining good oral health**
- **symptoms that may indicate infective endocarditis and when to seek expert advice**
- **the risks of undergoing invasive procedures, including non-medical procedures such as body piercing or tattooing.**

**Prophylaxis against infective endocarditis**

**1.1.3 Antibiotic prophylaxis against infective endocarditis is not recommended:**

- **for people undergoing dental procedures**
- **for people undergoing non-dental procedures at the following sites[1]**
    - **upper and lower gastrointestinal tract**
    - **genitourinary tract; this includes urological, gynaecological and obstetric procedures, and childbirth**
    - **upper and lower respiratory tract; this includes ear, nose and throat procedures and bronchoscopy.**

**1.1.4 Chlorhexidine mouthwash should not be offered as prophylaxis against infective endocarditis to people at risk of infective endocarditis undergoing dental procedures.**

**Infection**

**1.1.5 Any episodes of infection in people at risk of infective endocarditis should be investigated and treated promptly to reduce the risk of endocarditis developing.**

**1.1.6 If a person at risk of infective endocarditis is receiving antimicrobial therapy because they are undergoing a gastrointestinal or genitourinary procedure at a site where there is a suspected infection, the person should receive an antibiotic that covers organisms that cause infective endocarditis.**

**[1] The evidence reviews for this guideline covered only procedures at the sites listed in this recommendation. Procedures at other sites are outside the scope of the guideline (see appendix P for details).**

## 1.3 Patient-centred care

This guideline offers best practice advice on the care of adults, young people and children with infective endocarditis.

Patients and healthcare professionals have rights and responsibilities as set out in the NHS Constitution for England – all NICE guidance is written to reflect these. Treatment and care should take into account individual needs and preferences. Patients should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If the person is under 16, their family or carers should also be given information and support to help the child or young person make decisions about their treatment. Healthcare professionals should follow the Department of Health's advice on consent. If someone does not have the capacity to make decisions, healthcare professionals should follow the code of practice that accompanies the Mental Capacity Act and the supplementary code of practice on deprivation of liberty safeguards. In Wales, healthcare professionals should follow advice on consent from the Welsh Government.

If a young person is moving between paediatric and adult services, care should be planned and managed according to the best practice guidance described in the Department of Health's Transition: getting it right for young people.

Adult and paediatric healthcare teams should work jointly to provide assessment and services to young people with infective endocarditis. Diagnosis and management should be reviewed throughout the transition process, and there should be clarity about who is the lead clinician to ensure continuity of care.

## 1.4 Methods

This update was developed based on the process and methods described in the The Manual 2014. Where there are deviations from the process and methods, these are clearly stated in the interim process and methods guide for updates pilot programme 2013.

# 2 Evidence review and recommendations

## 2.1 Epidemiological review

### 2.1.1 Overview of epidemiology: incidence and trends of infective endocarditis

Infective endocarditis (IE) is an uncommon condition with an annual incidence of fewer than 10 per 100,000 cases in the normal population. Despite advances in diagnosis and treatment, IE remains a life-threatening disease with significant mortality (approximately 20%) and morbidity. IE may arise following bacteraemia in any patient but most often affects those with a predisposing cardiac lesion. It causes an infection of the endocardium, particularly affecting the heart valves. The predisposing factors for the development of IE have changed in the past 50 years, mainly with the decreasing incidence of rheumatic heart disease and the increasing impact of prosthetic heart valves, nosocomial infection and intravenous drug misuse. However, the potentially serious impact of IE on the individual has not changed (Prendergast 2006). In an attempt to prevent this disease, over the past 50 years, at-risk patients have been given antibiotic prophylaxis before dental and certain non-dental interventional procedures, as recommended by different national and international clinical guidelines formed by expert groups based on their expert opinions [American Heart Association (AHA) 2007 (Wilson et al. 2007), British Society for Antimicrobial Chemotherapy (BSAC) 2006 (Gould et al. 2006), European Society of Cardiology (ESC) 2009 (Habib et al. 2009) and British Cardiac Society (BCS)/Royal College of Physicians (RCP) 2004 (Advisory Group of the British Cardiac Society Clinical Practice Committee 2004)].

Despite guidelines on antibiotic prophylaxis to prevent IE, the incidence of IE continues to increase across the world. A recent UK study in England from 2000 to 2013 (Dayer et al. 2014) showed that prescriptions of antibiotic prophylaxis for the prevention of infective endocarditis fell substantially after introduction of the NICE guideline in 2008, and the number of cases of IE increased significantly above the projected historical trend, by 0·11 cases per 10 million people per month (95% CI 0·05–0·16, p<0·0001). This increase in the incidence of IE was significant for both individuals at high risk of IE and those at lower risk. The study postulated that the significant increase of incidence of IE in England may be due to the introduction of the 2008 NICE guideline, although the authors stated the study could not establish a causal association based on the data from the study.

For the critique of this particular study (Dayer et al. 2014) please see section 2.1.2.

To further investigate the incidence of IE across the world for the past 2 decades, a literature search for published studies on the trend or incidence of IE in general, and the possible impact of other published guidelines on the incidence of IE was conducted. For the search strategy, please see appendix D. From this literature search, 2827 studies have been retrieved and full papers of 64 studies have been obtained for assessment. Out of the 64 studies, 7 studies were included for this review. The descriptive summary of these identified studies is summarised in Table 1 below.

Overall, 6 out of the 7 studies have suggested statistical significant upward trends of incidence of IE from 1980s to 2000s in different countries. Out of the 7 studies, 4 were from the USA and the findings from these 4 studies were as below:

- A study from 1970 to 2006 on adults in Olmsted county, USA suggested that there was a statistical significant increase in the incidence of IE from the period of 1970-1974 to the period of 2001-2006 (trend, p=0.02) (Correa et al. 2010).
- A study from 1999 to 2008 on adults and children in the USA (using the Nationwide Inpatient Sample [NIS], produced by the Agency for Healthcare Research and Quality, with approximately 8 million hospital records per year) suggested that there was a

statistical significant increase in the incidence of IE from 1999 to 2008 (trend, p<0.001) (Federspiel et al. 2012).

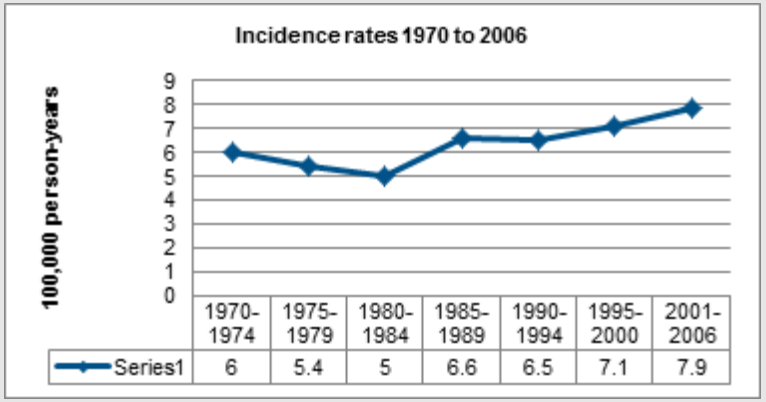
- Another study from 1998 to 2009 on adults and children in the USA (also using the NIS) suggested that there was again a statistical significant increase in the incidence of IE from 1998 to 2001 (trend, p<0.001) (Bor et al. 2013).
- The fourth study, from 2003 to 2010, which also assessed the impact of the AHA guideline (Wilson et al. 2007) on children using the Paediatric Health Information System (PHIS) Database (hospital n = 37) suggested that there was an upward increase in the raw number of IE cases over time but the increase before and after the AHA guidelines were published in 2007 was not statistically significant (p=0.7) (Pasquali et al. 2012).

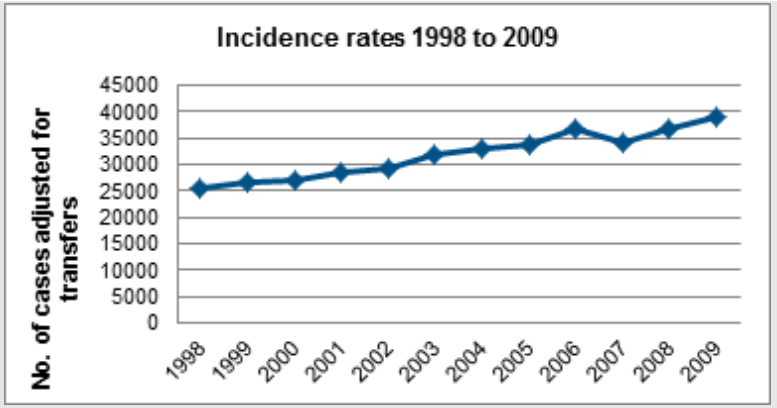
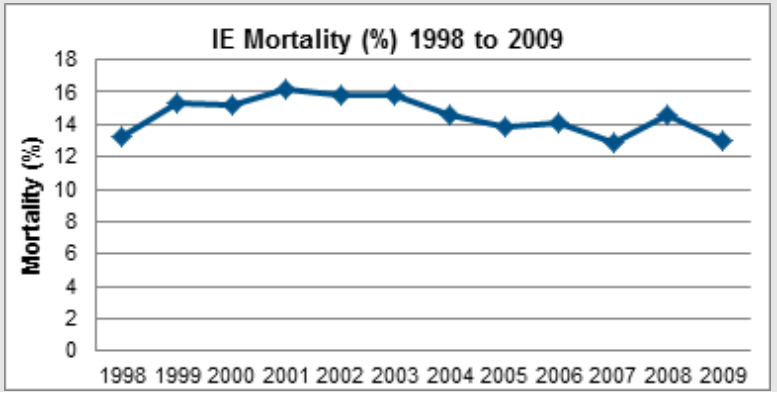
The other 3 studies were from Italy, Sweden and Taiwan. The findings from these 3 studies were as below:

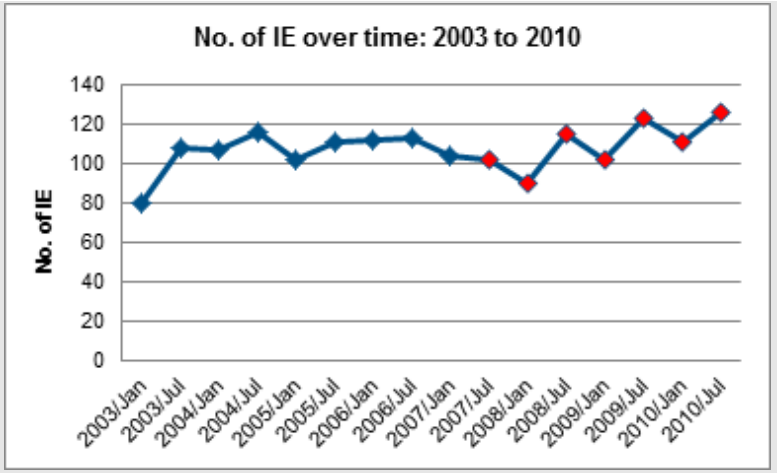
- An Italian study in the Veneto Region from 2000 to 2008 on adults and children suggested that there was a statistically significant increase in the number of cases of IE from the period of 2000-2002 to the period of 2006-2008 (trend, p=0.003) (Fedeli et al. 2011).
- A Swedish nationwide population-based study from 1997 to 2007 on adults and children suggested that there was a statistically significant increase in the incidence of IE from 1997 to 2007 (trend, p=0.01) (Ternhag et al. 2013).
- A Taiwanese population-based study (using the NHI database, which contained >96% health data of all hospitals in Taiwan) from 1997 to 2002 on adults only suggested that there was a statistically significant increase in the incidence of IE from 1997 to 2002 (trend, p<0.001) (Lee et al. 2007).

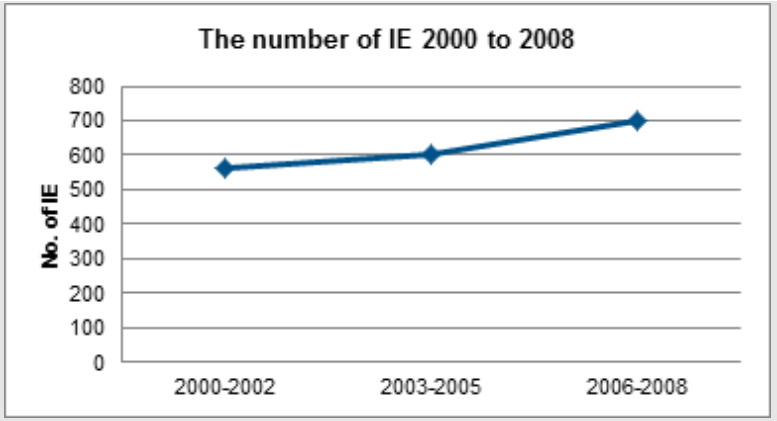
Generally, 6 out of the 7 studies have suggested statistically significant upward trends of incidence of IE over time. These findings are particularly interesting because in the USA studies and the European studies, the incidence of IE continues to increase despite the fact that these countries have more conservative antibiotic prophylaxis guidelines compared to the UK NICE guideline (NICE CG64). The authors of these studies postulated that, the increase of the incidence of IE may be due to aging populations with multi-morbidity, increase of degenerative valves, increase of hemodialysis, an increasing population of intravenous drug users and people with HIV and change of microbiology. To further validate these postulations, a well-designed longitudinal epidemiology study will need to be conducted to provide valid evidence to explain such phenomena.

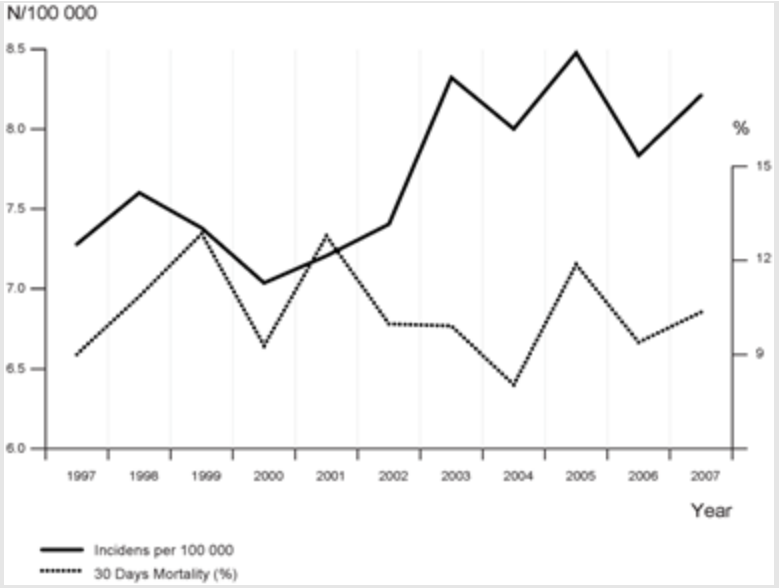
1 **Table 1: Summary of included studies**

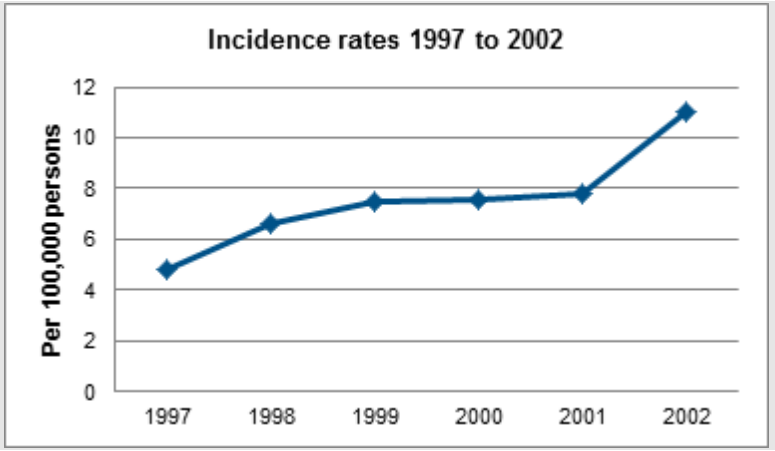
| Study reference | Study population/ country | Time period | Methods | Results |
|---|---|---|---|---|
| Correa (2010)<br>ID: 699 | The Endocarditis Registry of the Division of Infectious Diseases of Olmsted county, USA.<br><br>Residents 18 years or older. | 1970 to 2006 | Multivariable Poisson regression was used to examine temporal trends in the incidence of IE from 1970 to 2006, with the period grouped into 5-year intervals and fit as continuous, adjusted for age and gender. | The age- and gender-adjusted incidence rates of IE ranged from 6.0 cases per 100,000 person-years (1970-1974) to 7.9 cases per 100,000 person-years (2001-2006).<br>  |
| Bor (2013)<br>ID: 241 | Agency for Healthcare Research and Quality's Nationwide Inpatient Sample (NIS) for hospital discharge data for about 8 million inpatient stays annually. The NIS provides weights to allow extrapolation to all US hospitalizations.<br><br>USA.<br>Adults and children | 1998 to 2009 | Changes in endocarditis hospitalization rates between 1998 and 2009 were compared using Census Bureau figures and the direct method to adjust for population growth and aging.<br>Cochran-Armitage tests were used to evaluate time trends. | After adjustment for transfer to another hospital within the NIS sampling frame, the number of unique IE hospitalizations was 25,511 in 1998 (9.3 per 100,000 population) rising to 38, 976 in 2009 (12.7 per 100,000 population) (trend: p<0001). After adjustment for population aging and growth, IE hospitalizations increased by 2.4% annually. |

| Study reference | Study population/ country | Time period | Methods | Results |
|---|---|---|---|---|
| | | | |  <br>  |
| Pasquali (2012)<br>ID: 368 | The Paediatric Health Information System (PHIS) Database, containing inpatient data from 41 children's hospitals in the US affiliated with the Child Health Corporation of America. The | 2003 to 2010 | Poisson regression was used to estimate the rate of change in the annual number of IE hospitalizations over time (both raw and indexed to the total number of annual hospital admissions). Time was modelled in 6 month intervals as a linear trend allowing for change in slope at the time when the new AHA guidelines were published | A total of 1157 cases of hospitalization for IE during the study period were identified. Analysis did not detect a significant change in the raw number of IE cases over time, before and after the new guidelines were published in 2007: +1.6% difference post vs. pre guidelines (95% CI −6.4 to +10.3%, p=0.7). |

| Study reference | Study population/ country | Time period | Methods | Results |
|---|---|---|---|---|
| | database contains information from >5 million inpatient discharges.<br><br>USA, children <18 years of age hospitalized with IE were included.<br>(n=37 hospitals) | | in 2007. |  |
| Federspiel (2012)<br>ID: 403 | The Nationwide Inpatient Sample (NIS), produced by the Agency for Healthcare Research and Quality. The NIS is the largest all-payer inpatient database in the United States (approx.8 million records per year).<br><br>USA. Adults and children. | 1999 to 2008 | Incidence was estimated using the rate of IE-related discharges per 100,000 US population years.<br>Data were calculated quarterly based on discharge date; the denominator was adjusted annually based on the US population. Trends in admission rate were evaluated using joinpoint methods, allowing the trend to change over time | Of the 78.2 million records in the 1999–2008 NIS, 93,511 met inclusion criteria. Using weights, these records correspond to 457,690 discharges nationwide.<br>After exclusion of 9,538 admissions ending in inpatient transfer and 273 (0.3%) with unknown disposition, the main study sample consisted of 83,700 discharges (409,665 weighted).<br>Between the first quarter of 1999 and the first quarter of 2006, the rate of bacterial IE-related hospitalizations increased from 11.4 per 100,000 population-years to 16.6 per 100,000 population-years (trend, $p < 0.001$). This trend corresponds to an average percent change (APC) of 1.1% per quarter (95% CI: 0.9% to 1.3%). |
| Fedeli (2011)<br>ID: 555 | The total population of the Veneto Region was 4,885,548 in 2009, with 65 hospitals, there were | 2000 to 2008 | The first hospitalization (day-case excluded) for IE in the years 2000-2008 was selected<br>The presence of time trends across the time periods was assessed by means of the Chi- | 1,863 residents in the Veneto Region were hospitalized for IE in the period 2000-2008. The number of incident IE increased from 562 in 2000-2002 to 700 in 2006-2008 (+25%), with a corresponding crude rate rising from 4.1 to 4.9 per 100,000 person-years (+17%; $p = 0.003$). |

| Study reference | Study population/ country | Time period | Methods | Results |
|---|---|---|---|---|
| | approximately 900,000 discharges from these hospitals each year.<br><br>Veneto region, Italy. Adults and children. | | square test for linear trend or a non-parametric trend test derived from the Wilcoxon rank-sum test, as appropriate. |  <br>  |
| Ternhag (2013)<br>ID: 187 | A nation-wide population-based register study of patients with IE (hospitalized and treated for IE during 1997 to 2007 in Sweden). The Swedish Hospital | 1997 to 2007 | In order to explore possible increases in long-term relative mortality risks, the crude mortality rates were directly standardised using age- and gender-stratified mortality rates from the general population of Sweden as the reference population. | There were 7817 cases of IE, with an average annual incidence of 7.7 per 100000. The incidence rate has increased during the study period (slope of the line 0.01, p-value for trend 0.01). |

| Study reference | Study population/ country | Time period | Methods | Results |
|---|---|---|---|---|
| | Discharge Register collects individual data from all hospitals and more than 99% of the discharges in somatic care are covered by the register.<br><br>Sweden. Adults and children | | The time trend for the annual incidence and mortality rate of IE was explored in a linear regression model using a quasi-Poisson distribution and t-test for significance. |  <br>Figure: Incidence Rate and 30-days Mortality (%) of Infective endocarditis (IE) hospitalizations in Sweden during 1997 through 2007.<br>The all-cause 30-days crude mortality rate was 10.4%. The mortality rate fluctuates annually during 1997–2007 with no obvious trend through the years (slope of the line 20.006, p-value for trend 0.7). |
| Lee (2007)<br>ID: 1082 | Hospitalization data from the NHI database, which contained >96% health data of all hospitals in Taiwan. The population in Taiwan was approx. 22 million for all 6 years study period. Population | 1997 to 2002 | The annual incidence of IE was calculated by dividing the number of IE-associated hospitalizations by the general population of the same age as reported between 1997 and 2002. A Poisson regression model was used to examine the temporal trend in the incidence of IE. | 7240 hospitalized patients>18 years of age with a principal discharge diagnosis of IE were identified.<br>The mean annual incidence of IE was 7.6 per 100,000 inhabitants during the 6-year period, which significantly increased from 4.8 per 100,000 persons in 1997 to 11 per 100,000 persons in 2002 (linear trend, p<0.001). |

| Study reference | Study population/ country | Time period | Methods | Results |
|---|---|---|---|---|
| | data also obtained from the Department of Statistics of the Ministry of the Interior of Taiwan.<br><br>Taiwan.<br>Adults >18 years of age | | |  |

*Pasquali (2012): Red diamonds in the graph indicated time period after the introduction of the AHA guideline.*

### 2.1.21 Critique of Dayer et al. (2014) study

In response to the Dayer et al. (2014) study, an independent critical review of the study has been conducted as part of this update by a non-voting topic expert on interrupted time series analysis (Ramsay 2015). A brief summary of the critique is below:

- There were no factual errors with the modelling approach undertaken in the paper.
- Data for incidence of endocarditis (Figure 2 in the original paper) and incidence of high and low risk cases (Figure 3 in the original paper) were abstracted from the graph and original paper analysis confirmed.
- Exploratory investigation of the data suggested that two straight lines (a single change point during the time period) might not be an adequate description of the series, implying that the change in slope (different trends between 2 time period) in original paper is likely biased.
- Multiple change-points throughout the time period seem possible rather than only one at the point of guideline publication in 2008.
- Reanalysis of the series suggests the change in slope estimate is primarily driven by whether the post-intervention data is a straight line (as in the original paper) or not.
- If an additional interruption (increase of cases) occurs at June 2011, the change in slope at guideline introduction is reduced to zero, suggesting no effect of guidance publication on trends.
- Applying the Cochrane Effective Practice and Organisation of Care risk of bias assessment for interrupted time series suggests the study is at high risk of bias.
- Considering all evidence, Ramsey believes the effect of change in slope is biased and the published estimates are likely too high.

For the full critical review paper from Ramsay (2015), please see appendix O .

# 2.2 Review question 1a, 1b and 2

1a) Which pre-existing cardiac conditions, in adults and children increase the risk of developing infective endocarditis (IE)?

1b) Which pre-existing cardiac conditions are not associated with increased risk of developing IE?

2) Which pre-existing cardiac conditions are associated with relatively poorer outcomes from IE?

## 2.2.1 Clinical evidence review

Patients with certain cardiac conditions are known to be at risk of developing IE. Guidelines and discussion on prophylaxis against IE start from the principle that it is possible to classify those with underlying cardiac conditions into those who are at increased risk and those whose risk is considered to be the same as, or little greater than the general population. We therefore sought to review which underlying cardiac conditions affect a person's risk of developing IE/outcome of IE because it will influence decisions made about offering prophylaxis.

A systematic search was conducted (see appendix D) for question 1a, 1b and 2 which identified 4566 articles in total. The titles and abstracts were screened and 156 articles were identified as potentially relevant. Full-text versions of these articles were obtained, and reviewed against the criteria specified in the review protocol (appendix C). Of these, 131 were excluded as they did not meet the criteria and 25 met the criteria and were included. In addition all 12 of the studies included in CG64 were reviewed against the protocol criteria. Of these 8 were excluded as they did not meet the criteria and 4 were included. This gave a final total of 29 included studies.

Question 1a and b included 4 new studies plus 3 from the original 7 (total 7) and question 2 includes 21 new studies plus 1 study from the original 5 (total 22). One study has been included for both questions (double counted).

A review flowchart is provided in appendix E, and the excluded studies (with reasons for exclusion) are shown in appendix F.

## 2.2.2 Methods

### Summary of review protocols

The population included adults and children with/without underlying structural cardiac conditions and a history of IE, or adults and children who have previous had IE irrespective of whether they had a known underlying cardiac condition. It did not include people with rhythmic disorders and/or pacemakers, people at increased risk of IE who do not have underlying cardiac conditions (such as intravenous drug users or people on haemodialysis) and people with fungal IE and non-infective causes of endocarditis.

The topic expert members identified the following outcomes of interest, ranked in order of importance, for question 2: mortality, cardiac surgery, recurrence, stroke, length of stay and acute kidney injury.

Single case reports, case series and qualitative studies were excluded.

### Quality assessment - risk of bias

As this is a review question on assessing associations between different risk factors and IE, GRADE methodology is not appropriate for quality assessment for this particular question.

The quality of individual studies was assessed using the checklist for prognostic/prediction/association studies by Hayden et al., 2006, as guided in Developing NICE guidelines - the Manual, 2014This checklist addresses 6 main areas including study participation, study attrition, prognostic factor measurement, outcome measurement, confounding measurement and account and finally the analysis used in the study. We assessed each individual study against this criteria and assigned an overall quality rating using the following thresholds:

- all 6 criteria on checklist met: no risk of bias
- at least 4 out of 6 criteria met: low risk of bias
- anything else: high risk of bias

**Statistical analysis**

Conventional meta-analyses were not conducted due to the variations and heterogeneity in population and outcome measures from study to study.

Where appropriate, summary measures such as adjusted or unadjusted odds ratios (with 95% confidence intervals, where available) were presented in the evidence summary. Where the reviewer calculated these, this has been footnoted.

All findings are based on statistical significance as the aim of review question is to investigate whether there are any statistically significant associations between the risk factors and outcomes of interest.

**Overall Summary**

For a summary of included studies please see table 2 below (for the full evidence tables and full result summary tables please see appendix G and appendix H respectively).

The body of evidence for each risk factor is of variable quality and consistency, making it difficult to rate risk factors for IE/IE outcome.

The following reasons are examples of potential bias in the included studies:

- Just under half of the included studies were retrospective in design (potential selection bias) and several studies were conducted in tertiary centres (potential referral bias).
- Often the data for adults and children were combined.
- Often there was insufficient detail about the recruitment of control participants.
- In some cases both definite and possible diagnoses of IE (according to Duke/modified Duke criteria) were combined.
- Unclear statistical analyses or omission of results - even where multivariate analysis was conducted, it was often with small sample size and hence lack of power.

Please see the comments section of individual evidence tables (Appendix G) for individual study ratings for risk of bias.

**1a) Which pre-existing cardiac conditions, in adults and children increase the risk of developing infective endocarditis (IE)?**

**1b) Which pre-existing cardiac conditions are not associated with increased risk of developing IE?**

**Table 2: Summary of included studies**

| Study reference (including study design) | Study population | Predictors (or risk factors) | Outcomes | Effect estimates (including analysis used) | Comments |
|---|---|---|---|---|---|
| Alagna et al 2014<br><br>Prospective cohort | 1874 Adult patients with definite IE enrolled onto International Collaboration on Endocarditis Prospective Cohort Study. | • Prosthetic Valve<br>• Previous IE<br>• Congenital heart disease | IE (single episodes and repeat episodes (recurrent or relapse)). | **Univariate analysis**<br>Congenital heart disease – OR 1.06 (0.50-2.22)*<br>Prosthetic valve – OR 1.49 (0.86-2.59)*<br>Multivariate analysis results not reported<br><br>**Multivariate analysis**<br>History of Previous endocarditis – adjusted OR 2.8 (1.5-5.1)<br><br>*calculated by reviewer | High risk of bias<br>3/6 criteria met<br>See Evidence table. |
| Ammar et al 2013<br><br>Retrospective case-control study | 175 Adult patients with definite IE from an IE database at Cardiology Dept, Cairo University Hospital.<br>Plus 175 control cases without IE matched for age, sex and underlying heart disease. | • Known structural heart disease<br>• Congenital heart disease<br>• Valvular heart disease<br>• Prosthetic valve<br>• Previous IE | IE | **Univariate analysis**<br>Known structural heart disease – OR 1.16 (0.74-1.80)*<br>Congenital heart disease – OR 1.26 (0.58-2.73)*<br>Valvuar heart disease – OR 0.97 (0.62-1.53)*<br>Prosthetic Valve – OR 1.12 (0.70-1.80)*<br>Previous IE – OR 4.69 (0.998-22.03)<br><br>**Multivariate analysis**<br>Previous IE – adjusted OR - 5.841 (1.2-28.4) P=0.029<br><br>*calculated by reviewer | High risk of bias<br>3/6 criteria met<br>See Evidence table. |
| Clemens et al | 51 Adult hospital | Mitral valve | IE | **Univariate analysis** | Low risk of bias |

| Study reference (including study design) | Study population | Predictors (or risk factors) | Outcomes | Effect estimates (including analysis used) | Comments |
|---|---|---|---|---|---|
| 1992 [from CG64]<br><br>Case-control study | inpatients with IE (with echo, lacking any known cardiovascular risk factors for endocarditis except mitral valve prolapse).<br>153 Controls without (adult inpatients). | prolapse | | Mitral valve prolapse - Matched OR - 4.7 (1.1-19.5) | 4/6 criteria met<br>See Evidence table. |
| Hickey et al 1985 [from CG64]<br><br>Case-control study | 56 Cases - People age >15 admitted to hospital who met diagnostic criteria for IE.<br>168 Controls without IE Matched for age, sex and date of echo. | Mitral valve prolapse | IE | Mitral valve prolapse - Matched OR - 6.8 (2.1-22.0) | High risk of bias<br>3/6 criteria met<br>See Evidence table. |
| Richet et al 2008<br><br>Case-control study | 402 Adult and paediatric patients consulting hospital or hospitalised with definite IE. Patients with rejected IE served as | Prior Valve Damage<br>(Prosthetic valves, pacemaker or congenital heart disease) | IE | **Multivariate analysis**<br>Prior Valve Damage – adjusted OR 8.2 (5-13.3) | Low risk of bias<br>4/6 criteria met<br>See Evidence table. |

| Study reference (including study design) | Study population | Predictors (or risk factors) | Outcomes | Effect estimates (including analysis used) | Comments |
|---|---|---|---|---|---|
| | controls. | | | | |
| Rushani et al 2013<br><br>Population based cohort | 47,518 children with CHD followed for 458109 pt/years generating 185 cases of IE.<br><br>(matched on calendar time with 20 controls (who also had congenital heart diseases) | Congenital Heart Diseases (CHD) incl.<br>• Cyanotic CHD<br>• Endocardial cushion defects<br>• L/R sided lesions<br>• Patent ductus arteriosus<br>• Ventricular septal defect<br>• Atrial septal defect<br><br>Cardiac Surgery in past 6 months. | IE | **Univariate and multivariate analysis**<br>Cyanotic CHD – OR 6.38 (4.02-10.13), adjusted OR 6.44 (3.95-10.5)<br>Endocardial cushion – OR 4.37 (2.35-8.15) adjusted OR 5.47 (2.89-10.36)<br>L sided lesions - OR 1.57 (0.86-2.88) adjusted OR 1.88 (1.01-3.49)<br>R sided lesions - OR 1.12 (0.49-2.59) adjusted OR 1.22 (0.52-2.86)<br>Patent ductus arteriosus - OR 1.33 (0.54-3.27) adjusted OR 1.25 (0.50-3.13)<br>Ventricular septal defect - OR 0.95 (0.56-1.62) adjusted OR 0.97 (0.56-1.66)<br>Atrial septal defect – OR 0.449 (0.33-0.75)*<br><br>Cardiac Surgery in past 6 months – OR 15.52 (8.08-29.80 adjusted OR 5.34 (2.49-11.43)<br><br>*Calculated by reviewer | Low risk of bias<br>5/6 criteria met<br>See Evidence table. |
| Strom et al 1998 [from CG64]<br><br>Population based case-control. | 273 Adults with Community acquired IE (not associated with IVDU) and 270 matched controls without IE (community residents). | • Mitral valve prolapse<br>• Valvular heart disease<br>• Congenital heart disease<br>• Rheumatic fever<br>• Previous IE | IE | **Univariate and multivariate analysis**<br>Mitral valve prolapse – matched OR 19.4 (6.4-58.4)<br>Valvular heart disease – adjusted OR 0.62 (0.34-1.14)<br>Congenital heart disease – adjusted OR 6.7 (2.3-19.4)<br>Rheumatic fever – adjusted OR 13.4 (4.5-39.5)<br>Previous IE – adjusted OR 37.2 (4.4-317) | Low risk of bias<br>5/6 criteria met<br>See Evidence table. |

## 2) Which pre-existing cardiac conditions are associated with relatively poorer outcomes from IE?

**Table 3: Summary of included studies**

| Study reference (including study design) | Study population | Predictors (or risk factors) | Outcomes | Effect estimates (including analysis used) | Comments |
|---|---|---|---|---|---|
| Alagna et al 2014<br><br>Prospective cohort | 1874 Adult patients with definite IE enrolled onto International Collaboration on Endocarditis Prospective Cohort Study. | • Prosthetic Valve<br>• Previous IE<br>• Congenital heart disease | Recurrence | **Univariate analysis**<br>Prosthetic valve – OR 0.73 (0.42-1.25)*<br>Congenital heart disease - OR 1.49 (0.86-2.59)*<br><br>*Calculated by reviewer | High risk of bias<br>3/6 criteria met<br>See Evidence table. |
| Aksoy et al 2007<br><br>Longitudinal cohort study | 333 Adult patients with IE. | • Congenital heart disease.<br>• Aortic valve involvement | Cardiac surgery | **Univariate analysis**<br>Congenital heart disease – OR 0.41 (0.19-0.87)*<br>Aortic valve involvement – OR 11.61 (0.64-211.63)*<br><br>*Calculated by reviewer | Low risk of bias<br>4/6 criteria met<br>See Evidence table. |
| Alonso-Valle et al 2010<br><br>Retrospective cohort<br>study | 133 cases of IE (in 122 patients) of the prosthetic valve. | • Previous IE<br>• Previous valve replacement<br>• Mechanical prosthesis implantation | Mortality | **Univariate analysis**<br>Previous IE - (RR) 1.7 (0.7-4.4)<br>Previous valve replacement - (RR) 0.9 (0.4-2.1).<br>Mechanical prosthesis implantation - (RR) 1.1 (0.5-2.4). | High risk of bias<br>3/6 criteria met<br>See Evidence table. |
| Bannay et al 2011<br><br>Long term prospective follow-up study | 449 Adults with Left sided IE selected from a prospective, population based study. | • Predisposing cardiac diseases (Valvular diseases with/without prosthesis)<br>• Valvular prosthesis | Mortality, cardiac surgery | **Mortality**<br>Previous valve replacement/prosthetic valve – HR 1.09 (0.72-1.67)<br><br>**Univariate analysis**<br>**Cardiac surgery**<br>Valvular prosthesis only - OR 0.95 (0.57-1.56)* | Low risk of bias<br>4/6 criteria met<br>See Evidence table. |

| Study reference (including study design) | Study population | Predictors (or risk factors) | Outcomes | Effect estimates (including analysis used) | Comments |
|---|---|---|---|---|---|
| | | • Previous IE | | Native and prosthetic valves OR1.08 (0.79-1.46)*<br>Previous IE – OR 1.49 (0.75-2.96)*<br>*calculated by reviewer | |
| Da costa et al 2007<br><br>Retrospective observational study | 186 Adults and children with IE. | • Prosthetic heart valve<br>• Rheumatic disease | Mortality | **Univariate and Multivariate analysis**<br>Prosthetic heart valve – OR 4.57 (1.89-11.07), Adjusted OR 4.77 (1.44, 15.76).<br><br>**Univariate analysis**<br>Rheumatic disease – OR 0.70 (0.31-1.56)*<br><br>*Calculated by reviewer | Low risk of bias<br>4/6 criteria met<br>See evidence table. |
| Delahaye et al 2007<br><br>Population based survey | 653 Adults with IE living in one of the study regions. | • Prosthetic valve<br>• Rheumatological manifestations | Mortality | Prosthetic valve - Reported as significant p value only (p=0.004) after univariate analysis. Not possible to back calculate due to missing data.<br><br>Rheumatological manifestations - Reported as significant p value only (p=0.001) after univariate analysis. Not possible to back calculate due to missing data. | High risk of bias<br>3/6 criteria met<br>See evidence table. |
| Erbay et al 2010<br><br>Retrospective cohort design | 107 Adults with IE admitted to hospital. | • Congenital heart disease<br>• Predisposing heart disease<br>• Rheumatic heart disease<br>• Degenerative heart disease<br>• Bicuspid aortic valve<br>• Prosthetic valve<br>• Previous IE | Mortality | **Univariate analysis**<br>Congenital heart disease - OR 1.08 (0.20-5.86)*<br>Predisposing heart disease – OR 1.09 (0.58-2.04)*<br>Rheumatic heart disease – OR 2.24 (0.64-7.91)*<br>Degenerative heart disease – OR 0.98 (0.29-3.32)*<br>Bicuspid aortic valve – OR 5.38 (0.47-61.60)*<br>Prosthetic valve – OR 0.73 (0.32-1.65)*<br><br>Previous IE - HR 3.5 (1.2-11.0) p=0.026 | Low risk of bias<br>4/6 criteria met.<br>See evidence table. |

| Study reference (including study design) | Study population | Predictors (or risk factors) | Outcomes | Effect estimates (including analysis used) | Comments |
|---|---|---|---|---|---|
| | | | | *Calculated by reviewer | |
| Fenandez-Guerrero et al 2007<br><br>Retrospective cohort study | 44 Adults with IE (enterococcal) (hospital based) | Prosthetic valve | Mortality, surgery, stroke | **Univariate analysis**<br>**Mortality**<br>Prosthetic valve – OR 0.21 (0.04-1.04)*<br>**Surgery**<br>Prosthetic valve – OR 0.87 (0.27-2.78)*<br>**Stroke**<br>Prosthetic valve – OR 1.27 (0.30-5.41)*<br><br>*Calculated by reviewer | High risk of bias<br>3/6 criteria met.<br>See evidence table. |
| Fernandez-Guerrero et al 2010<br><br>Retrospective cohort study | 84 Adults (?) with IE (staphylococcal) with data recorded on a patient records database. | Prosthetic valve | Mortality, surgery, stroke | **Univariate analysis**<br>**Mortality**<br>Prosthetic valve – OR 0.53 (0.21-1.37)<br>**Surgery**<br>Prosthetic valve – OR 0.24 (0.09-0.64)<br>**Stroke**<br>Prosthetic valve – OR 0.72 (0.27-1.89) | High risk of bias.<br>2/6 criteria met.<br>See evidence table. |
| Galvez-Acebal et al 2010<br><br>Observational multi-centre study | 705 Adults and children with Left sided IE | Prosthetic valve | Mortality | **Univariate and multivariate analysis**<br>Prosthetic valve - OR 1.48 (1.17-1.87).<br>Adjusted OR 1.99 (1.26-3.14) | Low risk of bias.<br>4/6 criteria met.<br>See evidence table. |
| Lin et al 2013<br><br>Retrospective analysis | 47 Children with IE (consecutive patients) | Congenital heart disease (cyanotic only) | Mortality, surgery. | **Univariate analysis**<br>**Mortality**<br>Cyanotic CHD – OR 1.41 (0.42-4.66)*<br>**Surgery (all cardiac)**<br>Cyanotic CHD – OR 0.75 (0.28-1.98)*<br>**Valve replacement surgery**<br>Cyanotic CHD – OR 0.36 (0.09-1.42)*<br>*Calculated by reviewer | High risk of bias.<br>3/6 criteria met.<br>See evidence table. |

| Study reference (including study design) | Study population | Predictors (or risk factors) | Outcomes | Effect estimates (including analysis used) | Comments |
|---|---|---|---|---|---|
| Murakami et al 2012<br><br>Retrospective observational Cohort | 239 Adults and children with IE | • Congenital heart disease (plus cardiac surgery)<br>• Previous IE | Surgery | **Univariate analysis**<br>Congenital heart disease (plus cardiac surgery) – OR 0.27 (0.11-0.65)<br>Previous cardiac surgery - OR 0.68 (0.38-1.22)<br>Previous IE – OR 0.67 (0.22-2.06) | Low risk of bias.<br>4/6 criteria met.<br>See evidence table. |
| Murdoch et al 2009<br><br>Prospective cohort study | 2781 Adults with IE | • Congenital heart disease<br>• Prosthetic valve | Mortality | **Multivariate analysis**<br>Congenital heart disease – Adjusted OR 1.22 (0.74-2.02)<br>Prosthetic valve - Adjusted OR 1.47 (1.13-1.90) | Low risk of bias.<br>4/6 criteria met.<br>See evidence table |
| San Roman et al 2007<br><br>Prospective study | 317 Adults with left sided IE (consecutive patients) | Prosthetic valve<br>Rheumatic heart disease<br>Degenerative heart disease | Events (death or surgery) | **Univariate analysis**<br>Prosthetic valve – OR 0.96 (0.63-1.47)*<br>RHD – OR 0.79 (0.38-1.63)*<br>DHD – OR 0.86 (0.40-1.84)*<br><br>*Calculated by reviewer | High risk of bias.<br>3/6 criteria met.<br>See evidence table. |
| Smith et al 2007<br><br>Prospective cohort | 87 Adults with IE (hospitalised patients) | Previous cardiac surgery<br>Mechanical prosthesis | Mortality | **Univariate analysis**<br>Mechanical prosthesis – OR 0.77 (0.16-3.80)*<br>Previous cardiac surgery - OR 1.10 (0.28-4.36)*<br><br>*Calculated by reviewer | Low risk of bias.<br>4/6 criteria met.<br>See evidence table. |
| Ternhag et al 2013<br><br>Retrospective cohort | 7063 Adults with IE (hospitalised and treated patients) from Swedish National inpatient register. | Prosthetic valve | Mortality | Standardised mortality ratio – 2.3 (1.9-2.7) | Low risk of bias.<br>4/6 criteria met.<br>See evidence table. |
| Thuny et al 2012<br><br>Observational cohort | 328 Adults with IE (consecutive hospitalised patients) | Underlying heart disease<br>Prosthetic valve | Mortality | **Univariate analysis**<br>Underlying heart disease - OR 0.85 (0.52-1.37)*<br>Prosthetic valve – OR 0.85 (0.52-1.37)*<br>*Calculated by reviewer | Low risk of bias.<br>4/6 criteria met.<br>See evidence table. |

| Study reference (including study design) | Study population | Predictors (or risk factors) | Outcomes | Effect estimates (including analysis used) | Comments |
|---|---|---|---|---|---|
| | | | | | |
| Thuny et al 2007<br><br>Prospective study | 496 Adults with IE (consecutive hospitalised patients) | Prosthetic valve<br>Underlying heart disease | Stroke | **Univariate analysis**<br>Underlying heart disease – OR 0.97 (0.68-1.39)*<br>Prosthetic valve – OR 0.99 (0.60-1.63)*<br><br>*Calculated by reviewer | Low risk of bias.<br>4/6 criteria met.<br>See evidence table. |
| Tleyjeh et al 2007<br><br>Retrospective/Prospective study | 546 Adults with IE (consecutive patients diagnosed and treated) | Previous IE | Surgery | **Univariate analysis**<br>Previous IE – OR 1.20 (0.66-2.21)*<br><br>*Calculated by reviewer | High risk of bias.<br>3/6 criteria met.<br>See evidence table. |
| Wang et al 2007 [from CG64]<br><br>Observational cohort | 2670 Adults with IE of prosthetic valve enrolled in ICE-PCS (International Collaboration on Endocarditis-Prospective Cohort study) | Previous IE and prosthetic valve | Mortality | **Univariate analysis**<br>Previous IE and prosthetic valve– unadjusted OR 0.74 (0.49-1.12). | Low risk of bias.<br>4/6 criteria met.<br>See evidence table. |
| Wong et al 2009<br><br>Retrospective review | 47 Adults with IE | Rheumatic heart disease (RHD)<br>Aortic stenosis<br>Mitral valve prolapse<br>Prosthetic valve | Recurrence | **Univariate analysis**<br>RHD – OR 0.61 (0.07-5.58)*<br>Aortic stenosis – OR 4.88 (0.60-39.91)*<br>Mitral valve prolapse – OR 0.70 (0.08-6.47)*<br>0.41 (0.05-3.58)*<br><br>*Calculated by reviewer | Low risk of bias.<br>3/6 criteria met.<br>See evidence table. |
| Yoshinaga et al 2008.<br><br>Retrospective observational review | 137 Adults and children with congenital heart disease and IE | Cyanotic CHD<br>Prosthetic heart valve<br>Previous cardiac surgery (for CHD)<br>Previous IE | Mortality | **Univariate analysis**<br>Cyanotic CHD – OR 5.34 (1.66-17.2)<br>Prosthetic heart valve – OR not reported<br>Previous cardiac surgery – OR 4.69 (1.25-17.6)<br>Previous IE – OR 3.46 (0.81-14.7) | High risk of bias.<br>2/6 criteria met.<br>See evidence table. |

## 2.2.31 Clinical evidence statements

2 **Question 1:**

3 Particular types of congenital heart disease (cyanotic congenital heart disease, endocardial
4 cushion defects and left sided lesions in children), rheumatic heart disease, previous cardiac
5 surgery and previous IE appear to be significantly associated with increased odds of
6 developing IE (low to high risk of bias).

7 Pre-existing cardiac conditions that do not appear to increase risk of IE include prosthetic
8 valves (based on two studies with high risk of bias) and particular types of congenital heart
9 disease in children (patent ductus arteriosus and ventricular and atrial septal defects (one
10 study of low risk of bias).

11 People with mitral valve prolapse may have an increased risk of IE (based on three studies,
12 two with low and one with high risk of bias).

13 **Congenital heart disease**

14 People with congenital heart disease appear to have significantly increased odds of getting
15 IE than people without congenital heart disease, based on one study with low risk of bias,
16 however this finding was not consistent across all studies.

17 Particular types of congenital heart disease in children appear to significantly increase the
18 odds of IE. These include cyanotic CHD, endocardial cushion defects and left sided lesions
19 (based on one study with low risk of bias).

20 **Rheumatic heart Disease (RHD)**

21 People with RHD have significantly increased odds of getting IE than people without RHD,
22 based on one study of low risk of bias.

23 **Valvular heart disease**

24 People with valvular heart disease (when dealt with collectively) may have significantly
25 increased odds of developing IE than people without valvular heart disease, based on one
26 study with low risk of bias, however two studies found no significant difference in odds (high
27 and low risk of bias respectively)

28 **Mitral valve prolapse (MVP)**

29 People with MVP appear to have significantly increased odds of developing IE than people
30 without MVP, based on 3 studies with variable risk of bias (2 low risk and 1 high risk of bias),
31 however these odds are unadjusted for other factors that may predispose to IE

32 **Prosthetic heart valve**

33 People with prosthetic heart valves do not appear to be at increased odds of developing IE
34 than people without h prosthetic heart valves, based on two studies of high risk of bias.

35 **Previous IE**

36 People who have had previous infective endocarditis appear to have significantly increased
37 odds of developing a further IE than people who have not had previous IE, based on three
38 studies (one low and two high risk of bias).

39 **Question 2:**

40 In people with certain pre-existing cardiac conditions, the evidence for having a poorer
41 outcome after IE is inconsistent and based on studies of low and high risk of bias.

People with prosthetic valves may be at increased risk of in-hospital death (three studies of low risk of bias).

Pre-existing cardiac conditions where there is no evidence of an increased risk of death or recurrence include rheumatic heart disease, degenerative heart disease, aortic valve disease and mitral valve prolapse (based on evidence of predominantly low risk of bias).

**Congenital heart disease**

The evidence for risk of mortality in people with congenital heart disease is inconsistent. (Three studies indicating no increased risk, low and high risk of bias, one study indicating increased risk of in hospital death and one study indicating reduced risk of death at 5 years (high and low risk of bias).

In people with CHD who get IE there is evidence of a reduced odds of cardiac surgery (based on one study with low risk of bias, but is unadjusted for other factors leading to surgery).

In people with CHD who get IE, there is no evidence of a difference in IE recurrence (based on one study with high risk of bias).

**Rheumatic Heart Disease and Degenerative Heart Disease**

In people with rheumatic heart disease or degenerative heart disease who get IE, there are no significantly increased odds of death, recurrence or cardiac surgery (based on five studies, four with low and one with high risk of bias).

**Aortic Valve Disease / Mitral Valve prolapse**

In people with aortic valve disease or mitral valve prolapse who get IE, there are no significantly increased odds of death or recurrence (based on three studies, all with low risk of bias).

**Previous Valve Replacement/Prosthetic Valve**

In people with previous valve replacement (prosthetic valve) who get IE, the odds of death are inconsistent. Three studies of low risk of bias indicate a significantly increased odds of in-hospital death and 4 studies of high and low risk of bias) suggest there is no difference.

In people with previous valve replacement who get IE, there is no significantly increased odds of death beyond the hospital stay, need for cardiac surgery, recurrence or stroke.

**Previous cardiac surgery**

In people who have had previous cardiac surgery who get IE, there may be increased odds of death (based on one study with high risk of bias). Two further studies indicate no difference in the odds of further cardiac surgery (low risk of bias).

**Previous IE**

In people who have had IE previously, who get it again, there may be a significantly increased likelihood of death but the evidence is inconsistent (based on four studies, two with low and two with high risk of bias). There are no increased odds of further cardiac surgery (based on three studies, two with low and one with high risk of bias).

### 2.2.40 Evidence to recommendations

| | Committee discussions |
|---|---|
| **Relative value of** | The committee noted the presented limitations around the outcome of IE |

| | Committee discussions |
|---|---|
| **different outcomes** | and the outcomes associated with IE but had no further comment about this point.<br>The Committee discussed and agreed that the critical outcome for review question 1a and 1b was to establish whether there is a clear relationship between having a pre-existing cardiac condition and the risk of developing IE. Therefore, the only critical outcome is the measurement of such an association and the precision and certainty for these measurements reported in the included studies (i.e. odds ratios and risk ratios, adjusted or unadjusted).<br>The Committee also discussed review question 2. As the aim of this question was to identify who would have poorer outcomes within this patient pathway:<br>• People with a pre-existing cardiac condition/or have had IE before --> experienced an episode of IE --> who are likely to die; and for those who survived, who would have the poorer outcomes.<br>The Committee agreed that the critical outcomes for review question 2 are mortality; cardiac surgery; stroke/systemic embolism; length of hospital stay; recurrent attacks of IE; and acute kidney injury. |
| **Quality of evidence** | The committee sought clarification on the quality assessment criteria used to identify risk of bias and we invited the topic experts to identify any ratings that they felt might need amending. None were received.<br>The Committee discussed the quality assessment tool (Hayden's checklist) used to assess the quality of included studies. The Committee commented that the criteria in the checklist did not account for other important complex elements that were relevant to this review question, for example, how different cardiac conditions are diagnosed and how this has changed over time; aging population and its associated multi-morbidity; and others.<br><br>The committee expressed some surprise at the effect estimates and associated quality levels for each pre-existing cardiac condition in that the findings did not indicate as much of an increased risk of IE or as much of an increase in poorer outcomes as had been previously widely accepted.<br>The Committee noted that the majority of the evidence was of high risk of bias, and that it was difficult to draw conclusion on whether people with a pre-existing cardiac condition, were more at risk of developing IE over time, though there was some evidence that sugghested people who have previously had IE may be more at risk of developing further IE. The Committee also noted that, from this particular update, the evidence is still inconclusive to assess for those within the potential high-risk groups, who would have poorer outcomes (e.g. there was inconsistent evidence on mortality, cardiac surgery, stroke and recurrent IE).<br><br>The topic experts commented on the generalisability of older studies. For example, these may have included older or obsolete practices, diagnostic criteria that no longer used and altered causative organism profiles that could affect the study quality and potentially the uncertainty around the effect estimates. In particular, this point was made in relation to the three studies cited for mitral valve prolapse (published in 1992, 1985 and 1998 respectively) which were all included in the original guideline. |
| **Trade-off between benefits and harms** | As the aim of this review question is to investigate the relationship between having a pre-existing cardiac condition and the risk of developing IE (to explore the pathogenesis of IE) , the discussion of trade-off between benefits and harms was not relevant for this question. |
| **Trade-off between net health benefits and resource use** | There is no impact on resource use related to these review questions per se. Section 2.6.4 contains a systematic review of economic evaluations that investigate the cost-effectiveness of antibiotic prophylaxis. |

| | Committee discussions |
|---|---|
| **Other considerations** | The Committee discussed the exclusion of people with implantable cardiac electronic devices and agreed that the exclusion is appropriate, as this population will merit their own separate clinical guideline on antibiotic prophylaxis.<br><br>Due to the inconsistencies in the evidence and the number of studies that were deemed to be at high risk of bias or of questionable quality the Committee felt there was insufficient evidence to justify making an amendment to the current recommendation on high risk groups (please see recommendation 1.1.1). |

1
2

# 2.3 Review question 3

Which dental and other interventional procedures are associated with increased incidence of IE in those considered at risk of IE?

## 2.3.1 Clinical evidence review

Infective endocarditis (IE) is a rare condition and therefore it is difficult to determine which interventional procedures may be associated with an increased incidence of IE in those with defined pre-existing cardiac conditions. It has been suggested that some interventional procedures can cause bacteraemia, eliminated naturally in most people, most of the time. However, those with certain conditions may be at risk of this bacteraemia leading to the development of IE. It is therefore important to consider any evidence of significant post-procedure bacteraemia that may be potentially contribute to the risk of developing IE.

The aim of this review is to identify which interventional procedures are associated with increased incidence of IE in those considered at risk of IE (those with pre-existing cardiac conditions and those who have had IE previously). The interventional procedures covered by this review are listed below (defined by the original scope – appendix P):

- Dental procedures
- Interventional procedures that cover the following sites:
  - Upper and lower gastrointestinal (GI) tract
  - Genitourinary tract (includes urological, gynaecological and obstetric procedures)
  - Upper and lower respiratory tract (includes ENT and bronchoscopy procedures)

A systematic update search using the original search strategy from CG64 was conducted (see appendix D) which identified 1081 articles. The titles and abstracts were screened and 13 articles were identified as potentially relevant. Full-text versions of these articles were obtained and reviewed against the criteria specified in the review protocol (appendix C). Of these, 12 were excluded as they did not meet the criteria. One study met the criteria and was included. Due to the substantial overlaps between this particular question and question 1 and 2, a very broad inclusive search with only endocarditis terms was also sifted for this review question to ensure no potential studies were missed. This additional search identified 2 more studies that met the inclusion criteria. With the 3 included studies from the original guideline CG64, there are 6 total included studies for this review question.

A review flowchart is provided in appendix E, and the excluded studies (with reasons for exclusion) are shown in appendix F.

## 2.3.21 Methods

### 2 Summary of review protocols

3 The population included adults and children undergoing interventional procedures (with
4 underlying cardiac condition, or who have had previous IE) including dental, upper and lower
5 gastrointestinal tract, genitourinary tract (this includes urological, gynaecological and
6 obstetric procedures including childbirth), upper and lower respiratory tract (includes ear
7 nose and throat and bronchoscopy procedures). No subgroups were identified for this
8 question.

9 The topic experts identified the following outcome as of interest for this review:

10 • Any statistical tests that assessed the association between the interventional procedures
11 mentioned above and the outcome of interest (number of IE).

### 12 Quality assessment - risk of bias

13 As this is a review question on assessing the association between different risk factors and
14 IE, GRADE methodology is not appropriate for quality assessment for this particular
15 question. The quality of individual studies was assessed using the checklist for
16 prognostic/prediction/association studies by Hayden et al., 2006, as guided in Developing
17 NICE guidelines - the Manual, 2014. This checklist addresses 6 main areas including study
18 participation, study attrition, prognostic factor measurement, outcome measurement,
19 confounding measurement and account and finally the analysis used in the study. Each
20 individual study was assessed against this criteria and an overall quality rating was assigned
21 using the following thresholds:

22 • all 6 criteria on checklist met: no risk of bias

23 • at least 4 out of 6 criteria met: low risk of bias

24 • anything else: high risk of bias

### 25 Statistical analysis

26 Conventional meta-analyses were not conducted due to the variations and heterogeneity in
27 population and outcome measures from study to study.

28 Where appropriate, summary measures such as adjusted or unadjusted odds ratios (with
29 95% confidence intervals, where available) were presented in the evidence summary.

30 All findings are based on statistical significance, as the aim of review question is to
31 investigate whether there are any statistical significant associations between rsk factors and
32 outcome of interest.

### 33 Overall summary of evidence

34 For a summary of included studies please see below table 4 (for the full evidence tables
35 please see appendix G). For the full details on quality assessment of the individual included
36 studies using the Hayden's checklist please see appendix M.

37 Overall, 6 studies were included in this review (3 from the update search, 3 from the original
38 guideline). All 6 included studies were of various degrees of risk of bias due to the following
39 reasons:

40 • Most included studies had unclear loss to follow-up due to the retrospective nature of the
41 study design (e.g. the quality of the databases data retrieved from).

- Most included studies did not report clearly how they accounted for potential confounders that may impact on the association between the risk factors (interventional procedures) and the outcome of interest (development of IE).
- Unclear statistical analyses that were used in the included studies, and even if multivariate analysis was conducted, it was of small sample size and therefore lacked power.

**Table 4: Summary of included studies**

| Study reference (including study design) | Study population | Predictors (or risk factors) | Outcomes | Effect estimates (including analysis used) | Quality |
|---|---|---|---|---|---|
| Mohee (2014)<br>Case-control study | 384 adult patients treated for IE split into 4 groups:<br>-Enterococcal IE group<br>-CoNS IE group<br>-Streptococcus bovis group<br>-Oral streptococcal IE group<br><br>(N=384) | Procedure related risk factors were identified from the data (procedures undertaken ≤1 year before the development of IE). | Odds of IE | Univariate ananlysis in patients with IE:<br>*Enterococcal IE group (n=111)*<br>Upper GI procedures: OR = 0.95 (95%CI: 0.33 to 2.72)<br>Lower GI procedures: OR = 1.25 (95%CI: 0.41 to 3.73)<br>Urological procedures: OR = 7.28 (95%CI: 3.35 to 15.8)<br><br>*CoNS IE group (n=86)*<br>Upper GI procedures: OR = 1.19 (95%CI: 0.65 to 4.93)<br>Lower GI procedures: OR = 0.86 (95%CI: 0.24 to 3.14)<br>Urological procedures: OR = 0.44 (95%CI: 0.15 to 1.28)<br><br>*Streptococcus bovis group (n=36)*<br>Upper GI procedures: OR = 1.22 (95%CI: 0.27 to 5.55)<br>Lower GI procedures: OR = 0.68 (95%CI: 0.09 to 5.36)<br>Urological procedures: OR = 0.58 (95%CI: 0.13 to 2.54)<br><br>*Oral streptococcal IE group (n=151)*<br>Upper GI procedures: OR = 0.43 (95%CI: 0.14 to 1.33)<br>Lower GI procedures: OR = 0.77 (95%CI: 0.26 to 2.29)<br>Urological procedures: OR = 0.19 (95%CI: 0.06 to 0.54)<br><br>Multivariate analysis in patients with enterococcal IE:<br>Urological procedures: adj OR = 8.56 (95%CI: 3.69 to 19.85) | Low risk of bias |
| Chen (2013)<br>Case-control study | 736 adult patients diagnosed with IE, and 7360 matched controls without IE. | The frequency of dental scaling within 2 years before the | Odds of IE | Logistic regression was used to analysis the associations between procedures and IE. | Low risk of bias |

| Study reference (including study design) | Study population | Predictors (or risk factors) | Outcomes | Effect estimates (including analysis used) | Quality |
|---|---|---|---|---|---|
| | (N=8096) | enrolment of the study. | | *Frequency of dental scaling:*<br>1 time in 2 years: adj OR = 0.845 (95%CI: 0.693 to 1.012)<br>At lease 1 time per year: adj OR = 0.696 (95%CI: 0.542 to 0.894) | |
| Ammar (2013)<br>Case-control study | 175 adult patients with definite IE according to modified Duke Criteria for diagnosis of IE and 175 adult controls without IE were identified.<br>(N=350) | Procedure related risk factors were identified from data collected from the cases and control. | Odds of IE | Simple Pearson's chi-square test was used to analysis the associations between procedures and IE.<br><br>Procedure-related risk factors:<br>*Dental procedures:*<br>Cases = 6 (3.4%); control = 8 (4.6%), P>0.05<br>*Gynaecological procedures:*<br>Cases = 1 (0.6%); control = 4 (2.3%), P>0.05<br>*Urinary catheterization:*<br>Cases = 2 (1.1%); control = 6 (3.4%), P>0.05 | High risk of bias |
| Duval (2006)<br>Cross sectional study (epidemiological study)<br><br>[from CG64] | Of the 2805 interviewed adults, there were 182 cases of IE, 12 occurred in adults with known PCC after dental procedures and were considered to be caused by an oral microorganism (n = 10 unprotected).<br>(N=2805) | Investigated the estimated risk of endocarditis in adults with predisposing cardiac conditions (PCC) undergoing dental procedures with or without antibiotic prophylaxis. | Odds of IE | The risk was estimated using the formula: risk = annual number of IE cases after at-risk dental procedures in adults with known PCC /annual number of at-risk dental procedures in adults with known PCC. The prevalence of PCC from the data from the study was 104 native valve and 24 prosthetic valve conditions.<br><br>The estimated risk of IE after dental procedure in adults with known PCC was as follow:<br>• 1 case per 46,000 (95% CI 36,236 to 63,103) for unprotected dental procedures<br>• 1 case per 54,300 (95% CI 41,717 to 77,725) for unprotected dental procedures in those with native valve PCC<br>• 1 case per 10,700 (95% CI 6000 to 25,149) for unprotected dental procedures in those with prosthetic valve PCC<br>• 1 case per 149,000 (95% CI 88,988 to 347,509) for | High risk of bias |

| Study reference (including study design) | Study population | Predictors (or risk factors) | Outcomes | Effect estimates (including analysis used) | Quality |
|---|---|---|---|---|---|
| | | | | protected dental procedures | |
| Lacassin (1995)<br>Case-control study<br><br>[from CG64] | A case–control study interviewed 171 adults following diagnosis of IE (based on the Von Reyn's criteria) within 180 days of the onset of symptoms, with one control identified for each case. Of the cases, with 89 (20.8%) having undergone a procedure for which prophylaxis was indicated.<br>88 (51.5%) of the cases and 70 (41%) of the controls had undergone at least one procedure.<br>(N=342) | Procedure related risk factors were identified from data collected from the cases and control. | Odds of IE | The results of the association are as follow:<br>Univariate analysis adjusted for other procedures:<br>*Any dental procedures:*<br>Cases = 37 (22%); control = 33 (19%); OR = 1.2 (95%CI: 0.7 to 2.1)<br>*Any urological procedures:*<br>Cases = 6 (3.5%); control = 2 (11%); OR = 3.1 (95%CI: 0.6 to 15.7)<br>*Any GI procedures:*<br>Cases = 14 (8.2%); control = 8 (4.7%); OR = 1.2 (95%CI: 0.7 to 4.1)<br><br>*Multivariate analysis:*<br>Urological procedure: adj OR = 6.1 (95%CI: 0.9 to 39.7)<br>Scaling: adj OR = 2.7 (95%CI: 0.8 to 9.0)<br>Canal treatment: adj OR = 1.7 (95%CI: 0.5 to 5.2)<br><br>Both the univariate and multivariate analyses suggested that none of the interventional procedures being investigated were significantly associated with increased risk of IE. | High risk of bias |
| Strom (1998)<br>Case-control study<br><br>[from CG64] | 273 adult patients who had definite, probableor possible IE were identified as cases. There was one control for each case matched for age, sex, ethnicity, education, occupation and dental insurance status; controls were selected | A case–control study that considered dental risk factors and the risk factors of oral hygiene and non-dental procedures. | Odds of IE | In the multivariate analysis, the associations of interventional procedures and risk of IE were as below:<br><br>*Multivariable adjusted OR (in previous 3 months):*<br>*Pulmonary procedures (inc. lung biopsy & bronchoscopy):*<br>Cases = 3 (1.1%); control = 3 (1.1%); adj OR = 0.27 (95%CI: 0.01 to 5.46)<br>*Barium enema:*<br>Cases = 11 (4%); control = 1 (0.4%); adj OR = 11.9 | High risk of bias |

| Study reference (including study design) | Study population | Predictors (or risk factors) | Outcomes | Effect estimates (including analysis used) | Quality |
|---|---|---|---|---|---|
| | from the community for each case patient using a modified random-digit method.<br>(N=546) | | | (95%CI: 1.34 to 106)<br>*Lower GI endoscopy:*<br>Cases = 14 (5.1%); control = 8 (2.9%); adj OR = 1.95 (95%CI: 0.58 to 6.53)<br>*Upper GI endoscopy:*<br>Cases = 8 (2.9%); control = 4 (1.5%); adj OR = 1.36 (95%CI: 0.26 to 6.99)<br>*Urinary catheterization:*<br>Cases = 12 (4.4%); control = 4 (1.5%); adj OR = 0.58 (95%CI: 0.11 to 3.10)<br>*Gynecological surgery:*<br>Cases =3 (1.1%); control = 0 (0.0%); adj OR = N/A<br>*Other genitourinary procedures (inc. cystoscopy, lithotripsy, vasectomy):*<br>Cases = 4 (1.5%); control = 3 (1.1%); adj OR = 0.61 (95%CI: 0.06 to 5.80)<br><br>Only barium enema remained significant after multivariate adjustment OR 11.9 (CI; 1.34 to 106), p=0.026 | |

1

### 2.3.31 Clinical evidence statements

One case-control study with low risk of bias (n=111) suggested that enterococcal IE was significantly associated with urological procedures (positive association) but a negative significant association was also identified between oral streptococcal IE and urological procedures (n=151). Another case-control study suggested a negative significant association between dental scaling (at least 1 time per year) and IE (n=8096, low risk of bias).

However, there were also 3 case-control studies with high risk of bias (N = 350, 341, 546) that showed conflicting evidence. With the exception of barium enema, these 3 studies have suggested there were no statistical significant association between dental procedures, gynaecological procedures, urinary/urological procedures, pulmonary procedures, GI procedures and the development of infective endocarditis in adults.

Another cross sectional study with high risk of bias (N = 2805) also suggested the estimated risk of IE after dental procedure in adults with known pre-existing cardiac conditions was very low:

- 1 case per 46,000 (95% CI 36,236 to 63,103) for unprotected dental procedures
- 1 case per 54,300 (95% CI 41,717 to 77,725) for unprotected dental procedures in those with native valve pre-existing cardiac conditions
- 1 case per 10,700 (95% CI 6000 to 25,149) for unprotected dental procedures in those with prosthetic valve pre-existing cardiac conditions

### 2.3.40 Evidence to recommendations

| | Committee discussions |
|---|---|
| **Relative value of different outcomes** | The Committee discussed and agreed that the critical outcome for this review question was to establish whether there is a clear relationship between specific interventional procedures and the development of IE in people who have pre-existing cardiac conditions or have had an episode of IE before (with or without known origin). Therefore, the only critical outcome is the measurement of such an association and the precision and certainty for these measurements reported in the included studies. |
| **Quality of evidence** | The Committee discussed the utility of the Hayden's checklist (2007) to assess the quality of evidence for this particular review question. It was acknowledged and agreed that the 6 criteria in the Hayden's checklist were not comprehensive nor detailed enough to fully assess the complex methodology and assumptions used in the included studies for this particular question.<br>The Committee further discussed and acknowledged that the study design of Mohee (2014) study was different to the other included studies, and that the study investigated the relationship between the actual bacteria that caused IE and the interventional procedures (instead of just the events of IE). The Committee further noted that data on *staphylococcus aureus* was omitted from this particular study, which may or may not be a source of bias.<br>The Committee also discussed and commented that baseline oral hygiene of the study population in the included studies on dental procedures could be a major confounder for the presence or absence of an association in this review question. As all the studies are retrospective and the baseline characteristic data is unclear, it was difficult to assess whether the association (or lack of association) was due to the specific dental procedures at index time, or the different degrees of oral hygiene of the individuals in the studies. This same concern also applied to the Chen (2013) study on scaling.<br>Finally, the Committee commented that the estimated risk of IE after dental procedures in adults reported in the Duval (2006) study was based on a |

| | Committee discussions |
|---|---|
| | huge assumption that antibiotic prophylaxis is effective, which is still an area of high uncertainty (please see question 6). In addition, the pre-existing cardiac conditions were not clearly defined in the study.<br>The Committee also further noted that the study on barium enema (Strom 1998) is relatively old, and that barium enema is seldom carried out in current practice.<br><br>Overall, the Committee felt there is very limited evidence on this subject and there was high uncertainty due to the poor quality of the majority of the included studies. |
| **Trade-off between benefits and harms** | As the aim of this review question is to investigate the relationship between interventional procedures and the development of IE (to explore the pathogenesis of IE to inform the model structure of the health economic evaluation [please sections for question 6]), the discussion of trade-off between benefits and harms was not relevant for this question. |
| **Trade-off between net health benefits and resource use** | There is no impact on resource use related to this review question per se. Section 2.6.4 contains a systematic review of economic evaluations that investigate the cost-effectiveness of antibiotic prophylaxis. |
| **Other considerations** | For dental and non-dental procedures assessed in this review questions, the Committee felt that the studies have provided inconclusive evidence on the association between interventional procedures and the development of IE. The Committee agreed that current evidence is still insufficient to support the hypothesis that interventional procedures lead to the development of IE in people with pre-existing cardiac conditions.<br>To answer this review question, a complex longitudinal study on the pathogenesis of IE (with a large sample size) needs to be conducted. The study may involve genetic sampling to investigate the origin of IE. |

1

# 2.4 Review question 4

What levels of bacteraemia are associated with interventional procedures, both pre and post-procedure (including consideration of what is considered significant bacteraemia)?

## 2.4.1 Clinical evidence review

In current practice, decisions on which interventional procedures merit antibiotic prophylaxis for people who are at risk of IE are drawn from the postulation that, bacteraemia that arises following interventional procedures could be part of the causative process in the development of IE. The aim of this review is to identify what levels of bacteraemia are associated with the following interventional procedures as defined in the guideline scope (appendix P):

- Dental procedures
- Interventional procedures that cover the following sites:
  - Upper and lower gastrointestinal (GI) tract
  - Genitourinary tract (includes urological, gynaecological and obstetric procedures)
  - Upper and lower respiratory tract (includes ENT and bronchoscopy procedures)

A systematic update search using the original search strategy from CG64 was conducted (see appendix D) which identified 1081 articles. The titles and abstracts were screened and 74 articles were identified as potentially relevant. Full-text versions of these articles were obtained and reviewed against the criteria specified in the review protocol (appendix C). Of these, 58 were excluded as they did not meet the criteria and 16 met the criteria and were included. With the 14 included studies from the original guideline CG64, there are 30 total included studies for this review question.

A review flowchart is provided in appendix E, and the excluded studies (with reasons for exclusion) are shown in appendix F.

## 2.4.2 Methods

### Summary of review protocols

The population included adults and children undergoing interventional procedures (irrespective whether they have underlying cardiac condition, or whether they have had previous IE) including dental, upper and lower gastrointestinal tract, genitourinary tract (this includes urological, gynaecological and obstetric procedures including childbirth), upper and lower respiratory tract (includes ear nose and throat and bronchoscopy procedures). No subgroups were identified for this question.

The topic experts identified the following outcomes of interest for this review:

- Bacteraemia levels/intensity/bacterial counts per unit volume at one or more time points following the procedure (definition of intensity may vary by study)
- Duration of bacteraemia following a procedure
- Number/incidence/odds of having positive blood samples before and after procedure

In order to establish any possible association between an interventional procedure and bacteraemia, only studies that had compared bacteraemia before and after a procedure, or compared bacteraemia between 2 groups (bacteraemia in interventional procedure group vs control group) were included.

**Quality assessment - risk of bias**

As this is a review question on assessing associations between interventional procedures and bacteraemia, GRADE methodology is not appropriate for quality assessment for this particular question. The quality of individual studies was assessed using the checklists as guided in Developing NICE guidelines - the Manua, 2014 based on the study designs. Of the total 30 included studies, 14 studies were intervention studies where the control arm data could be extracted for this particular question. As only the control arm data was used in these 14 studies (comparing the baseline pre-procedure data to the post-procedure data within the control group only), these 14 studies were re-assessed as before-and-after studies. The other 16 included studies were of primary within-subject before-and-after studies. Together, the risk of bias of these 30 included studies were assessed using the Cochrane effective and organisation of care review group (EPOC) checklist for before-and-after studies (as guided in Developing NICE guidelines - the Manual, , 2014). For more information for quality assessment, please see appendix M. Each individual study was assessed against the 7 criteria and an overall quality rating was assigned using the following thresholds:

- The EPOC tool (7 criteria)
  - Studies that have met all 7 criteria: no risk of bias
  - Studies that have met at least 4 out of the 7 criteria: low risk of bias
  - Studies that have met less than 4 out of the 7 criteria: high risk of bias

**Statistical analysis**

Conventional meta-analyses were not conducted, due to the variations and heterogeneity in population and outcome measures from study to study.

All findings are based on statistical significance, as the aim of review question is to investigate whether there are any statistical significant associations between interventional procedures and bacteraemia.

**Overall summary of evidence**

For a summary of included studies please see below table 5 (for the full evidence tables please see appendix G). For the full details on quality assessment of the individual included studies please see appendix N.

There are 30 included studies in total for this particular review question. Only 5 out of the 29 studies were on children (Lucas 2002; Roberts 1998, 2000, 2006; Sonbol 2009). The number of included studies for different interventional procedures are as follow:

- Dental procedures: 15 studies (5 old, 10 new)
- Upper and lower respiratory tract procedures: 4 studies (1 old, 3 new)
- Upper and lower GI procedures: 11 studies (8 old, 3 new)
- Genitourinary tract procedures: no study identified met the inclusion criteria

16 of the included studies were within-subjects before-and-after studies, 13 were randomised controlled trials (where the data from the control arm was extracted), and 1 cohort study. The majority of the included studies were of high risk of bias due to the following reasons:

- Unclear baseline characteristics
- Risk of selection bias and unclear data on those who withdrew from the studies
- Difficulty in establishing the association between procedures and bacteraemia (where multiple time points of blood samples were obtained, it was not clear whether the number of positive bacteraemia at different time points were from the same patients during the study).
- Small sample size and short follow-ups

- Inappropriate or lack of statistical comparison (only provided p-values from various non-parametric tests).

**Table 5: Summary of included studies**

| Study reference (including study design) | Study population | Procedures | Outcomes | Effect estimates (including analysis used) |
|---|---|---|---|---|
| Tuna (2012), ID: 165<br><br>RCT | Total number = 34; control group = 10 (group of interest)<br>[the other 24 patients had povidone iodine or chlorhexidine prophylaxis].<br><br>Adults:<br>Gender: 5 males; 5 females<br>Mean age: 26.8 years old (SD: 4.8) | Dental:<br>Third molar extraction. | Bacteraemia<br><br>Peripheral venous blood samples were collected from each patient at baseline (before the injection of local anaesthesia with articaine and adrenaline), 1 minute and 15 minutes after completion of the extraction. | Prevalence of bacteraemia:<br><br>Baseline= 5/10 (50%); 1st min = 4/10 (40%); 15th min = 3/10 (30%); McNemar's p = 0.810. |
| DuVall (2013), ID: 80<br><br>RCT | Total number = 30; control group = 10 (group of interest)<br>[the other 20 patients had amoxicilin or chlorhexidine prophylaxis].<br><br>Adults:<br>Gender (total): 23 males; 7 females<br>Mean age (total): 21.8 years old (range: 18 to 29) | Dental:<br>Third molar extraction | Bacteraemia<br><br>4 blood samples (BS) were obtained through IV access line for each patient in the following manner:<br>• Baseline (before placebo tablet) (BS1)<br>• 1.5 min following initiation of the mucogingival flap #32 (BS2)<br>• 1.5 min following initiation of the mucogingival flap #17 (BS3)<br>• 10 min following initiation of the mucogingival flap #17 (BS4) | Incidence of bacteraemia (defined as at least one positive culture of the 4 BS per patient):<br>6/10 (60%)<br><br>Magnitude of bacteraemia (mean CFU/ml per BS with SD):<br><br>BS1 = 0.00 (SD:0.00); BS2 = 1.26 (SD: 3.67); BS3 = 1.90 (SD: 5.36); BS4 = 0.45 (SD: 0.83); Kruskal-Wallis P = 0.031 |
| Lockhart (2008), ID: 457 | Total number = 290; control group = 96 (group of interest) | Dental:<br>Tooth extraction | Bacteraemia | Prevalence and duration of bacteraemia: |

| Study reference (including study design) | Study population | Procedures | Outcomes | Effect estimates (including analysis used) |
|---|---|---|---|---|
| RCT | [the other 194 patients either had amoxicilin prophylaxis or on brushing intervention].<br><br>Adults:<br>Mean age = 40.5 years old (SD: 10.9)<br>Gender = 51 males; 45 females. | | 6 blood samples (BS) were drawn as follow:<br>• The baseline blood sample (20 mL) was then drawn and 7-8 mL was inoculated directly into both aerobic and anaerobic BACTEC® bottles for bacterial culturing.<br>• Subsequent blood draws of 20 mL were taken at 1.5 min and at 5 min after the initiation of surgery.<br>• Additional blood samples (20 mL) were drawn 20, 40, and 60 min following the end of the procedure. | Baseline = 0/89 (0%); 1.5 min = /84 (45%); 5 min = 42/84 (50%); 20 min = 8/83 (10%); 40 min = 4/83 (5%); 60 min = 4/82 (5%), p=0.03 |
| Assaf (2007), ID: 687<br><br>Split-mouth trial | Total number = 22<br><br>Adults:<br>Gender: 14 females; 8 males<br>Age range: from 21 years to 50 years<br>Mean age: 31.8 years for females; 33 years for males. | Dental:<br>Ultrasonic scaling (US) with or without diode lasers (DL) (on all patients, split-mouth design) | Bacteraemia<br><br>Blood sample of 10 mL was drawn just before and 3 min after initiation of US on the control side.<br>Following the completion of US on the control side, laser energy was applied to the gingival crevices of the teeth present on the experimental side (DL+US).<br>Thirty minutes later, blood was drawn again just before and 3 min after initiation of US in the previously lased teeth. | Prevalence of bacteraemia:<br><br>US: Baseline = 0/22 (0%); 3 min = 15/22 (68%), p<0.05<br><br>US+DL: Baseline = 0/22 (0%); 3 min = 8/22 (36%); RR = 1.87 (95%CI: 1.01 to 3.49), p=0.001 |
| Cherry (2007), ID: | Total = 60; control group = 30 (group of interest) | Dental:<br>Ultrasonic scaling. | Bacteraemia | Prevalence of bacteraemia: |

| Study reference (including study design) | Study population | Procedures | Outcomes | Effect estimates (including analysis used) |
|---|---|---|---|---|
| 1075<br><br>RCT | [the other 30 patients had povidone–iodine wash prophylaxis].<br><br>Adults:<br>Mean age: 43.9 years old (SD: 20.8)<br>Gender: 7 males; 23 females | | 10 ml of blood was sampled as a baseline measurement immediately following rinsing with either NaCl or POV–I and before scaling commenced, to ensure the absence of a pre-existing bacteraemia.<br>10 ml of blood was sampled 30 s after scaling was commenced and a further 10 ml of blood was sampled at the completion of 2 min of scaling. | Baseline = 0/30 (0%); 30s = 4/30 (13%); 2 min = 9/30 (30%), p=0.001<br><br>Overall, a positive bacteraemia of oral origin was found in 33% of the patients in the group. |
| Morozumi (2010), ID: 381<br><br>RCT | Total = 30; Control group = 10 (group of interest)<br><br>Adults:<br>Gender: 8 males; 2 females<br>Mean age: 55.4 years old (SD:9.3) | Dental:<br>Scaling and root planing | Bacteraemia<br><br>At baseline, peripheral blood and subgingival plague were collected. The second sample of peripheral blood was taken 6 min after the initiation of SRP. | Prevalence of bacteraemia:<br><br>Baseline = 0/10 (0%); 6 min = 9/10 (90%), p<0.05 |
| Pineiro (2010), ID: 395<br><br>RCT | Total = 50; control group = 30 (group of interest)<br>[the other 20 patients had chlorhexidine prophylaxis].<br><br>Adults:<br>Mean age: 55 years old (SD: 13.5)<br>Gender: 8 males; 22 females | Dental:<br>Dental implant placement | Bacteraemia<br><br>A peripheral venous blood sample (10 ml) was collected from each patient before the start of the surgical procedure to determine the prevalence of bacteraemia before intervention (baseline). Further peripheral blood samples (10 ml) were taken 30 s after insertion of the last implant and at 15 min after the completion of suturing of the muco-periosteal flap. | Prevalence of bacteraemia:<br><br>Baseline = 1/30 (3.3%); 30 s = 2/30 (6.6%); 15 min = 1/30 (3.3%), p>0.05 |
| Yagci | Total = 29 | Dental: | Bacteraemia | Prevalence of bacteraemia: |

| Study reference (including study design) | Study population | Procedures | Outcomes | Effect estimates (including analysis used) |
|---|---|---|---|---|
| (2013), ID: 112<br><br>Before-and after study | Adults and children:<br>Gender: 22 female, 7 male<br>Mean age: 18.2 years old (SD: 3.4, range, 14.7-24.3) | Orthodontic stripping | All blood samples were collected from the patients under sterile conditions at 2 time points: before and soon after stripping. | Baseline = 0/29 (0%); Post stripping = 1/29 (3.4%) [*Streptococcus sanguis*], p=0.312 |
| Sonbol (2009), ID: 545<br><br>RCT | Total = 205 (at randomisation)<br><br>Children:<br>Gender: 102 boys; 103 girls<br>Mean age: 10.8 years old (SD: 3.67), range 4.00–17.5 years old.<br><br>43 were withdrawn with final total number of 162 children. | Dental:<br><br>Rubber dam and clamp: N=41<br>Fast drill: N=40<br>Slow drill: N=40<br>Matrix band and wedge: N=41 | Bacteraemia<br><br>Blood samples of 6 ml pre-procedure and then another 6 ml 30 s after the procedure were drawn. | Prevalence of bacteraemia:<br><br>Rubber dam and clamp: Baseline = 12/41 (29%); post-procedure = 22/41 (54%); p=0.01<br>Fast drill: Baseline = 6/40 (15%); post-procedure = 9/40 (22%); p=0.5<br>Slow drill: Baseline = 4/40 (10%); post-procedure = 9/40 (22%); p=0.2<br>Matrix band and wedge: Baseline = 13/41 (32%); post-procedure = 27/41 (66%); p=0.001<br><br>Intensity of bacteraemia (detectable ≥0.33 CFU/ml):<br><br>Anaerobic:<br>Rubber dam and clamp: Baseline = 7/41 (17%); post-procedure = 17/41 (41%); p=0.005<br>Fast drill: Baseline = 4/40 (10%); post-procedure = 7/40 (18%); p=0.6<br>Slow drill: Baseline = 2/40 (5%); post-procedure = 9/40 (23%); p=0.02<br>Matrix band and wedge: Baseline = 9/40 (23%); post-procedure = 18/40 (45%); p=0.002<br><br>Aerobic: |

| Study reference (including study design) | Study population | Procedures | Outcomes | Effect estimates (including analysis used) |
|---|---|---|---|---|
| | | | | Rubber dam and clamp: Baseline = 6/41 (15%); post-procedure = 16/41 (39%); p=0.001<br>Fast drill: Baseline = 4/40 (10%); post-procedure = 5/40 (13%); p=0.4<br>Slow drill: Baseline = 2/40 (5%); post-procedure = 1/40 (3%); p=1.0<br>Matrix band and wedge: 6/40 (15%); post-procedure = 21/40 (53%); p=0.0001 |
| Zhang (2013), ID: 155<br><br>Before-and-after study | Total = 30<br><br>Adults:<br>Gender: 12 males and 18 females<br>Mean age: 47 years old (SD: 9.5) | Dental:<br>Scaling and root planning (SRP) | Bacteraemia<br><br>A 20 ml blood sample was obtained as a baseline at the beginning of prior to SRP. Another 20 ml of blood was sampled at 5 min after the initiation of SRP, and at 30 s and 10 min after the completion of SRP. | Prevalence of bacteraemia:<br><br>Baseline VSB = 0/30 (0%); 5 min after initiation = 6/30 (20%); 30 s post = 2/30 (6.7%); 10min post = 0/30 (0%), p=N/A<br><br>Magnitude of bacteraemia (mean CFU/ml):<br><br>VSB: 5 min after initiation = 0.4 (SD: 0.2); 30 s post = 0.3 (SD: 0.1); 10min post = 0.0, p=N/A |
| Lucas (2002), ID: 9668<br><br>RCT | Total = 142<br><br>Children:<br>Mean age 13.5yrs (range 9.2 to 17.9), n = 64 males, n = 78 females | Dental:<br>Upper alginate impression (n=39);<br>Separator (n=42);<br>Fit/placement of band (n=25);<br>Archwire adjustment (n=36) | Bacteraemia<br><br>Blood samples: baseline sample and 30 second sample taken after the orthodontic procedure. | Prevalence of bacteraemia:<br><br>Upper alginate impression: Baseline = 9/39 (23%); post-procedure = 12/39 (31%), p>0.05<br>Separator: Baseline = 12/42 (27%); post-procedure = 15/42 (36%), p>0.05<br>Fit/placement of band: Baseline = 9/25 (36%); post-procedure = 11/25 (44%), p>0.05<br>Archwire adjustment: Baseline = 12/36 (23%); post-procedure = 7/36 (31%), p>0.05<br><br>Intensity of bacteraemia (mean and SD cfu per ml of blood): |

| Study reference (including study design) | Study population | Procedures | Outcomes | Effect estimates (including analysis used) |
|---|---|---|---|---|
| | | | | Upper alginate impression: Baseline = 0.2 (0.7); post-procedure = 0.3 (0.6), p>0.05<br>Separator: Baseline = 0.9 (0.2); post-procedure = 2.2 (9.1), p<0.02<br>Fit/placement of band: Baseline = 0.1 (0.2); post-procedure = 0.3 (0.6), p>0.05<br>Archwire adjustment: Baseline = 0.2 (0.7); post-procedure = 0.04 (0.1), p>0.05 |
| Roberts (2000)<br>ID: 460<br><br>RCT | Total = 257<br><br>Children:<br>n = 141 male, n = 116 female, mean age 9yrs 1mth (range 2yrs to 19yrs 6mths) | Dental:<br>Rubber dam placement (n=51);<br>Matrix band & wedge (n=56);<br>Slow drill (n=49);<br>Fast drill (n=47);<br>Baseline (no procedure) (n=54) | Bacteraemia<br><br>Blood samples: before procedure, 30 s after procedure. | Prevalence of bacteraemia:<br><br>Baseline n = 5/54 (9.3%); rubber dam placement n = 16/51 (31.4%); slow drill n=6/49 (12.2%); fast drill n = 2/47 (4.3%; matrix band and wedge n = 18/56 (32.1%)<br><br>- baseline vs. rubber dam placement (p<0.005)<br>- baseline vs. matrix band & wedge (p<0.003)<br>- baseline vs. fast drill (p>0.05)<br>- baseline vs. slow drill (p>0.05) |
| Roberts (2006)<br>ID: 2375<br><br>RCT | Total = 500<br><br>Children:<br>Mean age of the children was 7.6yrs (range 3.4 to 18.9)<br><br>Children were allocated to one of the time groups in random permuted blocks; 10sec, 30sec, | Dental:<br>Dental extraction | Bacteraemia<br><br>Blood samples were taken from children according to their randomised time group. | Intensity of bacteraemia (median CFU/6ml sample):<br><br>10sec:<br>before extraction median 2.9 (range 0 to 46); after extraction median 9.8 (range 0 to 149), p=0.001<br>30sec:<br>before extraction median 0.5 (range 0 to 4); after extraction median 2.6 (range 0 to 17), p=0.001<br>1min:<br>before extraction median 0.4 (range 0 to 4); after extraction median 16.4 (range 0 to 247), p=0.003 |

| Study reference (including study design) | Study population | Procedures | Outcomes | Effect estimates (including analysis used) |
|---|---|---|---|---|
| | 1min, 2min, 4min, 7.5min, 15min, 30min, 45min, 1hr. | | | 2min:<br>before extraction median 1.2 (range 0 to 23); after extraction median 8.1 (range 0 to 162), p=0.009<br>4min:<br>before extraction median 0.4 (range 0 to 4); after extraction median 1.7 (range 0 to 15), p=0.002<br>7.5min:<br>before extraction median 0.4 (range 0 to 4); after extraction median 1.2 (range 0 to 14), p=0.002<br>15min:<br>before extraction median 1.7 (range 0 to 53); after extraction median 1.9 (range 0 to 33), p>0.05<br>30min:<br>before extraction median 0.3 (range 0 to 6); after extraction median 0.6 (range 0 to 8), not determined<br>45min:<br>before extraction median 0.7 (range 0 to 3); after extraction median 2.4 (range 0 to 46), p>0.05<br>1hr:<br>before extraction median 1.0 (range 0 to 28); after extraction median 2.1 (range 0 to 49), p>0.05<br><br>The intensity was significantly greater at the post-extraction time than at the pre-extraction time up to and including 7.5min; however by 15min and beyond, the difference was not significant.<br>The odds of having a positive culture were significantly greater in the post-extraction time than in the pre-extraction time (OR>1) at each time point up to an including a post-procedure time of 7.5min but not beyond this time |

| Study reference (including study design) | Study population | Procedures | Outcomes | Effect estimates (including analysis used) |
|---|---|---|---|---|
| Roberts (1998)<br>ID: 2440<br><br>RCT | Total = 143<br><br>Children:<br>Mean age = 8.7 years old | Dental:<br>Local anaesthetic injections:<br>Buccal infiltration (n=32);<br>Modified intraligamental (n=32);<br>Conventional intraligamental (n=29);<br>Baseline (no procedures) (n=50) | Bacteraemia<br><br>Blood samples: taken 30sec after injection | Prevalence of bacteraemia:<br><br>Baseline = 4/50 (8.0%; 0.5 to 15.5% 95% CI)<br>Buccal infiltration = 5/32 (15.6%; 2.8 to 28.5%, 95% CI)<br>Modified intraligamental = 16/32 (50.0%; 29.2 to 64.5% 95% CI)<br>Conventional intraligamental = 28/29 (96.6%; 75.2 to 99.2%, 95% CI)<br><br>- baseline vs. modified intraligamental (p<0.0001)<br>- baseline vs. conventional intraligamental (p<0.0001)<br>- baseline vs. buccal infiltration (p>0.05) |
| Tomas (2007)<br>ID: 27<br><br>RCT | Total = 106 (Control group = 53, group of interest)<br><br>Adults and children:<br>Male = 29(55%); female = 24(45%), mean age 26.1±12.3yrs (range 8 to 52 years). | Dental:<br>Dental extractions | Bacteraemia<br><br>Blood samples: baseline (after nasotracheal intubation and before local anaesthetic injection), 30sec after final dental extraction, 15min and 1hr after finishing the surgical procedure. | Prevalence of bacteraemia:<br><br>Baseline = 5/53 (9.4%); 30 s = 51/53 (96.2%), 15min = 34/53 (64.2%), 1hr = 11/53 (20%), p=0.103 |
| Sharif-Kashani (2010), ID: 368<br><br>Before-and-after | Total = 85<br><br>Adults:<br>Gender: 69 males (81%); 16 females (19%)<br>Mean age: 57 years old (SD: 28); range: 34-90 | Upper and lower respiratory tract:<br>Flexible fiberoptic bronchoscopy (FB) | Bacteraemia<br><br>Three aerobic and anaerobic cultures for venous blood and lavage fluid were drawn just prior, immediately following and 20 min after bronchoscopy. | Prevalence and duration of bacteraemia:<br><br>Baseline: 0/85 (0%); Immediately after FB: 7/85 (8%); 20 min after FB: 1/85 (1%), p=0.317 |

| Study reference (including study design) | Study population | Procedures | Outcomes | Effect estimates (including analysis used) |
|---|---|---|---|---|
| study | years old | | | |
| El Batrawy (2014), ID: 776<br><br>Before-and-after study | Total = 45<br><br>Overall mean range: 8 to 65 years old.<br><br>Adults: gender: 29 males; 7 females (total = 36)<br>Adults mean age: 48 years old (SD: 13.75)<br>Children: gender: 4 males; 5 females (total = 9)<br>Children mean age: 12.3 years old (SD: 2.8) | Upper and lower respiratory tract:<br>Bronchoscopy (rigid or flexible). | Bacteraemia<br><br>Blood sampling: three 10 mL blood samples were taken from the anti-cubical fossa one immediately before and two after bronchoscopy 10 min apart under complete aseptic conditions. | Prevalence of bacteraemia:<br><br>Baseline = 0/45; 10 min after = 0/45; 20 min after = 0/45, p=N/A |
| Saayman (2009), ID: 505<br><br>Before-and-after study | Total = 118; Non-antibiotics group = 57 (group of interest)<br><br>Adults:<br>Overall gender: 43 females and 75 males (subgroup not available)<br>Overall age range: 19–88 years of age (median 61) (subgroup not available) | Upper and lower respiratory tract:<br>Single-stage percutaneous dilatational tracheostomy. | Bacteraemia<br><br>Peripheral venous blood cultures were performed using full aseptic conditions immediately prior to the procedure (pre-tracheostomy). A second set of peripheral venous blood cultures were taken immediately after securing the tracheostomy tube (post-tracheostomy). | Prevalence of bacteraemia:<br><br>Baseline = 0/57 (0%); post PDT = 5/57 (8.7%), p=0.022 |
| Yokoyama (2014), ID: 74 | Total number = 42; control group = 21 (group of interest) | Upper and lower GI tract:<br>Oesophagectomy. | Bacteraemia<br><br>Blood samples (1ml) were collected | Prevalence of bacteraemia:<br><br>Baseline = 5/21 (24%); post-operative day 1 = |

| Study reference (including study design) | Study population | Procedures | Outcomes | Effect estimates (including analysis used) |
|---|---|---|---|---|
| RCT | Adults:<br>Gender: 18 males; 8 females<br>Mean age: 66 years old (range: 25 to 77 years old) | | into a test tube on the morning of the operation after induction of anaesthesia and just before laparotomy (baseline), and on post-operative day 1. | 12/21 (57%), p=0.027 |
| Ho (1991), ID: 829<br><br>Before-and-after study | Total = 72 (n = 126 endoscopies)<br><br>Adults:<br>Age ranged from 28 to 78 years; male = 58; female = 14. | Upper and lower GI tract:<br>Emergency endoscopy; emergency EVS; elective EVS. | Bacteraemia<br><br>Blood samples taken before endoscopy, at 5min and 30min after the procedure. | Prevalence of bacteraemia:<br><br>Emergency endoscopy group blood cultures:<br>Baseline = 0/37 (0%); 5 min = 2/37 (5%); 30 min = 3/37 (8%), p=0.076<br><br>Elective EVS sclerotherapy:<br>Baseline = 3/33 (9%); 5 min = 1/33 (3%); 30 min = 4/33 (12%), p=0.689<br><br>Emergency EVS sclerotherapy;<br>Baseline = 7/56 (13%); 5 min = 5/56 (9%); 30 min = 5/56 (9%), p=0.541 |
| Melendez (1991), ID: 9109<br><br>Before-and-after study | Total = 140<br><br>Adults:<br>Mean age 53±15 years (range 19 to 84 years), male = 69; female = 71 | Upper and lower GI tract:<br>Transoesophageal echocardiography (TOE) | Bacteraemia<br><br>Blood samples: immediately before the procedure, within 5mins after termination of the procedure, 1hr after the procedure. | Prevalence of bacteraemia:<br><br>Baseline = 4/140 (2.9%); 5 min = 2/140 (1.4%); 1 hour = 2/140 (1.4%), p=0.406 |
| Roudaut (1993), ID: 3797<br><br>Before- | Total = 82<br>n = 44 (group I)<br>n = 38 (group II)<br><br>Adults: | Upper and lower GI tract:<br>Transoesophageal echocardiography | Bacteraemia<br><br>Blood samples:<br>• Group I blood cultures taken before procedure, immediately | Prevalence of bacteraemia:<br><br>Group I: Baseline = 0/44 (0%); immediately after = 1/44 (2.3%); 15 min after = 0/44 (0%), p=N/A<br>Group II: Baseline = 0/38 (0%); 10 min into the |

| Study reference (including study design) | Study population | Procedures | Outcomes | Effect estimates (including analysis used) |
|---|---|---|---|---|
| and-after study | Mean age = 59 years (SD: 13); male = 46; female = 36. | | after the procedure, 15min after procedure.<br>• Group II blood cultures taken before procedure, during procedure (10min after the first attempt to introduce the endoscope), immediately after procedure. | procedure = 1/38 (2.6%); immediately after = 0/38 (0%), p=N/A |
| Shyu (1992), ID: 3820<br><br>Before-and-after study | Total = 132<br><br>Adults:<br>Male = 66; female = 66; mean age = 44.6 years (range from 17 to 73 years) | Upper and lower GI tract:<br>Transoesophageal echocardiography | Bacteraemia<br><br>Blood samples: 30 to 60mins before the procedure, immediately after, 180 to 240mins after the procedure. | Prevalence of bacteraemia:<br><br>Baseline (pre-): 3/270 (1.1%); immediately after = 0/270 (0%); 180 to 240 min after = 1/270 (0.4%), p=0.317 |
| Yildirim (2003), ID: 238<br><br>Before-and-after study | Total = 64<br><br>Group I = 33<br>Group II = 31<br><br>Adults:<br>Male = 28; female = 36; age ranged from 3 to 35 years old. | Upper and lower respiratory tract:<br>Tonsillectomy | Bacteraemia<br><br>Group I: Blood samples: pre-operative (after intubation), early post-operative (within 2mins after tonsillectomy) and post-operative (60mins after tonsillectomy).<br>Group II: Blood samples: pre-operative (after intubation), post-operative (15 and 60mins after tonsillectomy). | Prevalence of bacteraemia:<br><br>Group I: Baseline = 0/33 (0%); 2 min = 9/33 (27.3%); 60 min = 0/33 (0%), p=N/A<br>Group II: Baseline = 0/31 (0%); 15 min = 2/31 (6.5%); 60 min = 0/31 (0%), p=N/A |
| Zuccaro (1998), ID: 5981<br><br>Cohort | Total = 103<br><br>Adults:<br>Male = 73; female = 30 | Upper and lower GI tract:<br>Esophageal stricture dilation | Bacteraemia<br><br>Blood samples: pre-procedure, 5, 20 and 30mins after the procedure | Prevalence of bacteraemia (viridans streptococcus):<br><br>Baseline (before) = 0/103 (0%); 1 min = 19/81 (23%); 5 min = 16/96 (17%); 20-30 min = 3/63 (5%) |
| Min (2008), | Total = 40 (conventional | Upper and lower | Bacteraemia | Prevalence of bacteraemia: |

| Study reference (including study design) | Study population | Procedures | Outcomes | Effect estimates (including analysis used) |
|---|---|---|---|---|
| ID: 617<br><br>Before-and-after study | EMR = 30; EMR-P = 3; ESD = 7)<br><br>Adults:<br>Gender: 28 males; 12 females<br>Median age of 60.0 years old (range 44 to 80 years old) | GI tract:<br>Endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) | Blood cultures were obtained immediately before, 5 minutes after, and 30 minutes after the procedure. | Baseline = 0/40 (0%); 5 min = 0/40 (0%); 30 min = 1/40 (2.5%), p=0.312 |
| Chun (2012), ID: 238<br><br>Before-and-after study | Total = 64<br><br>Adults:<br>Gender: 35 males; 29 females<br>Mean age: 68.8 years old (SD: 10.8) | Upper and lower GI tract:<br>Colorectal stent placement. | Bacteraemia<br><br>The first set of blood sample was taken immediately before the procedure, and the second set was taken 30 min after colorectal stent insertion. | Prevalence of bacteraemia:<br><br>Baseline = 0/64 (0%); 30 min = 4/64 (6%), p=0.042 |
| Weickert (2006), ID: 42<br><br>Before-and-after study | Total = 100 patients<br>n = 50 (convention laparoscopy); n = 50 (mini-laparoscopy)<br><br>Adults:<br>Mean age = 53.5 years (range 19 to 81 years),; male = 59; female = 41 | Upper and lower GI tract:<br>Conventional laparoscopy and mimi-laparoscopy | Bacteraemia<br><br>Blood samples: immediately before laproscopy and within 5mins after the procedure. | Prevalence of bacteraemia:<br><br>Baseline (before): 0/100 (0%); 5 min after = 4/100 (4%), p=0.043 |
| Kullman (1992), ID: 10028<br><br>Before-and-after | Total = 180 patients (n = 194 examinations)<br>Diagnostic ERCP n = 115 participants (n = 126 procedures)<br>Therapeutic ERCP n = | Upper and lower GI tract:<br>Diagnostic ERCP<br>Therapeutic ERCP | Bacteraemia<br><br>Blood samples: before the examination, 5min after cannulation and at 5 and 15 min after the end of examination. | Prevalence of bacteraemia:<br><br>Diagnostic ERCP:<br>Baseline (before) = 1/126 (0.8%); during = 10/126 (7.9%); after 5 min =12/126 (9.5%); after 15 min = 14/126 (11.1%), p<0.001 |

| Study reference (including study design) | Study population | Procedures | Outcomes | Effect estimates (including analysis used) |
|---|---|---|---|---|
| study | 65 participants (n = 68 procedures)<br><br>Adults:<br>Median age 66 years (range 26–92 years); female = 104; male = 76 | | | Therapeutic ERCP:<br>Baseline (before) = 0/68 (0%); during = 10/68 (14.7%); after 5 min =10/68 (14.7%); after 15 min = 13/68 (19.1), p<0.001 |
| London (1986), ID: 952<br><br>Before-and-after study | Total = 50 (204 blood samples)<br><br>Adults:<br>Mean age 58.8 years (range 22 to 80 years); male = 24; female = 26 | Upper and lower GI tract:<br>Colonoscopy | Bacteraemia<br><br>Blood sample: before insertion (baseline); 5 min after insertion; 5 min after removal. | Prevalence of bacteraemia:<br><br>Baseline = 3/50 (6%); 10 min of insert = 1/50 (2%); 24 min of insert = 1/50 (2%); 42 min of insert = 1/50 (2%); 5 min after removal = 0/50 (0%), p=0.078. |

1 **Dental procedures**

2 **Table 6: Summary table: dental procedures - number of having positive blood samples before and after procedure**

| Study | Type of procedure (N) | Baseline (pre-procedure) | Time points post procedure/duration (surrogate) | | | | | | P-value[4] | Quality |
|---|---|---|---|---|---|---|---|---|---|---|
| Tuna (2012)[5] | Third molar extraction (N=10) | **5/10 (50%)** | | 1 min<br>4/10 (40%) | | 15 min<br>3/10 (30%) | | | P=0.810 | HRB |
| Lockhart (2008)[5] | Tooth extraction (N=89) | **0/89 (0%)** | | 1.5 min<br>38/84 (45%) | 5 min<br>42/84 (50%) | 20 min<br>8/83 (10%) | 40 min<br>4/83 (5%) | 60 min<br>4/82 (5%) | ***P=0.03*** | LRB |
| Tomas (2007)[1] | Tooth extraction (N=53) | **5/53 (9.4%)** | 30 s<br>51/53 (96%) | | | 15 min<br>34/53 (64%) | | 60 min<br>11/53 (20%) | P=0.103 | HRB |
| Assaf (2007)[6] | Ultrasonic scaling (N=22) | **0/22 (0%)** | | | 3 min<br>15/22 | | | | ***P<0.05*** | LRB |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | (68%) | | | | | |
| Assaf (2007)[6] | Ultrasonic scaling with diode lasers (N=22) | **0/22 (0%)** | | | 3 min 8/22 (36%) | | | | ***P=0.001*** | LRB |
| Cherry (2007)[5] | Ultrasonic scaling (N=30) | **0/30 (0%)** | 30 s 4/30 (13%) | 2 min 9/30 (30%) | | | | | ***P=0.001*** | HRB |
| Morozumi (2010)[5] | Scaling & root planning (N=10) | **0/10 (0%)** | | | 6 min 9/10 (90%) | | | | ***P<0.05*** | HRB |
| Zhang (2013)[6] | Scaling & root planning (N=30) | **0/30 (0%)** | 30 s 2/30 (6.7%) | | | 10 min 0/30 (0%) | | | N/A | HRB |
| Pineiro (2010)[5] | Implant placement (N=30) | **1/30 (3.3%)** | 30 s 2/30 (6.6%) | | | 15 min 1/30 (3.3%) | | | P>0.05 | HRB |
| Yagci (2013)[6] | Orthodontic stripping (N=29) | **0/29 (0%)** | Post[3] 1/29 (3.4%) | | | | | | P=0.312 | HRB |
| Sonbol (2009)[2,5] | Rubber dam & clamp (N=41) | **12/41 (29%)** | 30 s 22/41 (54%) | | | | | | ***P=0.01*** | HRB |
| Roberts (2000)[1,2,5] | Rubber dam & clamp (N=54) | **5/54 (9.3%)** | 30 s 16/51 (31%) | | | | | | ***P<0.005*** | HRB |
| Sonbol (2009) [2,5] | Fast drill (N=40) | **6/40 (15%)** | 30 s 9/40 (22%) | | | | | | P=0.5 | HRB |
| Roberts (2000)[1,2,5] | Fast drill (N=54) | **5/54 (9.3%)** | 30 s 6/49 (12%) | | | | | | P>0.05 | HRB |
| Sonbol (2009)[2,5] | Slow drill (N=40) | **4/40 (10%)** | 30 s 9/40 (22%) | | | | | | P=0.2 | HRB |
| Roberts (2000)[1,2,5] | Slow drill (N=54) | **5/54 (9.3%)** | 30 s 2/47 (4%) | | | | | | p>0.05 | HRB |
| Sonbol (2009)[2,5] | Matrix band & wedge (N=41) | **13/41 (32%)** | 30 s 27/41 (66%) | | | | | | ***p=0.001*** | HRB |
| Roberts (2000)[1,2,5] | Matrix band & wedge (N=54) | **5/54 (9.3%)** | 30 s 18/56 (32%) | | | | | | ***P<0.003*** | HRB |
| Lucas | Upper alginate | **9/39 (23%)** | 30 s | | | | | | P=0.441 | HRB |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| (2002)[1,2,5] | impression (N=39) | | 12/39 (31%) | | | | | | | |
| Lucas (2002)[1,2,5] | Separator (N=42) | **12/42 (27%)** | 30 s 15/42 (36%) | | | | | | P=0.483 | HRB |
| Lucas (2002)[1,2,5] | Fit/placement of band (N=25) | **9/25 (36%)** | 30 s 11/25 (44%) | | | | | | P=0.562 | HRB |
| Lucas (2002)[1,2,5] | Archwire adjustment (N=36) | **12/36 (23%)** | 30 s 7/36 (31%) | | | | | | P=0.180 | HRB |
| Roberts (1998)[1,2,5] | AJ: buccal infiltration (N=50) | **4/50 (8%)** | 30 s 5/32 (16%) | | | | | | p>0.05 | HRB |
| Roberts (1998)[1,2,5] | AJ: modified intraligamental (N=50) | **4/50 (8%)** | 30 s 16/32 (50%) | | | | | | ***P<0.0001*** | HRB |
| Roberts (1998)[1,2,5] | AJ:conventional intraligamental (N=50) | **4/50 (8%)** | 30 s 28/29 (97%) | | | | | | ***P<0.0001*** | HRB |

*AJ = Anaesthetic injection NRB = no risk of bias; LRB = low risk of bias; HRB = high risk of bias*
*[1] from CG64*
*[2] children*
*[3] only stated post-procedure, no timeframe*
*[4] p-value comparing baseline and last time point, from various non-parametric tests*
*[5] RCT (data from the control arm)*
*[6] Within-subjects before-and-after study*

## Intensity of bacteraemia

**Table 7: Summary table: dental procedures - intensity of bacteraemia**

| **Mean CFU/ml** | | | | | | | **Quality** |
|---|---|---|---|---|---|---|---|
| Duvall (2013)[8] | Third molar extraction (N=10) | Pre- procedure 0.00 | 1.5 min[1] 1.26 | 1.5 min[2] 1.90 | 10 min[3] 0.45 | ***p=0.031*** | HRB |
| Zhang (2013)[9] | Scaling & root planning (N=30) | Pre- procedure 0.00 | 5 min after initiation 0.4 | 30 s 0.3 | 10 min 0.0 | N/A | HRB |
| Lucas (2002)[6,7,8] | Upper alginate impression (N=39) | Pre- procedure 0.2 | 30 s 0.3 | | | p>0.05 | HRB |
| Lucas (2002)[6,7,8] | Separator (N=42) | Pre- procedure 0.9 | 30 s 2.2 | | | ***p<0.05*** | HRB |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Lucas (2002)[6,7,8] | Fit/placement of band (N=25) | Pre- procedure<br>0.1 | 30 s<br>0.3 | | | p>0.05 | HRB |
| Lucas (2002)[6,7,8] | Archwire adjustment (N=36) | Pre- procedure<br>0.2 | 30 s<br>0.04 | | | p>0.05 | HRB |
| **Detectable ≥0.33 CFU/ml** | | | | | | | **Quality** |
| Sonbol (2009)[7,8] | Rubber dam & clamp (N=41) | Pre- procedure<br>7/41 (17%)[4]<br>6/41 (15%)[5] | 30 s<br>17/41 (41%)[4]<br>16/41 (39%)[5] | | | ***P=0.005***[4]<br>***P=0.001***[5] | HRB |
| Sonbol (2009)[7,8] | Fast drill (N=40) | Pre- procedure<br>4/40 (10%)[4]<br>4/40 (10%)[5] | 30 s<br>7/40 (18%)[4]<br>5/40 (13%)[5] | | | P=0.6[4]<br>P=0.4[5] | HRB |
| Sonbol (2009)[7,8] | Slow drill (N=40) | Pre- procedure<br>2/40 (5%)[4]<br>2/40 (5%)[5] | 30 s<br>9/40 (23%)[4]<br>1/40 (3%)[5] | | | ***P=0.02***[4]<br>P=1.0[5] | HRB |
| Sonbol (2009)[7,8] | Matrix band & wedge (N=40) | Pre- procedure<br>9/40 (23%)[4]<br>6/40 (15%)[5] | 30 s<br>18/40 (45%)[4]<br>21/40 (53%)[5] | | | ***P=0.002***[4]<br>***P=0.0001***[5] | LRB |
| **Median CFU/6ml** | | | | | | | **Quality** |
| Roberts (2006)[6,7,8] | Tooth extraction (N=500) | 10 s before extraction = 2.9 (range 0 to 46); after extraction = 9.8 (range 0 to 149), ***p=0.001***<br>30 s before extraction = 0.5 (range 0 to 4); after extraction = 2.6 (range 0 to 17), ***p=0.001***<br>1 min before extraction = 0.4 (range 0 to 4); after extraction = 16.4 (range 0 to 247), ***p=0.003***<br>2 min before extraction = 1.2 (range 0 to 23); after extraction = 8.1 (range 0 to 162), ***p=0.009***<br>4 min before extraction = 0.4 (range 0 to 4); after extraction = 1.7 (range 0 to 15), ***p=0.002***<br>7.5 min before extraction = 0.4 (range 0 to 4); after extraction = 1.2 (range 0 to 14), ***p=0.002***<br>15 min before extraction = 1.7 (range 0 to 53); after extraction = 1.9 (range 0 to 33), p>0.05<br>30 min before extraction = 0.3 (range 0 to 6); after extraction = 0.6 (range 0 to 8), p>0.05<br>45 min before extraction = 0.7 (range 0 to 3); after extraction = 2.4 (range 0 to 46), p>0.05<br>1hr before extraction = 1.0 (range 0 to 28); after extraction = 2.1 (range 0 to 49), p>0.05 | | | | | HRB |

*LRB = low risk of bias; HBR = high risk of bias*
*[1] 1.5 min following initiation of the mucogingival flap #32*
*[2] 1.5 min following initiation of the mucogingival flap #17*
*[3] 10 min following initiation of the mucogingival flap #17*
*[4] Anaerobic*
*[5] Aerobic*
*[6] from CG64*

[7] *children*
[8] *RCT (data from the control arm)*
[9] *Within-subjects before-and-after study*

## Upper and lower respiratory tract procedures

**Table 8: Summary table: upper and lower respiratory tract procedures - number of having positive blood samples before and after procedure**

| Study | Type of procedure (N) | Baseline (pre-procedure) | Time points post procedure/duration (surrogate) | | | | P-value[2] | Quality |
|---|---|---|---|---|---|---|---|---|
| Sharif- Kashani (2010)[3] | Bronchoscopy (N=85) | **0/85 (0%)** | Immediate-post 7/85 (8%) | | 20 min 1/85 (1%) | | P=0.317 | HRB |
| El-Batrawy (2014)[3] | Bronchoscopy (N=45) | **0/45 (0%)** | | 10 min 0/45 (0%) | 20 min 0/45 (0%) | | N/A | HRB |
| Saayman (2009)[3] | Tracheostomy (N=57) | **0/57 (0%)** | Immediate-post 5/57 (8.7%) | | | | ***P=0.022*** | HRB |
| Yildirim (2003)[1,3,4] | Tonsillectomy (N=33) | **0/33 (0%)** | | 2 min 9/33 (27.3%) | | 60 min 0/33 (0%) | N/A | HRB |
| Yildirim (2003)[1,3,4] | Tonsillectomy (N=31) | **0/31 (0%)** | | 15 min 2/31 (6.5%) | | 60 min 0/31 (0%) | N/A | HRB |

*NRB = no risk of bias; LRB = low risk of bias; HRB = high risk of bias*
[1] *from CG64*
[2] *p-value comparing baseline and last time point, from various non-parametric tests*
[3] *Within-subjects before-and-after study*
[4] *Yildirim (2003): mixed adults and children population.*

## Upper and lower GI tract procedures

**Table 9: Summary table: upper and lower GI tract procedures - number of having positive blood samples before and after procedure**

| Study | Type of procedure (N) | Baseline (pre-procedure) | Time points post procedure/duration (surrogate) | | | | P-value[2] | Quality |
|---|---|---|---|---|---|---|---|---|
| Min (2008)[3] | Endoscopic sub/mucosal resection/dissection | **0/40 (0%)** | | 5 min 0/40 (0%) | | 30 min 1/40 (2.5%) | P=0.312 | HRB |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | (N=40) | | | | | | | |
| Chun (2012)[3] | Colorectal stent placement (N=64) | **0/64 (0%)** | | | | 30 min 4/64 (6%) | ***P=0.042*** | HRB |
| Weickert (2006)[1,3] | Laparoscopy/mimi-laparoscopy (N=100) | **0/100 (0%)** | | 5 min 4/100 (4%) | | | ***P=0.043*** | HRB |
| Kullman (1992)[1,3] | Diagnostic ERCP (N=126) | **1/126 (0.8%)** | During 10/126 (7.9%) | 5 min 12/126 (9.5%) | 15 min 14/126 (11%) | | ***P<0.001*** | HRB |
| Kullman (1992)[1,3] | Therapeutic ERCP (N=68) | **0/68 (0%)** | During 10/68 (15%) | 5 min 10/68 (15%) | 15 min 13/68 (19%) | | ***P<0.001*** | HRB |
| London (1986)[1,3] | Colonoscopy (N=50) | **3/50 (6%)** | 10 min of insert 1/50 (2%) | 24 min of insert 1/50 (2%) | 42 min of insert 1/50 (2%) | 5 min after removal 0/50 (0%) | P=0.078 | HRB |
| Yokoyama (2014)[5] | Oesophagectomy (N=21) | **5/21 (24%)** | | | | 24 hrs 12/21 (57%) | ***P=0.027*** | HRB |
| Ho (1991)[1,3] | Emergency endoscopy (N=37) | **0/37 (0%)** | | 5 min 2/37 (5%) | 30 min 3/37 (8%) | | P=0.076 | HRB |
| Ho (1991)[1,3] | Elective EVS (N=33) | **3/33 (9%)** | | 5 min 1/33 (3%) | 30 min 4/33 (12%) | | P=0.689 | HRB |
| Ho (1991)[1,3] | Emergency EVS (N=56) | **7/56 (13%)** | | 5 min 5/56 (9%) | 30 min 5/56 (9%) | | P=0.541 | HRB |
| Melendez (1991)[1,3] | Transesophageal echocardiography (N=140) | **4/140 (3%)** | | 5 min 2/140 (1.4%) | | 1 hr 2/140 (2.4%) | P=0.406 | HRB |
| Roudaut (1993)[1,3] | Transesophageal echocardiography (N=44) | **0/44 (0%)** | Immediate-post 1/44 (2.3%) | 15 min 0/44 (0%) | | | N/A | HRB |
| Roudaut (1993)[1,3] | Transesophageal echocardiography (N=38) | **0/38 (0%)** | 10 min during 1/38 (2.6%) | Immediate-post 0/38 (0%) | | | N/A | HRB |
| Shyu (1992)[1,3] | Transesophageal echocardiography (N=270) | **3/270 (1%)** | Immediate-post 0/270 (0%) | | | 3-4 hrs 1/270 (0.4%) | P=0.317 | HRB |
| Zuccaro (1998)[1,4] | Oesophageal stricture (N=103) | **0/103 (0%)** | 1 min 19/81 (23%) | 5 min 16/96 (17%) | 20-30 min 3/63 (5%) | | ***P=0.025*** | HRB |

*EVS = oesophageal variceal sclerotherapy; NRB = no risk of bias; LRB = low risk of bias; HRB = high risk of bias*
*[1] from CG64*
*[2] p-value comparing baseline and last time point, from various non-parametric tests.*
*[3] Within-subjects before-and-after study*
*[4] cohort study*
*[5] RCT (data from the control arm)*

**Genitourinary tract procedures**

No study identified met the inclusion criteria

### 2.4.31 Clinical evidence statements

**Dental procedures - Number of having positive blood samples before and after procedure**

Adults:

5 RCTs (data from the control arm) and 2 before-and-after studies (N = range from 10 to 89) with various degrees of risk of bias showed inconsistent evidence on the associations between different recent dental procedures (extraction, scaling and root planning, implant placement and orthodontic stripping) and bacteraemia in adults.

Conversely, 1 RCT (data from the control arm) and 1 before-and-after study (N = range from 22 to 30) with various degrees of risk of bias suggested that there were statistical significant associations between ultrasonic scaling and bacteraemia in adults. However, the time frame for post procedure bacteraemia was relative short and only p-values were reported for these 2 studies.

Children:

4 RCTs (data from the control arm) (N = range from 10 to 89) with high risk of bias showed inconsistent and inconclusive evidence on the associations between different recent dental procedures (fast and slow drill, alginate impression, separator, fit of band, archwire adjustment buccal infiltration and intraligamental) and bacteraemia in children.

Conversely, 3 RCTs (data from the control arm) (N = range from 10 to 50) with high risk of bias suggested that there were statistical significant associations between rubber dam and clamp, matrix band and wedge, intraligamentary injection, and bacteraemia in children. However, the time frame for post procedure bacteraemia was relative short (30 seconds post-procedure) and only p-values were reported for these 2 studies.

**Dental procedures - Intensity of bacteraemia**

3 RCTs (data from the control arm) and 1 before-and-after study (N = range from 10 to 500) with high risk of bias showed inconsistent and inconclusive evidence on the associations between different recent dental procedures and intensity of bacteraemia in adults and children, depending on which measurements that were used in the studies (mean CFU/ml, detectable ≥0.33 CFU/ml, median CFU/6ml).

**Dental procedures - Duration of bacteraemia following a procedure**

No included studies reported this particular outcome.

**Upper and lower respiratory tract procedures - Number of having positive blood samples before and after procedure**

3 before-and-after studies with high risk of bias (N = range from 31 to 85) suggested that there were no statistical significant associations between various upper and lower respiratory tract procedures (bronchoscopy and tonsillectomy) and bacteraemia in adults and children.

Conversely, 1 before-and-after study (N = 57) suggested that there were significant associations between tracheostomy and bacteraemia in adults. However, the time frame for post procedure bacteraemia was relative short (immediately post-procedure) and only p-value was reported for this study.

**Upper and lower respiratory tract procedures - Intensity of bacteraemia**

No included studies reported this particular outcome.

**Upper and lower respiratory tract procedures - Duration of bacteraemia following a procedure**

No included studies reported this particular outcome.

**Upper and lower GI tract procedures - Number of having positive blood samples before and after procedure**

6 before-and-after studies with high risk of bias (N = range from 33 to 270) suggested that there were no statistical significant associations between endoscopic sub/mucosal resection/dissection, colonoscopy, emergency endoscopy, elective or emergency EVS, transesophageal echocardiography and bacteraemia in adults.

Conversely, 1 RCT (data from the control arm), 1 cohort study and 3 before-and-after studies with high risk of bias (N = range from 21 to 126) suggested that there were associations between colorectal stent placement, laparoscopy/mimi- laparoscopy, diagnostic ERCP, therapeutic ERCP, oesophagectomy, oesophageal stricture and bacteraemia in adults. However, the time frame for post procedure bacteraemia was relative short and only p-values were reported for these studies.

**Upper and lower GI tract procedures - Intensity of bacteraemia**

No included studies reported this particular outcome.

**Upper and lower GI tract procedures - Duration of bacteraemia following a procedure**

No included studies reported this particular outcome.

**Genitourinary tract procedures**

No study identified met the inclusion criteria.

### 2.4.42 Evidence to recommendations

| | Committee discussions |
|---|---|
| **Relative value of different outcomes** | The Committee discussed and agreed that the critical outcome for this review question was to establish whether there is a clear relationship between specific interventional procedures and bacteraemia in the general population. Therefore, the only critical outcome is the measurement of such association and the precision and certainty for these measurements reported in the included studies. |
| **Quality of evidence** | The Committee discussed the utility of the EPOC checklist to assess the quality of evidence for this particular review question. It was acknowledged and agreed that the 7 criteria in the EPOC checklist were not comprehensive nor detailed enough to fully assess the complex methodology used in the included studies for this particular question, for example, how bacteraemia was measured, the different methods for blood samples collection, different methods for culturing and incubation, the issues of contamination and others. Therefore, the Committee has a degree of uncertainty around the quality of evidence based on the EPOC checklist.<br>The Committee further discussed the evidence base and commented that:<br>• The participants of 43% of the included studies (13/30) were already bacteraemic before the interventional procedure (positive blood samples pre-procedure) which is considered to be a major confounder<br>• The follow-up time points for post-procedure blood samples were very short (with most studies less than 60 min), and therefore it is difficult to establish the actual duration of bacteraemia.<br>• The sample sizes of the included studies were very small.<br>• It is very difficult to establish the association between procedures and |

| | Committee discussions |
|---|---|
| | bacteraemia because where multiple time points of blood samples were obtained, it was not clear whether the number of positive bacteraemia at different time points were from the same or different participants in the study.<br>• Only p-values from various non-parametric tests were reported, with high uncertainty on precision of the effect estimates.<br>• In most studies on dental procedures, there was also no information on the oral health of the participants. This could potentially be a confounder that participants with poor oral health and hygiene were possibly at higher risk of bacteraemia than those with good oral hygiene.<br>Overall, the Committee agreed that the evidence was of poor quality, and the evidence does not contribute much into the investigation of the hypothesis: *'people at risk --> undertaking interventional procedures --> bacteraemia --> the development of IE'*. |
| **Trade-off between benefits and harms** | As the aim of this review question is to investigate the relationship between interventional procedures and bacteraemia (to explore the pathogenesis of IE to inform the model structure of the health economic evaluation [please sections for question 6]), the discussion of trade-off between benefits and harms was not relevant for this question. |
| **Trade-off between net health benefits and resource use** | There is no impact on resource use related to this review question per se. Section 2.6.4 contains a systematic review of economic evaluations that investigate the cost-effectiveness of antibiotic prophylaxis. |
| **Other considerations** | For dental and non-dental procedures assessed in this review question, the Committee felt that there was some evidence that suggested some dental procedures could be associated with bacteraemia, however, there was still uncertainty for other interventional procedures. The Committee agreed that current evidence is inconclusive to draw a firm conclusion that bacteraemia that could be associated with some interventional procedures in adults and children would definitively contribute to the development of IE. |

1
2

# 2.5 Review question 5

What levels of bacteraemia are associated with everyday activities (toothbrushing/chewing/urination/defecation)?

## 2.5.1 Clinical evidence review

Everyday activities such as toothbrushing, are believed to introduce similar levels of bacteraemia compared to dental procedures such as an extraction. Therefore, to evaluate which groups may need antibiotic prophylaxis, the aim of this review is to identify what levels of bacteraemia are associated everyday activities.

An update search using the original search strategy was conducted (see appendix D) which identified 299 articles. The titles and abstracts were screened and 17 studies were identified as potentially relevant. Full-text versions of these articles were obtained and reviewed against the criteria specified in the review protocol (appendix C). Of these, 14 were excluded as they did not meet the criteria. Three new studies met the criteria and were included with an additional 3 studies from the original guideline; therefore a total of 6 included studies for the update.

A review flowchart is provided in appendix E, and the excluded studies (with reasons for exclusion) are shown in appendix F.

## 2.5.2 Methods

### Summary of review protocols

- The population included adults and children undergoing everyday activities irrespective of whether they have an underlying cardiac condition or not. No subgroups were identified for this question.
- For the above population, the incidence/level/duration of bacteraemia after an everyday activity was compared to that before or during the activity.
- The topic experts identified the following outcomes of interest for this clinical prediction review:
  - bacteraemia levels/intensity/bacterial counts per unit volume at one or more time points following the everyday activity (definition of intensity may vary by study)
  - duration of bacteraemia following an everyday activity
  - number/incidence/odds of having positive blood samples before and after procedure/everyday activity

### Risk of bias

- The quality of individual studies was assessed using the checklist for prognostic studies by Hayden et al., 2006 (Developing NICE guidelines - the Manual, 2014). This checklist addresses 6 main areas including study participation, study attrition, prognostic factor measurement, outcome measurement, confounding measurement and account and finally the analysis used in the study. Each individual study was assessed against this criteria and an overall quality rating was assigned using the following thresholds:
  - all 6 criteria on checklist met: no risk of bias
  - at least 4 out of 6 criteria met: low risk of bias
  - anything else: high risk of bias

**Statistical analysis**

- Meta-analyses were not conducted due to the variation in population and outcome measures from study to study.
- Where appropriate, summary measures such as mean differences or odds ratios (with 95% confidence intervals) were calculated using Review Manager 5.
- All findings are based on statistical significance.

**Overall summary of evidence**

6 studies were included for this review of which 5 were RCTs and one study was a prospective pre- and post- test design without a control group. 3 studies were from the UK and 3 studies from the USA. Sample size ranged from 30 to 735. The populations included subjects referred for dental treatment under general anaesthesia in 4 studies, patients presenting to urgent care service with the need for extraction of at least 1 erupted tooth in one study and mechanically ventilated subjects from the surgical trauma, medical respiratory and neuroscience intensive care units in one study. 4 studies were performed in children/adolescents and 2 studies in adults of varying age. All studies examined bacteraemia levels associated with toothbrushing (various regimens).

For a summary of included studies please see table 10 (for the full evidence tables please see appendix G).

**Table 10: Summary of included studies**

<table>
<tr><th>Study reference (including study design)</th><th>Study population</th><th>Predictors (or risk factors)</th><th>Outcomes and effect estimates</th><th>Overall quality</th></tr>
<tr><td>Lucas et al., 2008<br>(RCT)</td><td>Children and adolescents having dental treatment (extractions only) under general anaesthesia</td><td><u>Toothbrushing</u><br>1. Manual Oral B 30: n=32<br>2. Braun electric (rotary movement): n=35<br>3. Sonicare (oscillating movement): n=33<br>4. Dental handpiece and rubber cup: n=41</td><td>1. Intensity of bacteraemia
<table>
<tr><th colspan="6">a) Aerobic intensity of detectable bacteraemia (cfu/ml blood)</th></tr>
<tr><td rowspan="2">Type of toothbrush</td><td colspan="2">Baseline</td><td colspan="2">30 seconds after toothbrushing</td><td>Summary measure</td></tr>
<tr><td>Mean</td><td>SD</td><td>Mean</td><td>SD</td><td>Mean difference (95%CI)[1]</td></tr>
<tr><td>Oral B 30 (n=32)</td><td>0.05</td><td>0.21</td><td>0.39</td><td>1.34</td><td>0.34 (-0.13 to 0.84)</td></tr>
<tr><td>Braun electric (n=35)</td><td>0.05</td><td>0.11</td><td>0.28</td><td>1.15</td><td>0.23 (-0.15 to 0.61)</td></tr>
<tr><td>Sonicare electric (n=33)</td><td>0.02</td><td>0.06</td><td>0.51</td><td>2.35</td><td>0.49 (-0.31 to 1.29)</td></tr>
<tr><td>Dental handpiece and rubber cap (n=41)</td><td>0.02</td><td>0.07</td><td>1.00</td><td>3.10</td><td>0.98 (0.03 to 1.93)</td></tr>
</table>
<table>
<tr><th colspan="6">b) Anaerobic intensity of detectable bacteraemia (cfu/ml blood)</th></tr>
<tr><td rowspan="2">Type of toothbrush</td><td colspan="2">Baseline</td><td colspan="2">30 seconds after toothbrushing</td><td>Summary measure</td></tr>
<tr><td>Mean</td><td>SD</td><td>Mean</td><td>SD</td><td>Mean difference (95%CI)[1]</td></tr>
<tr><td>Oral B 30 (n=32)</td><td>0.01</td><td>0.04</td><td>0.46</td><td>1.8</td><td>0.45 (-0.17 to 1.07)</td></tr>
<tr><td>Braun electric (n=35)</td><td>0.02</td><td>0.07</td><td>0.11</td><td>0.43</td><td>0.09 (-0.05 to 0.23)</td></tr>
<tr><td>Sonicare electric (n=33)</td><td>0.04</td><td>0.10</td><td>0.79</td><td>3.68</td><td>0.75 (-0.51 to 2.01)</td></tr>
<tr><td>Dental handpiece and rubber cap (n=41)</td><td>0.008</td><td>0.04</td><td>0.94</td><td>2.87</td><td>0.93 (0.05 to 1.81)</td></tr>
</table>
2. Prevalence of bacteraemia in each group, n (%) of positive blood cultures</td><td>Low risk of bias[2]</td></tr>
</table>

<table>
<tr><th>Study reference (including study design)</th><th>Study population</th><th>Predictors (or risk factors)</th><th>Outcomes and effect estimates</th><th>Overall quality</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>Type of toothbrush</td><td>Baseline, n (%)</td><td>30 seconds after brushing for 1 minute, n (%)</td><td>Summary measure, OR (95% CI) [1]</td></tr>
<tr><td>Oral B 30 (n=32)</td><td>7 (22%)</td><td>6 (19%)</td><td>0.82 (0.24 to 2.79)</td></tr>
<tr><td>Braun electric (n=35)</td><td>9 (26%)</td><td>12 (34%)</td><td>1.51 (0.54 to 4.22)</td></tr>
<tr><td>Sonicare electric(n=33)</td><td>9 (27%)</td><td>11 (33%)</td><td>1.33 (0.46 to 3.83)</td></tr>
<tr><td>Dental handpiece and rubber cap (n=41)</td><td>6 (15%)</td><td>15 (37%)</td><td>3.37 (1.15 to 9.85)</td></tr>
</table>
</td><td></td></tr>
<tr><td>Lockhart et al., 2008 (RCT)</td><td>Patients presenting to urgent care service with the need for extraction of at least 1 erupted tooth</td><td>1. Toothbrushing (n=98)<br>2. Extraction-amoxicillin (n=96)<br>3. Extraction placebo (n=96)</td><td>
1. Magnitude of bacteraemia – all analysed samples were below the detection threshold of $10^4$ CFU per millilitre of blood<br><br>
2. Duration of bacteraemia at different time points
<table>
<tr><th colspan="3">a) overall duration of bacteraemia</th></tr>
<tr><td></td><td>Number of subjects (%) bacteraemic at 40 minutes after activity/procedure</td><td>Number of subjects (%) bacteraemic at 60 minutes after activity/procedure</td></tr>
<tr><td>Toothbrushing group</td><td>-</td><td>9 (9)</td></tr>
<tr><td>Extraction-amoxicillin group</td><td>2 (2)</td><td>-</td></tr>
<tr><td>Extraction-placebo group</td><td>-</td><td>2 (2)</td></tr>
</table>
<table>
<tr><th colspan="2">b) duration of bacteraemia from endocarditis-related bacterial species</th></tr>
<tr><td></td><td>Number of subjects (%) bacteraemic at 60 minutes after activity/procedure</td></tr>
<tr><td>Toothbrushing group</td><td>2 (2)</td></tr>
<tr><td>Extraction-amoxicillin group</td><td>-</td></tr>
</table>
</td><td>Low risk of bias[3]</td></tr>
</table>

| Study reference (including study design) | Study population | Predictors (or risk factors) | Outcomes and effect estimates | Overall quality |
|---|---|---|---|---|

| | |
|---|---|
| Extraction-placebo group | 5 (5) |

**3. Number/incidence/odds of having positive blood samples before and after everyday activity –** reported in study as a) overall incidence of bacteraemia at any of the 6 draws b) overall incidence of bacteraemia at the time of the procedures and c) incidence of bacteraemia from endocarditis related bacterial species

| **a) overall incidence of bacteraemia* at any of the 6 draws** | |
|---|---|
| Toothbrushing group | 32% |
| Extraction-amoxicillin group | 56% |
| Extraction-placebo group | 80% |
| $x^2$ | p<0.0001 |

| **b) overall incidence of bacteraemia* at the time of the procedures** | |
|---|---|
| Toothbrushing group | 28% |
| Extraction-amoxicillin group | 56% |
| Extraction-placebo group | 79% |
| $x^2$ | Not reported |

*'All baseline blood cultures were negative with the exception of 3 instances, likely from skin contamination eg: Staphylococcus epidermis'

| **c) cumulative incidence of bacteraemia** from endocarditis related bacterial species from all 6 blood draws** | |
|---|---|
| Toothbrushing group | 23% |
| Extraction-amoxicillin group | 33% |
| Extraction-placebo group | 60% |
| $X^2$ | p<0.0001 |

| **d) incidence of positive cultures** from endocarditis related bacterial species in the first 5 minutes of activity/procedure***** | |
|---|---|
| Toothbrushing group | 19% |
| Extraction-amoxicillin group | 33% |

<table>
<tr><th>Study reference (including study design)</th><th>Study population</th><th>Predictors (or risk factors)</th><th>Outcomes and effect estimates</th><th>Overall quality</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>Extraction-placebo group</td><td>58%</td></tr>
<tr><td>$X^2$</td><td>p=not reported</td></tr>
</table>
<table>
<tr><th colspan="2">e) incidence of positive cultures** from endocarditis related bacterial species at 20 minutes***</th></tr>
<tr><td>Toothbrushing group</td><td>1%</td></tr>
<tr><td>Extraction-amoxicillin group</td><td>1%</td></tr>
<tr><td>Extraction-placebo group</td><td>10%</td></tr>
<tr><td>$X^2$</td><td>p=0.001</td></tr>
</table>
**All baseline blood cultures were negative, with the exception of one patients (with 2 species) in the brushing group<br>
***The pattern observed at 20 minutes persisted to 40 minutes (numbers not reported)
</td><td></td></tr>
<tr><td>Jones et al., 2010<br>(Prospective pre- and post-test design without a control group)</td><td>Mechanically ventilated subjects from the surgical trauma, medical respiratory and neuroscience intensive care units</td><td>Toothbrushing</td><td>1. Incidence of transient bacteraemia by positive blood cultures before and after toothbrushing<br><br>None of the subjects had evidence of transient bacteraemia before or after toothbrushing.</td><td>Low risk of bias[4]</td></tr>
<tr><td>Lucas et al., 2000 [included in CG64, 2008]<br>(RCT)</td><td>Children referred for dental treatment under general anaesthetic</td><td>1. Toothbrushing: n= 52<br>2. Professional cleaning with a rubber cup: n= 53<br>3. Scaling: n=50</td><td>1. Incidence of bacteraemia (positive blood cultures)<br>There was NS difference in the number of positive blood samples in the groups studies [toothbrushing – 20/52 (39%), dental flossing (data from De Leo et al., 1974) – 6/7 (86%), dental polishing – 13/53 (25%), dental scaling – 20/50 (40%), dental extractions (data from Roberts et al., 1998b) – 17/44 (39%)]. p=0.305 (excluding dental flossing), p=0.305 (excluding dental flossing and extractions)<br><br>Intensity of bacteraemia<br>There was NS difference in the intensity of bacteraemia (colony forming units per millilitre of blood, mean (SD), range) in any of the 3 cleaning groups [toothbrushing – 32.2 (231), 0 to 1666, dental</td><td>Low risk of bias[5]</td></tr>
</table>

| Study reference (including study design) | Study population | Predictors (or risk factors) | Outcomes and effect estimates | Overall quality |
|---|---|---|---|---|
| | | | flossing – no data, dental polishing – 15.9 (83.5), 0 to 557, dental scaling – 2.2 (13.2), 0 to 93, dental extractions (from Roberts et al., 1998) – 0.23 (0.8), 0 to 4] | |
| Bhanji et al., 2002 [included in CG64, 2008] (RCT) | Children receiving dental care under general anaesthesia | Toothbrushing<br>1. Sonicare electric toothbrushing: n= 25<br>2. Manual toothbrushing: n=25 | **1. Incidence of positive blood cultures after* brushing, n (%, 95%CI)**<br>Manual group (n=24): 11/24 (46, 26 to 66)<br>Sonicare group (n=23): 18/23 (78, 62 to 95)<br>p=0.022<br>*3 patients had positive blood cultures before toothbrushing and were excluded | Low risk of bias[6] |
| Roberts et al., 1997 [included in CG64, 2008] (RCT) | Children referred for dental treatment under general anaesthetic | Toothbrushing<br>Various other predictors (see opposite) | **Positive blood cultures, n/N (%):**<br>- baseline n = 5/53 (9.4%)<br>- dental examination n = 9/53 (17.0%)<br>- toothbrushing n = 20/52 (38.5%)<br>- polishing teeth n = 13/53 (24.5%)<br>- scaling teeth n = 20/50 (40.0%)<br>- intraligamental injection n = 28/29 (96.6%)<br>- nasotracheal tube n = 3/31 (9.7%)<br>- rubber dam placement n = 15/51 (29.4%)<br>- slow drill n = 6/47 (12.8%)<br>- fast drill n = 2/47 (4.3%)<br>- matrix band placement n = 18/56 (32.1%)<br>- single extraction n = 17/44 (38.7%)<br>- multiple extractions n = 30/59 (50.9%)<br>- mucoperiosteal flap n = 20/51 (39.2%)<br>- cardiac patients n = 6/59 (10.2%)<br><br>**Comparison of proportions compared to baseline (95% CI):**<br>- dental examination -5.3 to 20.49%<br>- toothbrushing 12.8 to 45.4%<br>- polishing teeth 0.7 to 29.4%<br>- scaling teeth 14.0 to 47.2%<br>- intraligamental injection 76.9 to 97.3%<br>- nasotracheal tube -6.5 to 13.2% | Low risk of bias[7] |

| Study reference (including study design) | Study population | Predictors (or risk factors) | Outcomes and effect estimates | Overall quality |
|---|---|---|---|---|
| | | | - rubber dam placement 4.8 to 35.1%<br>- slow drill -8.9 to 15.6%<br>- fast drill -5.2 to 4.8%<br>- matrix band placement 7.4 to 38.0%<br>- single extraction 12.5 to 45.9%<br>- multiple extractions 24.2 to 58.6%<br>- mucoperiosteal flap 13.4 to 46.2%<br><br>NS; dental examination, nasotracheal tube, rubber dam placement, slow drill, fast drill, | |

[1] *Calculated by NICE technical team based on data reported in the article*
[2] *Study met 4/6 criteria on prognostic studies checklist. Limitations included: 1. period of recruitment not reported 2. sample size calculation not reported 3. details of toothbrushing intervention not reported 4. highly selected population undergoing dental treatment*
[3] *Study met 5/6 criteria on prognostic studies checklist. Limitations included: 1. Unclear if blood samples processed immediately 2. reporting of data in graphical form without accompanying numbers 3. highly selected population undergoing dental treatment*
[4] *Study met 4/6 criteria on prognostic studies checklist. Limitations included: 1. Study dates not reported 2. No comparison group so not possible to determine relative levels of bacteraemia associated with different activities as opposed to just toothbrushing 3. No sample size calculation 4. Subjects also given Biotene mouthwash which could contain active ingredients and therefore have reduced bacteraemia levels.*
[5] *Study met 5/6 criteria on prognostic studies checklist. Limitations included: sample size calculation not reported, intervention not well described (eg: whether standardised procedures were used and for how long intervention was carried out), highly selected population undergoing dental treatment*
[6] *Study met 5/6 criteria on prognostic studies checklist. Limitations included: 1. baseline characteristics (eg: gender, mean age etc) not reported*
[7] *Highly selected population undergoing dental treatment*

## 2.5.31 Clinical evidence statements

### 2 Levels of bacteraemia associated with toothbrushing

3 Six studies examined levels of bacteraemia associated with various types of toothbrushing.
4 Although all studies were at low risk of bias, the overall finding was inconsistent across
5 studies given the wide range of toothbrushing interventions examined and comparators
6 within individual studies. The majority of studies were also conducted in a highly selected
7 population with pre-existing dental disease. A narrative summary of each study follows.

8 One RCT including 141 children and adolescents found that there was no significant
9 difference in the intensity of bacteraemia (aerobic or anaerobic) 30 seconds after
10 toothbrushing compared to baseline for subjects brushing with Oral B 30, Braun electric
11 [rotary movement] or Sonicare [oscillating movement] but a slightly higher intensity of
12 bacteraemia following brushing with the dental handpeice and rubber cap. The same study
13 found no difference in the prevalence of bacteraemia compared to baseline following the first
14 three types of toothbrushing but a greater prevalence (3 times more) 30 seconds after
15 brushing with the dental handpeice. The evidence was at low risk of bias however, the
16 uncertainty around these effect estimates were high.

17 A second RCT with 290 adults found that the overall incidence of bacteraemia at any of the 6
18 blood draws was significantly lower in the toothbrushing group (32%) compared to the dental
19 extraction groups (extraction-amoxicillin group – 56%, extraction-placebo group – 80%;
20 $p<0.0001$). The cumulative incidence of bacteraemia from endocarditis related bacterial
21 species from all 6 blood draws was also significantly lower in the toothbrushing group
22 compared to the extraction-amoxicillin and extraction-placebo groups (23%, 33% and 60%
23 respectively; $p<0.0001$). Furthermore, the incidence of positive blood cultures from
24 endocarditis related bacteria species at 20 minutes was significantly lower in the
25 toothbrushing and extraction-amoxicillin group compared to the extraction-placebo group
26 (1%, 1% and 10% respectively; $p=0.01$). The same study examined the magnitude of
27 bacteraemia and found that all analysed samples were below the detection threshold of $10^4$
28 CFU per millilitre of blood set in the study.

29 One other study, which was a prospective pre-and post-test design including 30 adults that
30 found none of the subjects, had evidence of transient bacteraemia by positive blood cultures
31 before or after toothbrushing.

32 In a further RCT including 155 children, toothbrushing was found to have no significant
33 difference in the prevalence and intensity of bacteraemia when compared with other cleaning
34 methods, professional cleaning and scaling.

35 One RCT considered a comparison of transient bacteraemia between brushing with a
36 conventional toothbrush and with an electric toothbrush. Toothbrushing was associated with
37 positive blood cultures in 46% of manual toothbrush users and in 78% of those using the
38 electric toothbrush ($p = 0.022$).

39 In the final RCT including 735 children, the incidence of positive blood cultures was
40 significantly greater following toothbrushing (38.5%) compared to the baseline value of 9.4%.
41 This was alongside other non-everyday activities such as, polishing teeth, scaling teeth,
42 intraligamental injection, rubber dam placement, matrix band placement, single extraction,
43 multiple extractions and mucoperiosteal flap. The evidence was at no risk of bias.

44 No evidence relating to other everyday activities of interest to this question (chewing,
45 urination and defecation) were identified.

## 2.5.46 Evidence to recommendations

| | Committee discussions |
|---|---|

| | Committee discussions |
|---|---|
| **Relative value of different outcomes** | The Committee discussed and agreed that the critical outcome for this review question was to establish whether there is a clear relationship between specific everyday activities and bacteraemia (including the incidence, duration and level of bacteraemia) in the general population. Therefore, the only critical outcome is the measurement of such association and the precision and certainty for these measurements reported in the included studies. |
| **Quality of evidence** | The Committee discussed the utility of the Hayden checklist to assess the quality of evidence for this particular review question. It was acknowledged and agreed that the 6 criteria in the Hayden checklist were not comprehensive nor detailed enough to fully assess the complex methodology used in the included studies for this particular question, for example, how bacteraemia was measured, the different methods for blood sample collection, different methods for culturing and incubation and also the issues of contamination. Therefore, the Committee were uncertain about the quality of evidence based on the Hayden checklist.<br><br>The Committee further discussed the evidence and commented that:<br>• The participants of 83% of the included studies (5/6) were a highly selected population with pre-existing dental disease. Therefore, the applicability of findings from these studies to the general population was questionable.<br>• The participants of 50% of the included studies (3/6) were already bacteraemic before the everyday activity (positive blood samples pre-procedure), indicating that transient bacteraemias occur spontaneously<br>• The sample sizes of the included studies were very small.<br>• Only p-values from various non-parametric tests were reported, with high uncertainty on precision of the effect estimates.<br><br>The committee further commented that although the study by Lockhart et al, 2008 provides an interesting finding into the idea that the incidence of bacteraemia following toothbrushing and extraction with amoxicillin is similar; the study did not provide an insight into the relative magnitudes of bacteraemia associated with the different activities. The committee highlighted that the Hayden checklist was not comprehensive enough to fully assess these issues.<br><br>Overall, the Committee agreed that the evidence was of poor quality and largely undertaken in a highly selected population with pre-existing dental disease. The applicability of the evidence to the general population was therefore inadequate and the evidence does not contribute much into the investigation of whether everyday activities, such as toothbrushing, lead to similar levels of bacteraemia as dental procedures, such as extraction. The committee in addition noted the lack of evidence for other activities including chewing, urination and defecation. |
| **Trade-off between benefits and harms** | As the aim of this review question is to investigate the relationship between everyday activities and bacteraemia (to explore the pathogenesis of IE to inform the model structure of the health economic evaluation [please see sections for question 6], the discussion of trade-off between benefits and harms was not relevant for this question. |
| **Trade-off between net health benefits and resource use** | There is no impact on resource use related to this review question per se. Section 2.6.4 contains a systematic review of economic evaluations that investigate the cost-effectiveness of antibiotic prophylaxis. |
| **Other considerations** | The Committee felt that the studies have provided inconclusive evidence on the association between everyday activities and bacteraemia, given the type of toothbrushing and comparators within studies varied – some studies |

| | Committee discussions |
|---|---|
| | compared different types of toothbrushing with each other, whereas others compared toothbrushing with dental procedures which seemed to fit more closely with the aim of this review question. Furthermore, the committee noted that in some studies, subjects were bacteraemic at baseline before the everyday activity indicating that bacteraemias occur spontaneously. |

1

# 2.6 Review question 6a

Does antibiotic prophylaxis in those at risk of developing IE reduce the incidence of IE when given before a defined Interventional Procedure?

## 2.6.1 Clinical evidence review

Since 1955, antibiotic prophylaxis that aims to prevent endocarditis has been used in at-risk patients. The rationale for prophylaxis against IE is that endocarditis usually follows bacteraemia, certain interventional procedures cause bacteraemia with organisms that can cause endocarditis and these bacteria are usually sensitive to antibiotics; therefore, antibiotics should be given to patients with predisposing heart conditions before procedures that may cause bacteraemia. The aim of this review is to assess whether antibiotic prophylaxis in those at risk of IE and undergoing interventional procedures reduces the risk of IE.

An update search using the original search strategy was conducted (see appendix D) which identified 1341 articles (across questions 6a and 7a). The titles and abstracts were screened and 45 articles were identified as potentially relevant. Full-text versions of these articles were obtained and reviewed against the criteria specified in the review protocol (appendix C). None of these met the criteria for this review and all were excluded. An additional 3 studies from CG64 were included. Therefore a total of 3 included studies for the update.

A review flowchart is provided in appendix E, and the excluded studies (with reasons for exclusion) are shown in appendix F.

## 2.6.2 Methods

**Summary of review protocols**

- The population included:
  - adults and children with known underlying structural cardiac defects undergoing interventional procedures
- No subgroups (other than adults and children) were identified for this question.
- The intervention of interest was antibiotic prophylaxis (any) compared against no prophylaxis (including placebo).
- The topic experts outlined the following outcomes:
  - incidence/odds of developing IE in those receiving prophylaxis compared to those not receiving prophylaxis and incidence of adverse effects including anaphylaxis
- The studies did not report data on all these outcomes and in some situations synonymous outcomes are presented.
- GRADE methodology was used to assess the quality of evidence as follows:
- **Risk of bias:**
  - as only observational studies from the original guideline were included in this review, risk of bias for each individual study was assessed using the methodology checklist from Developing NICE guidelines - the Manual 2014.
- **Indirectness:**
  - details from the PICOs in the review protocol(s) (see appendix C) were used to assess the directness of the included studies.
- **Inconsistency**
  - given the variation in populations across studies (including the underlying cardiac condition, regimen of antibiotic subjects received as well as the variation in

interventional procedures subjects underwent), meta-analysis of the data was not appropriate for this question.

- **Imprecision**
  - a routine search of the COMET (Core Outcome Measures in Effectiveness Trials) Initiative database was conducted to identify any relevant thresholds for defining the clinical minimal important difference (MIDs). No information was identified in the COMET database. Information about specific MIDs used to assess imprecision were also not available from the original guideline CG64. Therefore, the following thresholds were used, as per the GRADE working group recommendations: for continuous outcomes, the standard MID of 0.5 standard deviation change and for dichotomous outcomes, RRR or RRI of 25%: 0.75 or 1.25.
- **Overall quality**
  - as only observational studies studies were identified for this review, the quality rating began at 'low' and was further downgraded for potential sources of bias.
- **Statistical analysis**
  - meta-analyses were not conducted due to the variation in population and outcome measures (as explained above) from study to study.
  - where appropriate, summary measures such as mean differences or odds ratios (with 95% confidence intervals) were calculated using Review Manager 5.
- **Description of included studies**
  - Two case-control studies and one retrospective cohort study were identified for this review. One study was from Germany , one from France and one from the Netherlands. The first study examined antibiotic prophylaxis in adults with prosthetic heart valves undergoing various interventional procedures including dental, urological, oropharyngeal and gynaecological procedures. The second study examined antibiotic prophylaxis in adults with underlying valvular disease (prosthetic or native valve) who had undergone a dental procedure. The remaining studies examined antibiotic prophylaxis in children and adults with known cardiac disease (native valve and cardiovascular anomalies) largely undergoing dental procedures. Cases of infective endocarditis and antibiotic use were most commonly identified by interviewing of subjects, and reviewing of medical records.

For a summary of included studies please see table 11 (for the full evidence tables and full GRADE profiles please see appendices G and H).

**Table 11: Summary of included studies**

| Study reference (including study design) | Study population | Intervention & comparator | Outcomes reported |
|---|---|---|---|
| Horskotte, 1987 (Retrospective cohort) | Subjects with prosthetic heart valves who underwent various interventional procedures including dental, urological, oropharyngeal and gynaecological procedures with (N=287) or without (N=390) antibiotics | Antibiotic prophylaxis vs no prophylaxis (various regimens) | - Incidence of prosthetic valve endocarditis |
| Lacassin, 1995 (Case-control) | 171 cases of IE and controls without IE interviewed about procedures and antibiotic use over the previous 3 months | Antibiotic prophylaxis vs no prophylaxis (various regimens) | - Incidence of infective endocarditis |
| Van der Meer, 1992 (Case-control) | Cases were patients with known cardiac disease in whom endocarditis developed within 180 days of a medical or dental procedure for which prophylaxis was indicated (N=48). Controls were patients with the same cardiac status in whom endocarditis did not develop within 180 days of a similar procedure (N=200) | Antibiotic prophylaxis vs no prophylaxis (various regimens) | - Incidence of infective endocarditis |

### 2.6.31 Clinical evidence statement

**Antibiotic prophylaxis for infective endocarditis (grade table 154) - Incidence of IE**

Very low quality evidence from two case-control studies and one retrospective cohort study including subjects with various underlying cardiac diseases were all inconclusive in the incidence of prosthetic valve endocarditis/infective endocarditis in those who received antibiotics compared to those who did not before undergoing an interventional procedure. The procedures included dental, urological, oropharyngeal and gynaecological procedures in the first study, dental in the second study and largely dental procedures in the third study. None of the studies reported on adverse events of prophylaxis.

### 2.6.40 Health Economics

#### 2.6.4.11 Methods

The Committee is required to make decisions based on the best available evidence of both clinical and cost effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected health benefits rather than the total implementation cost. Evidence on cost effectiveness related to the key clinical issues being addressed in the guideline update was sought.

A systematic literature search was undertaken to identify health economic evidence within published literature relevant to prophylaxis against infective endocarditis. The evidence was identified by conducting a broad search in the NHS Economic Evaluation Database (NHS EED), the Health Technology Assessment Database (HTA) and the Health Economic Evaluations Database (HEED) from 2007 (date of the last systematic review conducted for the previous version of the guideline) to 2014. The search also included Medline and Embase databases using an economic filter. Studies published in languages other than English were not reviewed. The search was conducted on 20 November 2014. The health economic search strategy is detailed in appendix I.

The health economist also sought out relevant studies identified by the surveillance review, Standing Committee members, or Topic experts.

##### *2.6.4.1.128 Inclusion and Exclusion criteria*

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost-utility, cost-effectiveness, cost-benefit and cost-consequence analyses) and comparative costing studies that address the review question in the relevant population were considered potentially includable as economic evidence.

Studies that only reported burden of disease or cost of illness were excluded. Literature reviews, abstracts, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded.

Remaining studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available, then other less relevant studies may not have been included. Where selective exclusions occurred on this basis, this is noted in the excluded economic studies table (appendix K).

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist contained in *Appendix H* of *Developing NICE Guidelines: the manual 2014*.

#### *2.6.4.1.21 Economic evidence profile*

The economic evidence profile summarises cost-effectiveness estimates. It shows an assessment of the applicability and methodological quality for each economic evaluation, with footnotes indicating the reasons for the assessment. These assessments were made by the health economist using the economic evaluation checklist from *Appendix H* of *Developing NICE Guidelines: the manual, 2014*. It also shows the incremental cost, incremental effect and incremental cost-effectiveness ratio for the base case analysis in the evaluation, as well as information about the assessment of uncertainty.

**Table 12: Explanation of fields used in the economic evidence profile**

| Item | Description |
|---|---|
| **Study** | This field is used to reference the study and provide basic details on the included interventions and country of origin. |
| **Applicability** | Applicability refers to the relevance of the study to specific review questions and the NICE reference case. Attributes considered include population, interventions, healthcare system, perspective, health effects and discounting. The applicability of the study is rated as:<br>• Directly applicable – the study meets all applicability criteria or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness.<br>• Partially applicable – the study fails to meet one or more applicability criteria and this could change the conclusions about cost effectiveness.<br>• Not applicable – the study fails to meet one or more of the applicability criteria and this is likely to change the conclusions about cost effectiveness. Such studies would usually be excluded from the review. |
| **Limitations** | This field provides an assessment of the methodological quality of the study. Attributes assessed include the relevance of the model's structure to the review question, timeframe, outcomes, costs, parameter sources, incremental analysis, uncertainty analysis and conflicts of interest. The methodological quality of the evaluation is rated as having:<br>• Minor limitations – the study meets all quality criteria or fails to meet one or more quality criteria, but this is unlikely to change the conclusions about cost effectiveness.<br>• Potentially serious limitations – the study fails to meet one or more quality criteria and this could change the conclusions about cost effectiveness<br>• Very serious limitations – the study fails to meet one or more quality criteria and this is highly likely to change the conclusions about cost effectiveness. Such studies would usually be excluded from the review. |
| **Other comments** | This field contains particular issues that should be considered when interpreting the study, such as model structure and timeframe. |
| **Incremental cost** | The difference between the mean cost associated with one strategy and the mean cost of a comparator strategy. |
| **Incremental effect** | The difference between the mean health effect associated with the intervention and the mean health effect associated with the comparator. This is usually represented by quality-adjusted life years (QALYs) in accordance with the NICE reference case. |
| **Incremental cost effectiveness ratio (ICER)** | The incremental cost divided by the incremental effect which results in the cost per quality-adjusted life year gained (or lost). Negative ICERs are not reported as they could represent very different conclusions: either a decrease in cost with an increase in health effects; or an increase in cost with a decrease in health effects. For this reason, the word 'dominates' is used to represent an intervention that is associated with decreased costs and increased health effects compared to the comparator, and the word 'dominated' is used to represent an intervention that is associated with an increase in costs and decreased health effects. |

| Item | Description |
|---|---|
| **Uncertainty** | A summary of the extent of uncertainty about the ICER. This can include the results of deterministic or probabilistic sensitivity analysis or stochastic analyses or trial data. |

#### *2.6.4.1.31 Cost-effectiveness criteria*

NICE's report Social value judgements: principles for the development of NICE guidance sets out the principles that GDGs should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- the intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- the intervention cost less than £20,000 per QALY gained compared with the next best strategy.

If the Committee recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'Recommendations and link to evidence' section of the relevant chapter, with reference to issues regarding the plausibility of the estimate or to the factors set out in *Social value judgements: principles for the development of NICE guidance.*

### 2.6.4.27 Results of economic literature review

The search retrieved 998 articles. The titles and abstracts were screened for possible inclusion and 8 articles were selected for further examination of the full text version. An additional 5 articles from the 2008 review for this guideline were also considered for inclusion along with the original economic evaluation conducted for the 2008 guideline. An economic evaluation that was not published at the time of the literature review, conducted by The University of Sheffield, was also included giving a total of 15 full-text economic evaluations that were considered. Four studies were selected for inclusion in the present update including the 2008 NICE model and the 2015 Sheffield model.

A review flowchart is provided in appendix J, and the excluded studies (with reasons for exclusion) are shown in appendix K.

Summaries of the included studies are provided as economic evidence profiles in table 13 for dental procedures (3 studies) and table 14 for non-dental procedures (1 study). The full economic evidence tables are provided in appendix L.

### 2.6.4.31 Economic evidence statement – dental procedures

Three economic evaluations were included in the literature review of economic evidence on antibiotic prophylaxis prior to dental procedures. All three studies were cost-utility analyses using a combined decision tree and Markov model structure.

A 2005 cost-utility analysis from the United States found that antibiotic prophylaxis was not cost effective for people with moderate risk of developing endocarditis. Cephalexin, clarithromycin and clindamycin were found to be cost effective for people at high risk of developing endocarditis. This study was partially applicable and downgraded due to the use of costs based on the United States healthcare system, utility weights based on the Quality of Wellbeing measure and the adoption of a societal perspective for costs. It had potentially serious methodological limitations due to key parameters based on limited evidence, some utility weights that were based on estimates, and probabilistic sensitivity analysis was not conducted.

Original modelling conducted for the 2008 NICE guideline (CG64) found that antibiotic prophylaxis was not cost effective for people with a moderate risk of developing infective endocarditis and mayt be cost effective for people with a high risk of developing infective endocarditis depending on other assumptions, such as antibiotic efficacy, that are put into the model. This study was directly applicable as it was based on the NICE reference case for economic evaluations. It had minor methodological limitations: the key parameters relating to the risk of developing infective endocarditis following a dental procedure and efficacy of antibiotic prophylaxis to reduce this risk was based on limited evidence; and probabilistic sensitivity analysis was not conducted.

The 2008 NICE model was updated by the University of Sheffield for the present 2015 update (the APPIE model). The base case analysis found that antibiotic prophylaxis using amoxicillin prior to dental procedures was not cost effective. The base case analysis found that antibiotic prophylaxis using clindamycin prior to dental procedures resulted in higher costs and reduced health effects compared with no prophylaxis, mainly due to the risk of fatal anaphylaxis associated with clindamycin. The results of the study were highly sensitive to the risk of developing infective endocarditis following a dental procedure, the efficacy of antibiotic prophylaxis to reduce this risk, and the cost of amoxicillin and clindamycin. Variation of these key parameters resulted in incremental cost-effectiveness ratios for antibiotic prophylaxis compared with no prophylaxis ranging from highly cost effective to highly cost ineffective and dominated (more costly and a reduction in health benefits). The study was directly applicable because it complied with the NICE reference case for economic evaluations. It had only minor methodological limitations due to the limited evidence on the risk of developing infective endocarditis following a dental procedure and the efficacy of amoxicillin and clindamycin to reduce that risk.

#### 2.6.4.4 Economic evidence statement – non-dental procedures

A 2004 cost-utility analysis from the United States found that antibiotic prophylaxis for febrile children who have cardiac lesions and undergo urinary catheterisation in the emergency department was not cost effective. This study was partially applicable with minor limitations.

**Table 13: Economic evidence profile – dental procedures**

| Study | Applicability | Limitations | Other comments | Incremental | | | Uncertainty |
|---|---|---|---|---|---|---|---|
| | | | | Cost | Effect | ICER | |
| Agha et al. 2005<br><br>7 pre-dental antibiotic prophylaxis regimens vs. no prophylaxis<br><br>United States | Partially applicable[1,2,3,4] | Potentially serious limitations[5,6,7] | Decision tree for short term effects and side effects combined with a Markov model to model long term consequences and survival | Not reported | Incremental QALYs gained per 10 million patients<br>1. Oral amoxicillin: -3303<br>2. Oral clarithromycin: +1125<br>3. Oral clindamycin: +1118<br>4. Oral cephalexin: +827<br>5. Intravenous or intramuscular ampicillin: -3030<br>6. Intravenous or intramuscular cefazolin: +827<br>7. Intravenous clindamycin: +1118 | All ICERs are compared with no prophylaxis and per QALY.[8]<br>1. Oral amoxicillin: dominated<br>2. Oral clarithromycin: $88007 2003 US dollars or £76155 2015 UK pounds<br>3. Oral clindamycin: $101142 2003 US dollars or £87522 2015 UK pounds<br>4. Oral cephalexin: $99373 2003 US dollars or £85991 2015 UK pounds<br>5. Intravenous or intramuscular ampicillin: dominated<br>6. Intravenous or intramuscular cefazolin: $199430 2003 US dollars or £172574 2015 UK pounds<br>7. Intravenous clindamycin: $411093 2003 US dollars or £355733 2015 UK pounds | No probabilistic sensitivity analysis conducted.<br><br>A range of one way sensitivity analyses were conducted showing cost-effectiveness is sensitive to a number of input parameters. Please refer to the appendix for a summary of these analyses. |
| NICE 2008<br><br>8 pre-dental antibiotic prophylaxis regimens vs. no prophylaxis<br><br>United | Directly applicable | Minor limitations[9,10] | Decision tree for short term effects combined with a Markov model to model long term conseque | 1. Oral amoxicillin: £26<br>2. Oral clindamycin: £160<br>3. Intravenous amoxicillin then oral amoxicillin: £53<br>4. Oral amoxicillin | 1. Oral amoxicillin: 0.00001<br>2. Oral clindamycin: 0.00001<br>3. Intravenous amoxicillin then oral amoxicillin: 0.00001<br>4. Oral amoxicillin | 1. Oral amoxicillin: £248,912<br>2. Oral clindamycin: £1,513,095<br>3. Intravenous amoxicillin then oral amoxicillin: £498,047<br>4. Oral amoxicillin before and oral amoxicillin after: £499,175<br>5. Amoxicillin plus | No probabilistic sensitivity analysis conducted.<br><br>A series of one-way sensitivity analyses were conducted. Notable findings include:<br>• The risk of developing IE had to be at least 16 per million procedures for the ICER to reduce to £20,000 per QALY. |

| Study | Applicability | Limitations | Other | Incremental | | | Uncertainty |
|---|---|---|---|---|---|---|---|
| Kingdom | | | nces | before and oral amoxicillin after: £53<br>5. Amoxicillin plus gentamicin then oral amoxicillin: £5193<br>6. Intravenous vancomycin then intravenous gentamicin: £796<br>7. Intravenous teicoplanin plus gentamicin: £1612<br>8. Intravenous clindamycin then oral or intravenous clindamycin: £389 | before and oral amoxicillin after: 0.00001<br>5. Amoxicillin plus gentamicin: 0.00001<br>6. Intravenous vancomycin then intravenous gentamicin: 0.00001<br>7. Intravenous teicoplanin plus gentamicin: 0.00001<br>8. Intravenous clindamycin then oral or intravenous clindamycin: 0.00001 | gentamicin: £49,005,022<br>6. Intravenous vancomycin then intravenous gentamicin: £7,514,982<br>7. Intravenous teicoplanin plus gentamicin: £15,212,810<br>8. Intravenous clindamycin then oral or intravenous clindamycin: £3,668,040 | • When the estimated costs and potential benefits of future prophylaxis are included in the analysis, this threshold rises to 48 per million.<br>• When the efficacy of prophylaxis was varied between 25% to 75%, the ICER for strategy 1 was £503,448 and £164,069 per QALY respectively, and the ICER for strategy 2 was £3,031,864 and £1,006,853 respectively. |

*Acronyms*
*ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year*
*[1] The analysis was based on the United States healthcare system.*
*[2] A societal perspective was adopted for both cost and health consequences.*
*[3] The discount rate used in the base case was 3% rather than 3.5%.*
*[4] Utilities used to calculate quality-adjusted life years were based on the Quality of Well-being index of a United States population, rather than the EQ-5D with United Kingdom general population preferences, estimates, and a combination of both.*
*[5] Many of the key parameters driving the model are based on poor and conflicting evidence from literature sources.*
*[6] Estimates of resource use include productivity losses due to the societal perspective.*
*[7] Probabilistic sensitivity analysis was not conducted.*
*[8] All ICERs converted to 2015 UK pounds by using the Campbell and Cochrane Economics Methods Group EPPI Cost Converter available at http://www.c-cemg.org/, accessed 21-22 January 2015*
*[9] No probabilistic sensitivity analysis*
*[10] No reasonable evidence was identified to support the assumptions that individual dental procedures can lead directly to the development of infective endocarditis or that antibiotic prophylaxis reduces that risk.*

**Table 14: Economic evidence profile – non-dental procedures**

| Study | Applicability | Limitations | Other comments | Incremental | | | Uncertainty |
|---|---|---|---|---|---|---|---|
| | | | | Cost | Effect | ICER | |
| Caviness et al. 2004<br><br>Amoxicillin or vancomycin vs. no prophylaxis for febrile children who have cardiac lesions and undergo urinary catheterisation in the emergency department<br><br>United States | Partially applicable [1,2,3,4] | Minor limitations [5,6,7,8,9] | Decision tree with most parameters taken from the literature | Amoxicillin US$495.30 (2000)<br><br>Vancomycin US$666.16 (2000) | Amoxicillin -0.00045 QALYs<br><br>Vancomycin 0.00005 QALYs | Amoxicillin Dominated<br><br>Vancomycin US$13323200/QALY (2000) or £12213677/QALY (2015) [10] | When all antibiotic-related deaths due to amoxicillin were excluded, the ICER was US$9,875,800 (2000) or £9053368 (2015).<br>When the prevalence of urinary tract infections is increased to 100% (from 3.9%), the ICER for amoxicillin was $311507 and $427966 for vancomycin.<br>The conclusions were robust to all other sensitivity analyses.<br>Probabilistic sensitivity analysis not conducted. |

*Acronyms*
*ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year*
[1] *Study based on the US healthcare system*
[2] *Societal perspective taken for costs*
[3] *Discount rate of 3% used*
[4] *Years of Healthy Life Measure used for utilities to derive quality adjusted life years*
[5] *Decision tree used for model structure whereas a Markov model may have been more appropriate to model long term consequences*
[6] *Parameters used for effectiveness were based on the limited evidence available in the literature*
[7] *Full range of sensitivity analyses not reported*
[8] *Probabilistic sensitivity analysis not done*
[9] *No conflicts declaration provided*
[10] *ICERs converted to 2015 UK pounds by using the Campbell and Cochrane Economics Methods Group EPPI Cost Converter available at http://www.c-cemg.org/, accessed 21-22 January 2015*

## 2.6.51 Evidence to recommendations

| | Committee discussions |
|---|---|
| **Relative value of different outcomes** | The Committee discussed and agreed that the critical outcome for this review question was to establish whether there is a clear relationship between antibiotic prophylaxis and the incidence of IE in people undergoing interventional procedures who have pre-existing cardiac conditions. Therefore, the critical outcome is the measurement of such association and the precision and certainty for these measurements reported in the included studies. In addition, the committee included adverse events including anaphylaxis as an outcome as this was an important factor for consideration if treatment with antibiotics was found to be clinically effective. In order for prophylaxis to be effective, a suitable regimen that gives a balance between side effects from prophylaxis and development of the disease would need to be considered. |
| **Quality of evidence** | The committee noted the very limited evidence identified for this question, in particular the retrospective nature of all 3 included studies and lack of RCTs in this area. The committee noted the need for RCTs to assess the efficacy of antibiotic prophylaxis for IE, however they indicated that it would be very challenging to conduct such a trial given the rare nature of the condition and therefore the difficulty in recruiting sufficient numbers of participants.<br><br>The committee further discussed the limited evidence and noted that:<br>• The methodology used by all three studies was poor with high risk of bias and uncertain study designs<br>• The retrospective nature of all 3 studies meant that the studies were reliant on the participant's memory for data regarding interventional procedures undergone and antibiotic use; in some studies, there was no indication that this data was verified in any way<br>• Power calculation was not reported in 67% of studies (2/3) and it was therefore unclear whether the inconclusive findings observed in individual studies was due to lack of power<br>• A wide variation in antibiotic regimen was used across the studies<br>• All 3 included studies did not address adverse events of antibiotics prophylaxis<br><br>Overall, the committee concluded that there is insufficient evidence to recommend prophylactic use of antibiotics in those at risk of IE undergoing interventional procedures. The lack of evidence has led to the use of post-procedure bacteraemia as a surrogate outcome measure for IE in some studies of antibiotic effectiveness (see section 2.41). |
| **Trade-off between benefits and harms** | All 3 studies included in this question were inconclusive as to whether antibiotics prophylaxis prevents the development of IE. The committee noted the lack of data on side effects including anaphylaxis from antibiotic prophylaxis and therefore the difficulty in establishing a balance between potential side effects and benefit of prophylaxis, if any. Furthermore, the occurrence of other effects of antibiotic usage including the risk of antibiotic resistance was noted but not covered by the evidence identified for this question. |
| **Trade-off between net health benefits and resource use** | Three studies were included in the literature review of economic evaluations examining the cost effectiveness of antibiotic prophylaxis against infective endocarditis prior to dental procedures.<br><br>The results of all three models were highly sensitive to the risk of developing infective endocarditis following a procedure and the efficacy of antibiotic prophylaxis to reduce that risk. The Committee noted there was limited evidence to quantify either of these parameters. |

| | Committee discussions |
|---|---|
| | Regarding the risk of developing infective endocarditis following a dental procedure, the Committee were of the opinion that, if such a risk existed, it was far less than 93 per million, the figure used in all three models to represent patients at a high risk of developing infective endocarditis, such as those with prosthetic valves.<br><br>The Committee were unable to establish whether or not prophylaxis was effective.<br><br>The 2015 update of the 2008 NICE model by the University of Sheffield (the APPIE model) was highly sensitive to the price of amoxicillin and clindamycin. Analysis of the results included scenarios where amoxicillin was found to be cost effective. Some Committee members noted that these lower prices may be likely to occur in practice, particularly if capsules were used rather than oral suspension powder. The price of oral suspension powder was used in the base case analysis and this is more expensive than amoxicillin capsules. In other words, the lower price of amoxicillin capsules would make antibiotic prophylaxis more likely to be cost effective. A lay member confirmed that capsules are preferred to oral suspension powder from a patient perspective. However, the Committee were of the opinion that the lack of evidence supporting the efficacy of antibiotic prophylaxis outweighed the results of these scenarios.<br><br>The Committee expressed some reservations about the methods used to estimate the efficacy of antibiotic prophylaxis in the APPIE model where it was assumed that at least a proportion of the increase in incidence of infective indocarditis since the 2008 NICE guideline CG64 was attributable to the reduction in use of antibiotic prophylaxis. Also, the base case analysis did not account for the general upward trend of the incidence of infective endocarditis.<br><br>The topic experts advised there were a number of confounding circumstances and events that could have contributed to the increase in incidence of infective endocarditis:<br>• Increasing survivors and survival times specifically of people with congenital heart disease;<br>• The severe sepsis campaign was extending into Europe at around this time with emphasis on blood culture sampling – improved case ascertainment would result as many diagnoses are made following positive blood cultures;<br>• Increased prevalence of those at risk within the population, such as people with prosthetic valves, implantable cardiac devices and dialysis patients;<br>• Increase in the number of older people with an inherent increase in degenerative valvular disease;<br>• Enhanced efforts to make coding of hospital activity more accurate;<br>• Some patients may have finished treatment as a day case rather than as an inpatient and this may have been coded multiple times for a single episode of infective endocarditis;<br>• Improved ability to establish the diagnosis with better cardiac imaging and increased awareness;<br>• Increased use of cardiac imaging in patients with S. Aureus bacteraemia;<br>• The change in remuneration of general dental practitioners in 2006.<br>• Migration may have increased the prevalence of people with previous rheumatic fever. |

| | Committee discussions |
|---|---|
| | • Echocardiograms are now required following a positive blood culture for staphylococci. So although absolute numbers of positive staphylococcal cultrues is falling, the increased surveillance may pick up additional cases.<br><br>The Committee considered the novel data regarding adverse drug reactions from antibiotics that were included in the model. The Committee noted that this data could be subject to case ascertainment bias as it relies on accurate reporting of all adverse reactions. That is, there could be more fatal and non-fatal reactions than reflected by this data. This would have the effect of underestimating the cost effectiveness of antibiotic prophylaxis.<br><br>The Committee discussed whether it would be possible to conduct economic modelling to establish the cost effectiveness of antibiotic prophylaxis for high risk groups only. Based on the evidence presented in the clinical systematic reviews, the Committee determined that it would be difficult to define the population that would be considered high risk and then establish what the risk of developing infective endocarditis was for that population.<br><br>Some Committee members were of the opinion that the 2008 NICE guideline had decreased cost and improved patient experience in dental clinics. For example, antibiotic prophylaxis may have been contraindicated for some patients due to already being on an antibiotic regimen – prior to the 2008 guideline this would have resulted in the dental procedure being deferred to another time.<br><br>One study was included in the literature review of economic evidence on the cost effectiveness of antibiotic prophylaxis prior to non-dental procedures. This 2004 cost-utility analysis from the United States found that antibiotic prophylaxis for febrile children who have cardiac lesions and undergo urinary catheterisation in the emergency department was not cost effective.<br><br>Overall, the Committee were of the opinion that antibiotic prophylaxis was unlikely to be cost effective. |
| **Other considerations** | For dental and non-dental procedures assessed in this review question, the Committee felt that the studies have provided inconclusive evidence on the association between antibiotic prophylaxis and incidence of IE. The Committee agreed that the current evidence is insufficient to support the hypothesis that antibiotic prophylaxis in those undergoing interventional procedures prevents the development of IE and therefore did not change the existing recommendation indicating that antibiotic prophylaxis against IE is not recommended.<br><br>Patient view of the use of antibiotics for IE: the lay member discussed with the committee the reluctance of patients with long history of antibiotic use in undergoing a sudden change (i.e. discontinuing antibiotic prophylaxis) in a well-established practice. On the other hand, it was noted that new patients may be more likely to accept this practice of no antibiotics before undergoing an interventional procedure. The issue of conflicting information being provided by cardiologists, dental practitioners and hygienists was raised as a potential significant problem and it was thought that the health care professional missed the finer detail of the guideline around patient choice. The committee therefore discussed the importance of clear and consistent information for patients and families and also that a balanced view of the lack of evidence indicating effectiveness of prophylaxis for IE as well as any potential harms of prophylaxis should be fully explained to the |

| | Committee discussions |
|---|---|
| | person considering treatment. This will in turn allow the patient to make an informed decision about continuing/discontinuing prophylaxis. The committee further highlighted that antibiotics is only one strategy for the prevention of IE. Many other strategies for reducing the risk of IE eg: dental hygiene measures to maintain good oral health that has not been covered by the scope of this guideline. In relation to this, the committee also noted that a new dental contract was introduced in 2006 for general dental practitioners. One consequence of the contract was that it changed the incentives for dentists to provide professional cleaning and education to patients.<br><br>In summary,given the lack of evidence relating to the use of antibiotics for IE, the committee decided to make a research recommendation in this area highlighting the need for a trial (see section 2.6.5). The committee concluded that the reasons for the increased incidence of IE (including within the low risk population, which is not covered by the scope of this guideline) indicated by the study (Dayer et al. 2014) that triggered this update are still unknown. The committee noted that the critique of this study (see section 2.1.2) indicates that the hypothesis of the change in slope after the introduction of the NICE guidance is biased and published estimates are likely too high. As found by the epidemiological review (see section 1.1.1), the committee noted that interestingly, the incidence of IE continues to increase also in the US and European studies, where more conservative antibiotic prophylaxis guidelines are in place compared to the UK. As the authors of these studies postulated, this may be due to the aging population with multi-morbidity, increase of degenerative valves, increase of haemodialysis and so on; these areas were outside of the scope for this update. |

## 2.6.6 Research recommendations

Does antibiotic prophylaxis in those at risk of developing IE reduce the incidence of IE when given before a defined interventional procedure?

**Why is this important?**

There is a gap in the evidence about the effectiveness of antibiotic prophylaxis in reducing the incidence of IE in those at risk of developing IE. The current evidence includes very limited data from observational studies indicating inconclusive findings. Therefore the Committee decided that there was insufficient evidence to make a recommendation about the use of antibiotic prophylaxis and also a lack of data on side effects from antibiotic prophylaxis. The committee agreed that the need for this piece of research should be supported. More evidence is needed to enable a recommendation to be made on the use of antibiotics in those at risk of developing IE. The study should be a randomised controlled trial with long term follow-up comparing antibiotics with no antibiotic prophylaxis in adults and children with underlying structural cardiac defects undergoing interventional procedures. Outcomes should include the incidence/odds of developing IE in those receiving prophylaxis compared to those not and also the incidence of adverse effects including anaphylaxis.

1 **Table 15: Criteria for selecting high-priority research recommendations**

| | |
|---|---|
| **PICO** | **Population:** adults and children with known underlying structural cardiac defects undergoing interventional procedures<br><br>**Intervention:** antibiotic prophylaxis (any)<br><br>**Comparison:** no antibiotic prophylaxis (including placebo)<br><br>**Outcomes:**<br>Incidence/odds of developing IE in those receiving prophylaxis compared to those not<br>Adverse events including anaphylaxis |
| **Current evidence base** | The current evidence base consists of 3 observational studies of antibiotics compared to no prophylaxis. The population of these studies is composed of adults with valvular disease (prosthetic or native) undergoing various interventional procedures. One study included children and adults however a subgroup analysis by age was not reported. The Committee considered that they were currently unable to make a recommendation on the use of antibiotics in those at risk of IE, as the limited evidence base was inconclusive as to whether antibiotics reduces the incidence of IE. The committee also noted the lack of data on side effects including anaphylaxis from antibiotic prophylaxis and therefore the difficulty in establishing a balance between potential side effects and the benefit of prophylaxis. |
| **Study design** | RCT |
| **Other comments** | The RCT will need to have sufficient length of follow up to prospectively identify cases of IE. |

2

3

4

# 2.71 Review question 7a

Does antibiotic prophylaxis given to those undergoing Interventional Procedures reduce the level and duration of bacteraemia?

## 2.7.14 Clinical evidence review

The aim of this review is to assess whether antibiotic prophylaxis in those undergoing interventional procedures reduces the level and duration of bacteraemia

The same update search as described in section 2.33 for question 6a was used for this question. Five new studies met the criteria and were included with an additional 13 studies from the original guideline; therefore a total of 18 included studies for the update.

A review flowchart is provided in appendix E, and the excluded studies (with reasons for exclusion) are shown in appendix F.

## 2.7.22 Methods

**Summary of review protocols**

- The population included:
  - adults and children undergoing interventional procedures (both dental and non-dental) irrespective of whether they have an underlying cardiac condition
- No subgroups (other than adults and children) were identified for this question.
- The intervention of interest was antibiotic prophylaxis (any) compared against no prophylaxis (including placebo).
- The topic experts outlined the following outcomes:
  - bacteraemia levels/intensity at one or more time points following prophylaxis versus before prophylaxis, duration of bacteraemia following prophylaxis versus before and number/incidence/odds of positive blood samples following prophylaxis versus before
- The studies did not report data on all these outcomes and in some situations synonymous outcomes are presented.
- GRADE methodology was used to assess the quality of evidence as follows:
- **Risk of bias:**
  - As only RCTs were included in this review, criteria suggested by the GRADE methodology (http://www.gradeworkinggroup.org/) were used for assessing risk of bias.
- **Indirectness:**
  - details from the PICOs in the review protocol(s) (see appendix C) were used to assess the directness of the included studies.
- **Inconsistency**
  - given the variation in populations across studies (including the regimen of antibiotic subjects received as well as the variation in interventional procedures the subjects underwent), meta-analysis of the data was not appropriate for this question. The age of the subjects and time point at which the incidence of bacteraemia was assessed post-procedure also varied from study to study; in some studies it was unclear whether the same subjects were bacteraemic at different time points therefore pooling this data could have led to double counting of subjects and thereby affected the accuracy of the results.
- **Imprecision**

- a routine search of the COMET (Core Outcome Measures in Effectiveness Trials) Initiative database was conducted to identify any relevant thresholds for defining the clinical minimal important difference (MIDs). No information was identified in the COMET database. Information about specific MIDs used to assess imprecision were also not available from the original guideline CG64. Therefore, the following thresholds were used, as per the GRADE working group recommendations: for continuous outcomes, the standard MID of 0.5 standard deviation change and for dichotomous outcomes, RRR or RRI of 25%: 0.75 or 1.25.

- **Overall quality**
  - as all evidence identified for this review came from RCTs, the quality rating started at high and was further downgraded for potential sources of bias.
- **Statistical analysis**
  - meta-analyses were not conducted due to the variation in population and outcome measures (as explained above) from study to study.
  - where appropriate, summary measures such as mean differences or odds ratios (with 95% confidence intervals) were calculated using Review Manager 5.
- **Description of included studies**
  - 18 studies were included in this review: 16 RCTs (1 meta-analysis and 1 systematic review. Five studies were from the UK, three from USA, two from Sweden, two from Spain, one from South Africa , one from Japan, one from Australia and one from Germany. The meta-analysis and systematic review included studies from various counties.
  - sample size ranged from 20 to 1394 subjects in the systematic review of RCTs.
  - 11 studies examined antibiotic prophylaxis in those undergoing dental procedures; 2 of these were in children. One study examined antibiotic prophylaxis in children undergoing respiratory procedures. A further three studies looked at antibiotic prophylaxis in adults undergoing genito-urinary procedures and the remaining three studies examined antibiotics for adults undergoing gastrointestinal procedures. All studies examined the efficacy of antibiotics of different regimens compared to no antibiotic or placebo.
  - Bacteraemia was assessed at various time points following the interventional procedure. 7 studies reported the incidence of bacteraemia at baseline however the defintions of baseline varied and ranged from before prophylaxis to before procedure and after intubation and eight did not. 2 studies excluded subjects with positive blood cultures at baseline before the procedure. The remaining study did not report incidence of bacteraemia before prophylaxis separately but combined this with the incidence at any of the blood draws taken.

For a summary of included studies please see tables 13 to 16 (for the full evidence tables and full GRADE profiles please see appendices F and G).

**Table 16: Summary of included studies: antibiotics for bacteraemia in those undergoing dental procedures**

| Study reference (including study design) | Study population | Intervention & comparator | Outcomes reported |
|---|---|---|---|
| Maharaj, 2012<br>(RCT) | N=80 for each comparison, adult black patients ≥18 years attending dental clinic for extraction of one tooth | 3g amoxicillin or 600mg clindamycin given orally 1 hour prior to extraction vs no prophylaxis prior to extraction | - Incidence of bacteraemia after extraction |
| Duvall, 2013<br>(RCT) | N=20, adults ≥18 presenting to the surgical centre, oral surgery clinic for third molar extractions | 2g amoxicillin* capsule and a placebo rinse** vs placebo rinse and placebo capsule<br><br>*taken orally 1 hour prior to procedure<br>**taken immediately before sedation medication administration; 15ml of the rinse for one minute and expectorated | - Bacteraemia levels/intensity<br>- Incidence of bacteraemia |
| Diz, 2006<br>(RCT)<br><br>[included in CG64] | N=109 for amoxicillin, 107 for clindamycin, 111 for moxifloxacin comparison, subjects >18 years who for behavioural reasons (autism, learning disabilities, phobias, etc) underwent dental extraction | 2g amoxicillin or 600mg clindamycin or 400mg moxifloxacin taken orally 1 to 2 hours before anaesthesia induction vs no prophylaxis | - Incidence of bacteraemia |
| Hall, 1993<br>(RCT)<br><br>[included in CG64] | N=40 per comparison, otherwise healthy adults aged 23 to 74 referred to the department of oral surgery for dental extraction | 2g penicillin V plus 4 tablets of amoxicillin placebo or 4 750mg amoxicillin tablets plus 2 tablets of penicillin V placebo vs 2 tablets of penicillin V placebo and 4 tablets of amoxicillin placebo all taken 1 hr before extraction | - Incidence of bacteraemia<br>- Bacteraemia levels/intensity (only medians without accompanying summary measures) |
| Roberts, 1987<br>(RCT)<br><br>[included in CG64] | N=94, children under 16 years requiring admission for extensive conservative dental work as well as the extraction of at least 1 tooth. | Oral amoxicillin 50mg/kg 2 hours before scheduled time for surgery vs no prophylaxis | - Incidence of bacteraemia |
| Hall, 1996<br>(RCT) | N=39, adults undergoing dental extraction | Two 0.5g Cefaclor tablets taken 1 hour prior to extraction vs two tablets | - Bacteraemia levels/intensity (reported as % reduction) |

| Study reference (including study design) | Study population | Intervention & comparator | Outcomes reported |
|---|---|---|---|
| [included in CG64] | | of placebo 1 hour prior to extraction | - Incidence of bacteraemia |
| Shanson, 1985<br>(RCT)<br><br>[included in CG64] | N=82, adults aged 18 to 78 years undergoing dental extractions in the outpatient department | 1.5g erythromycin stearate orally 1 hour before extraction vs matched placebo | - Incidence of bacteraemia<br>- Side effects |
| Wahlmann, 1999<br>(RCT)<br><br>[included in CG64] | N=59, adults with multiple tooth extraction in preparation for radiotherapy for oral cancer | 1.5g IV cefuroxime 10 minutes before multiple tooth extraction vs 0.9%NaCl placebo | - Incidence of bacteraemia |
| Lockhart, 2004<br>(RCT)<br><br>[included in CG64] | N=100, children who required dental extraction in the operating room setting because of behaviour, young age and/or the scope of treatment needs | Amoxicillin elixir 50mg/kg one hour before the anticipated time of intubation vs placebo | - Incidence of bacteraemia |
| Morozumi, 2010<br>(RCT) | N=20, systemically healthy subjects who possessed a minimum of 20 teeth and had geenralised moderate to severe chronic periodontitis undergoing scaling and root planning | Azithromycin 500mg once a day 3 days before quadrant scaling and root planning vs no prophylaxis | - Incidence of bacteraemia |
| Lockhart, 2008<br>(RCT) | N=192 adults presenting to urgent care service with the need for extraction of at least 1 erupted tooth | Amoxicillin prophylaxis according to AHA recommendations 1 hour before extraction vs placebo | - Incidence of bacteraemia<br>- Bacteraemia levels/intensity |

1 **Table 17: Summary of included studies: antibiotics for bacteraemia in those undergoing respiratory procedures**

| Study reference (including study design) | Study population | Intervention and comparator | Outcomes reported |
|---|---|---|---|
| Sanchez-Carrion, 2006<br>(RCT) | N=101 children under 14 years scheduled for adenoidectomy (without tonsillectomy) | Cefazolin 30 to 40mg/kg given at induction of anaesthesia vs no prophylaxis | - Incidence of bacteraemia |

**Table 18: Summary of included studies: antibiotics for bacteraemia in those undergoing urogenital procedures**

| Study reference (including study design) | Study population | Intervention and comparator | Outcomes reported |
|---|---|---|---|
| Allan, 1985<br>(RCT)<br>[included in CG64] | N=100, adults undergoing transurethral prostatectomy | 2g intravenous mezlocillin about the time of induction of anaesthesia vs no prophylaxis | - Incidence of bacteraemia |
| Bhattacharya, 1995<br>(RCT)<br>[included in CG64] | N=116 women with menorrhagia undergoing either transcervical resection or laser ablation of the endometrium | 1.2g augmentin IV at the induction of anaesthesia vs no antibiotic | - Incidence of bacteraemia<br>- Adverse events |
| Qiang, 2005<br>(Systematic review of RCTs)<br>[included in CG64] | N= 10 trials, 1394 men undergoing transurethral prostatic resection | Anitbiotic vs placebo or no prophylaxis (various regimens) | - Incidence of bacteraemia |

**Table 19: Summary of included studies: antibiotics for bacteraemia in those undergoing gastrointestinal procedures**

| Study reference (including study design) | Study population | Intervention and comparator | Outcomes reported |
|---|---|---|---|
| Selby, 1994<br>(RCT)<br>[included in CG64] | N=39, adults presenting with bleeding esophageal varices and who underwent emergency endoscopic sclerotherapy, defined as performed within 48 hours of bleeding | 1g cefotaxime IV immediately before endoscopic sclerotherapy vs no antibiotic | - Incidence of bacteraemia<br>- Adverse events |
| Rolando, 1993<br>(RCT)<br>[included in CG64] | N=97 adults admitted for sclerotherapy for bleeding oesophageal varicies | IV imipenem/cilastatin over 20min vs IV dextrose-saline | - Incidence of bacteraemia |
| Harris, 1999<br>(Meta-analysis of 4 RCTs)<br>[included in CG64] | N=478, adults undergoing diagnostic or therapeutic ERCP and had a variety of underlying pathologies | Antibiotic (various regimens) vs placebo | - Incidence of bacteraemia |

## 2.7.3 Clinical evidence statements

### 2.7.3.1 Antibiotic prophylaxis for bacteraemia in those undergoing dental procedures (grade table 155/156)

#### Incidence of bacteraemia before and after prophylaxis

11 RCTs reported on incidence of bacteraemia at various time points. The overall finding was inconsistent across studies; quality of the evidence ranged from moderate to very low. A narrative summary of the findings is presented below; studies have been grouped by the timing of outcomes using arbitrary thresholds. Where studies have examined more than one time interval, the longest time point was used to decide which group the study should go into.

#### Incidence of bacteraemia up to 10 minutes post procedure

7 RCTs, one of which was in children (N= range from 20 to 94) ranging from moderate to very low quality showed inconsistent evidence on the associations between antibiotic prophylaxis and incidence of bacteraemia following various dental procedures. However the time frame for post procedure blood samples were relatively short (up to 10 minutes post procedure) and the incidence of bacteraemia before prophylaxis was not reported in 3 studies.

#### Incidence of bacteraemia up to 20 minutes post procedure

Low quality evidence from one RCT including 192 adults found that there may be a clinically important decrease in the incidence of bacteraemia in the first 5 minutes of tooth extraction and 20 minutes after in those receiving amoxicillin compared to placebo; this estimate was however imprecise.

#### Incidence of bacteraemia up to 30 minutes post procedure

Moderate quality evidence from 1 RCT including 59 adults found that there is a clinically important decrease in the incidence of bacteraemia at both 10 and 30 minutes after extraction in those receiving cefuroxime compared to placebo. However, incidence of bacteraemia before prophylaxis was not reported.

#### Incidence of bacteraemia up to 45 minutes post procedure

Low quality evidence from 1 RCT including 100 children found that there was a statistically significant decrease in the incidence of bacteraemia after intubation, 15 minutes after extraction and 45 minutes after extraction in those receiving amoxicillin compared to those receiving placebo. Baseline blood samples performed after intubation were significantly lower in the amoxicillin group. Clinical significance could not be assessed in both studies as data was presented as crude percentages without accompanying confidence intervals in the study.

#### Incidence of bacteraemia up to 1 hour post procedure

Low quality evidence from one RCT including around 110 adults found that there was a statistically significant decrease in the incidence of bacteraemia at both 30 seconds and 1 hour after extraction in those receiving amoxicillin or moxifloxacin but not in those receiving clindamycin. The incidence of bacteraemia before dental manipulation (but after intubation) however was not comparable between the groups.

#### Duration of bacteraemia

No studies reported on this outcome.

#### Bacteraemia levels/intensity before and after prophylaxis

Very low quality evidence from one RCT including 20 adults was inconclusive in the total mean magnitude of bacteraemia (cfu/ml) in those receiving amoxicillin compared to placebo. The same study examined the mean magnitude of bacteraemia per blood draw and found there may be no clinical difference between the groups after draw 4 but the evidence for draws 2 and 3 were inconclusive.

A further study found that the magnitude of bacteraemia was reduced by 75% in 10 minute blood samples in both groups however the average count of colony forming units was not reported.

1 other study found that all analysed samples were below the detection threshold of $10^4$ CFU per millilitre of blood.

**Adverse events**

Moderate quality evidence from 1 RCT including 82 adults showed that there is a clinically important increase in side effects including mild or transient nausea, abdominal discomfort or flatulence usually occurring within a few hours of extraction in those receiving erythromycin compared to placebo. This effect estimate was precise.

### 2.7.3.2 Antibiotic prophylaxis for bacteraemia in those undergoing respiratory procedures (grade table 157)

**Incidence of bacteraemia before and after prophylaxis**

Moderate quality evidence from 1 RCT including 101 children showed that there is a clinically important decrease in the incidence of bacteraemia 30 seconds after adenoidectomy (without tonsillectomy) in those receiving cefazolin compared to those receiving no prophylaxis. Very low quality evidence from the same study was inconclusive for difference in incidence of bacteraemia observed at 20 minutes after adenoidectomy. The incidence of bacteraemia before prophylaxis was not reported.

**Duration of bacteraemia, bacteraemia levels/intensity before and after prophylaxis, adverse events**

No studies reported on the above outcomes.

### 2.7.3.3 Antibiotic prophylaxis for bacteraemia in those undergoing gastrointestinal procedures (grade table 158)

**Incidence of bacteraemia before and after prophylaxis**

Very low quality evidence from two RCTs including 39 and 97 adults respectively and 1 meta-analysis of 4 RCTs including 478 adults was inconclusive in the incidence of bacteraemia (5 minutes after endoscopic sclerotherapy in the first study, 30 minutes post sclerotherapy in the second study and post endoscopic retrograde cholangiopancreatography (ERCP) in the third study) in those receiving antibiotic (various regimens) compared to no antibiotic/placebo. In the first study, all participants were negative 20 minutes after sclerotherapy in both groups and any participants who were positive before the procedure were excluded. In the second study, 2 participants (unclear from which group) were positive for bacteraemia before endoscopy and therefore excluded. In the third study, it was unclear how many of the subjects, if any, may have been bacteraemic before prophylaxis.

**Duration of bacteraemia, bacteraemia levels/intensity before and after prophylaxis**

No studies reported on the above outcomes.

**Adverse events**

Very low evidence from one RCT including 39 adults was inconclusive in the incidence of mortality observed in those receiving cefotaxime compared to no antibiotic.

#### 2.7.3.43 Antibiotic prophylaxis for bacteraemia in those undergoing genitourinary procedures (grade table 159)

##### Incidence of bacteraemia before and after prophylaxis

Moderate quality evidence from 1 RCT including 100 adults and one systematic review of 10 RCTs including 1394 men found that there is a clinically important decrease in the incidence of bacteraemia after completion of transurethral prostatectomy in those receiving antibiotic compared to no prophylaxis/placebo. The incidence of bacteraemia at baseline before prophylaxis was not reported and the incidence of bacteraemia first day post-op and after removal of the catheter was non-significant in the first study.

Low quality evidence from 1 RCT including 116 women found that there may be a clinically important decrease in the incidence of bacteraemia immediately after transcervical resection or laser ablation of the endometrium in those receiving augmentin compared to no antibiotic; however this estimate was imprecise. The incidence of bacteraemia before prophylaxis was not reported.

##### Duration of bacteraemia, bacteraemia levels/intensity before and after prophylaxis

No studies reported on the above outcomes.

##### Adverse events

Low and very low quality evidence respectively from 1 RCT showed that there may be no clinical difference in the incidence of pain and inconclusive evidence for the incidence of offensive discharge within 2 weeks of endometrial ablation in those receiving augmentin compared to no antibiotic. Low quality evidence from the same study found there may be a clinically important increase in the incidence of fever within 2 weeks of endometrial ablation in those receiving augmentin compared to no antibiotic; this estimate was also imprecise.

### 2.7.46 Evidence to recommendations

| | Committee discussions |
|---|---|
| **Relative value of different outcomes** | The Committee discussed and agreed that the critical outcome for this review question was to establish whether there is a clear relationship between antibiotic prophylaxis and the level and duration of bacteraemia in people undergoing interventional procedures regardless of whether they have a pre-existing cardiac condition. Bacteraemia, including the incidence, duration and intensity before and after prophylaxis were therefore considered to be the critical outcomes for the measurement of such association and furthermore, a surrogate outcome for IE as endocarditis usually follows bacteraemia. In addition, the committee included adverse events including anaphylaxis as an outcome as this was an important factor for consideration if treatment with antibiotics was found to be clinically effective. |
| **Quality of evidence** | The Committee discussed the utility of GRADE methodology to assess the quality of evidence for this particular review question. It was acknowledged the assessment of imprecision using the GRADE default MIDs were not suitable for this prophylaxis question examining bacteraemia as the outcome given that clinical significance for bacteraemia, a surrogate outcome for IE, could not be defined due to uncertainty in the level that may be significant for the development of IE. Therefore, the committee are uncertain about the clinical significance of evidence presented using GRADE methodology. |

| | Committee discussions |
|---|---|
| | The committee further discussed the evidence and noted that:<br>• The majority of evidence came from those undergoing dental procedures (11/18 studies)<br>• Power calculation was not reported in a number of studies<br>• A wide variation in antibiotic regimen was used across the studies<br>• There was very limited data on adverse events of antibiotic prophylaxis<br>• The number bacteraemic before prophylaxis was not reported in 7 studies and of the studies that did report this, it was unclear whether this was number bacteraemic before prophylaxis or just before the procedure<br>• The follow-up time points for post-procedure blood samples were very short (with most studies less than 60 minutes), making it difficult to establish the actual duration of bacteraemia<br>• The sample sizes of the included studies were small<br>It was difficult to establish the association between antibiotic prophylaxis and bacteraemia because where blood samples were obtained at multiple time points it was not clear whether the number positive for bacteraemia at different time points were from the same participants or not.<br><br>Overall, the Committee concluded that although in some studies, antibiotic prophylaxis reduces the frequency of detection of bacteraemia post procedure, antibiotic prophylaxis does not eliminate bacteraemia following dental/non-dental procedures. The committee agreed that the evidence was of poor quality for investigation of whether antibiotic prophylaxis reduces the level and duration of bacteraemia and therefore the development of IE. |
| **Trade-off between benefits and harms** | Overall, there was inconsistent evidence across the studies with some studies indicating that antibiotic prophylaxis reduces the incidence of bacteraemia post-procedure but does not eliminate it. The committee noted the lack of data on side effects including anaphylaxis from prophylaxis and therefore the difficulty in establishing a balance between side effects and any potential benefit of prophylaxis in terms of preventing IE. Furthermore, the occurrence of other effects of antibiotic usage including the risk of antibiotic resistance was noted but not covered by the evidence identified for this question. |
| **Trade-off between net health benefits and resource use** | There is no impact on resource use related to this review question per se. Section 2.6.4 contains a systematic review of economic evaluations that investigate the cost-effectiveness of antibiotic prophylaxis. |
| **Other considerations** | This question somewhat overlapped with question 6a and therefore no further issues other than that outlined in section 2.35 were identified. |

# 2.8 Review question 6b and 7b

Q6b) Does oral chlorhexidine prophylaxis in those at risk of developing IE reduce the risk of developing IE when given before a defined Interventional Procedure?

Q7b) Does oral chlorhexidine prophylaxis given to those undergoing Interventional Procedures reduce the level and duration of bacteraemia?

## 2.8.1 Clinical evidence review

Chlorhexidine is often used as an active ingredient in mouthwash designed to reduce dental plaque and oral bacteria. The aim of this review is to assess whether chlorhexidine prophylaxis reduces the incidence of IE in those at risk and also the level and duration of bacteraemia when given before an interventional procedure.

An update search using the original search strategy was conducted (see appendix D) which identified 674 articles (across question 6b and 7b). The titles and abstracts were screened and 22 articles were identified as potentially relevant. Full-text versions of these articles were obtained and reviewed against the criteria specified in the review protocol (appendix E). Of these, 18 were excluded as they did not meet the criteria. No studies were included for question 6b from both the original guideline and update search therefore a total of 0 included studies for question 6b. 4 new studies met the criteria for question 7b and were included with an additional 6 studies from the original guideline; therefore a total of 10 included studies for the update of question 7b.

A review flowchart is provided in appendix E, and the excluded studies (with reasons for exclusion) are shown in appendix F.

## 2.8.2 Methods

**Summary of review protocols**

- The population included:
  - for Q6b) adults and children with known underlying structural cardiac defects undergoing interventional procedures
  - for Q7b) children and adults undergoing interventional procedures (both dental and non-dental) irrespective of whether have an underlying cardiac condition.
- No subgroups (other than adults and children) were identified for this question.
- The intervention of interest was chlorhexidine prophylaxis (any concentration) compared against no chlorhexidine prophylaxis (including placebo).
- The topic experts outlined the following outcomes for this review question:
  - for Q6b) incidence/odds of developing IE in those receiving prophylaxis compared to those not receiving prophylaxis, incidence of adverse effects including anaphylaxis
  - for Q7b) bacteraemia levels/intensity at one or more timepoints following prophylaxis versus before prophylaxis, duration of bacteraemia following prophylaxis versus before, number/incidence/odds of having positive blood samples following prophylaxis versus before.
- The studies did not report data on all these outcomes and in some situations synonymous outcomes are presented.

GRADE methodology was used to assess the quality of evidence as follows:

**Risk of bias**

- As only RCTs were included, criteria suggested by the GRADE methodology (http://www.gradeworkinggroup.org/) were used for assessing risk of bias.

**Indirectness**

- Details from the PICOs in the review protocol(s) (see appendix C) were used to assess the directness of the included studies.

**Inconsistency**

- Given the variation in populations across studies (including the formulation and concentration of chlorhexidine subjects received as well as the variation in interventional procedures the subjects underwent), meta-analysis of the data was not appropriate for this question. The age of the subjects and time point at which the incidence of bacteraemia was assessed post-procedure also varied from study to study; in some studies it was unclear whether the same subjects were bacteraemic at different time points therefore pooling this data could have led to double counting of subjects and thereby affected the accuracy of the results.

**Imprecision**

- A routine search of the COMET (Core Outcome Measures in Effectiveness Trials) Initiative database was conducted to identify any relevant thresholds for defining the clinical minimal important difference (MIDs). No information was identified in the COMET database. Information about specific MIDs used to assess imprecision were also not available from the original guideline CG64. Therefore, the following thresholds were used, as per the GRADE working group recommendations: for continuous outcomes, the standard MID of 0.5 standard deviation change and for dichotomous outcomes, RRR or RRI of 25%: 0.75 or 1.25.

**Statistical analysis**

- Meta-analyses were not conducted due to the variation in population and outcome measures (as explained above) from study to study.
- Where appropriate, summary measures such as mean differences or odds ratios (with 95% confidence intervals) were calculated using Review Manager 5.

**Overall summary of evidence**

10 RCTs were included in this review 1 study was from the UK, 3 from the USA, 2 from Spain, 1 from South Africa, 1 from Turkey, 1 from Finland and 1 from Germnay. Sample size ranged from 22 to 106 subjects.

All studies included subjects undergoing some form of dental treatment such as molar extraction, placement of dental implants or intraligamental injection. 3 studies included adolescents and adults however a subgroup analyses by age was not presented. All other studies were performed in adults.

All studies used chlorhexidine as a mouth rinse however the formulation and concentrations varied with 6 studies using 0.2% chlorhexidine; 2 studies 0.12% chlorhexidine; one study 0.5% chlorhexidine; and the remaining study 1% chlorhexidine. Of the 10 RCTs, 6 compared a pre-procedural chlorhexidine rinse with some form of placebo. In the remaining 4 studies, the comparator was no prophylaxis. Bacteraemia was assessed at various time points following the dental procedure. 5 studies reported the incidence of bacteraemia at baseline but the definition of baseline ranged from before prophylaxis/ before procedure or after intubation and 3 did not. 1 study excluded subjects with positive blood cultures

preoperatively. The remaining study did not report incidence of bacteraemia before prophylaxis separately but combined this with the incidence at any of the blood draws taken.

For a summary of included studies please see table 17 (for the full evidence tables and full GRADE profiles please see appendices F and G).

**Table 20: Summary of included studies**

| Study reference (including study design) | Study population | Intervention & comparator | Outcomes reported |
|---|---|---|---|
| Maharaj, 2012 (RCT) | N=80, adult black patients ≥18 years attending the dental clinic for extraction of one tooth | 10ml 0.2% chlorhexidine rinse for 1 minute (rinsing repeated one minute later) given 1 hour prior to extraction vs no prophylaxis prior to extraction | - Incidence of bacteraemia |
| Pineiro, 2010 (RCT) | N=50, adults ≥18 years suitable for oral rehabilitation using osseointegrated implants | 10ml 0.2% chlorhexidine rinse for 1 minute given before surgery vs no prophylaxis prior to implant placement | - Incidence of bacteraemia |
| Duvall, 2013 (RCT) | N=20, adults ≥18 years presenting to the surgical centre, oral surgery clinic for third molar extractions | 15ml 0.12% chlorhexidine rinse for 1 minute given immediately before conscious sedation medication administration + placebo capsule* vs 15ml placebo rinse for 1 minute also given before conscious sedation medication administration + placebo capsule*<br><br>*placebo capsule for both groups given with a small amount of water 1 hour prior to procedure | - Bacteraemia levels/intensity<br>- Incidence of bacteraemia |
| Tuna, 2012 (RCT) | N=22, adults >18 years undergoing surgical removal of impacted mandibular third molar extraction | 15ml 0.2% chlorhexidine rinse for 1 minute before surgical procedure vs 0.9% NaCl (sterile saline) solution | - Incidence of bacteraemia |
| Brown, 1998 (RCT)<br><br>[included in CG64] | N=55, adolescents/adults aged 15 to 35 requiring removal of third molar which would require at least 8 sutures | 30 cubic centimetres 0.12% chlorhexidine rinse for 1 minute before extraction vs no treatment before extraction | - Incidence of bacteraemia |
| Jokinen, 1978 (RCT)<br><br>[included in CG64] | N=76, adolescents/adults aged 16 to 75 from various departments of the hospital for a cleaning of the mouth or because of acute symptoms in the teeth or periodontal tissues indicating dental extraction | Operative field isolation and disinfection with 0.5% chlorhexidine gluconate solution vs operative field isolation with sterile cotton rolls and saliva ejector | - Incidence of bacteraemia |

| Study reference (including study design) | Study population | Intervention & comparator | Outcomes reported |
|---|---|---|---|
| Lockhart, 1996<br><br>[included in CG64] | N=70, adults >18 years undergoing dental extractions | 10ml 0.2% chlorhexidine hydrochloride rinse for 30 seconds (rinsing repeated 1 minute later) given prior to extraction vs 10ml placebo rinse for 30 seconds (rinsing repeated 1 minute later) | - Incidence of bacteraemia |
| MacFarlane, 1984<br>(RCT)<br><br>[included in CG64] | N=40, adolescents and adults aged 16 to 70 years requiring extraction of a single premolar or first or second molar tooth (extractions confined to lower teeth in order to reduce variability) | 10ml 1% chlorhexidine rinse for 2 minutes before extraction vs 10ml normal saline | - Incidence of bacteraemia |
| Rahn, 1995<br>(RCT)<br><br>[included in CG64] | N=80, adults aged 22 to 77 undergoing dental treatment involving either intraligamental injection or molar extraction | 0.2% chlorhexidine solution for 2 minutes vs sterile water | - Incidence of bacteraemia |
| Tomas, 2007<br>(RCT)<br><br>[included in CG64] | N=106, adults with mental and behavioural disabilities undergoing dental extractions | 0.2% digluconate chlorhexidine solution for 30 seconds before dental manipulation vs no prophylaxis | - Incidence of bacteraemia |

1

## 2.8.31 Clinical evidence statements

### 2.8.3.12 0.12% chlorhexidine (grade table 160 and 161)

#### 3 Incidence of bacteraemia before and after prophylaxis

4 Very low quality evidence from two RCTs including 20 adults in the first and 55
5 adolescents/adults in the second was inconclusive in the incidence of bacteraemia (in at
6 least one of the four blood draws taken (including before prophylaxis) up to 10 minutes
7 following initiation of the mucogingival flap in the first study and 90 seconds after intraoral
8 suture removal in the second study) in subjects receiving chlorhexidine compared to
9 placebo/no prophylaxis before third molar extraction. Pre-treatment blood samples in the
10 second study were all negative.

#### 11 Duration of bacteraemia

12 No studies examining 0.12% chlorhexidine reported on this outcome.

#### 13 Bacteraemia levels/intensity before and after prophylaxis

14 Very low quality evidence from one RCT including 20 adults was inconclusive in the total
15 mean magnitude of bacteraemia (cfu/ml) in those receiving chlorhexidine prophylaxis
16 compared to those receiving placebo before third molar extractions. The same study found
17 that there may be a clinically important decrease in the magnitude of bacteraemia at blood
18 draw 4, no difference at blood draw 1 and inconclusive evidence at blood draw 2 and 3.

#### 19 Adverse events

20 No studies examining 0.12% chlorhexidine reported on this outcome.

### 2.8.3.21 0.2% chlorhexidine (grade table 162)

#### 22 Incidence of bacteraemia before and after prophylaxis

23 Six RCTs reported on incidence of bacteraemia at various time points. The overall finding
24 was inconsistent across studies; quality of the evidence ranged from moderate to very low. A
25 narrative summary of the findings is presented below; studies have been grouped by the
26 timing of outcomes using arbitrary thresholds. Where studies have examined more than one
27 time interval, the longest time point was used to decide which group the study should go into.

#### 28 Incidence of bacteraemia up to 15 minutes post procedure

29 Very low quality evidence from 4 RCTs including 80, 50, 22 and 80 adults respectively was
30 inconclusive in the incidence of bacteraemia (3 minutes following tooth extraction in the first
31 study, at both 30 seconds and 15 minutes following dental implant placement in the second
32 study, at both 1 minute and 15 minutes following extraction in the third study and upto 6
33 minutes post dental treatment (intraligamental injection or extraction of molar) in the fourth
34 study) in those receiving chlorhexidine compared to no prophylaxis/placebo. The incidence of
35 bacteraemia at before prophylaxis was not reported for either group in the first study. The
36 incidence of bacteraemia before the procedure was lower but not significantly lower in the
37 chlorhexidine group of the second study but it was unclear if this was incidence before
38 prophylaxis. In the third study, subjects with positive preoperative blood cultures were
39 excluded and in the fourth study, all samples were negative.

40 Moderate quality evidence from one other RCT including 70 subjects showed no clinically
41 important difference in the incidence of bacteraemia at 1 or 3 minutes postextraction in those
42 receiving chlorhexidine prophylaxis compared to those receiving a placebo rinse; this effect
43 estimate was precise. The incidence of bacteraemia before prophylaxis was not reported.

**Incidence of bacteraemia up to 1 hour post procedure**

Low quality evidence from the final RCT including 106 adults showed there may be no clinically important difference in the incidence of bacteraemia at 30 seconds postextraction and there may be a clinically important decrease at 1 hour postextraction in those receiving chlorhexidine compared to those receiving no prophylaxis. The incidence of bacteraemia at baseline before dental manipulation but after endotracheal intubation was higher in the chlorhexidine group however this was not a significant difference.

**Duration of bacteraemia**

No studies examining 0.2% chlorhexidine reported on duration of bacteraemia.

**Bacteraemia levels/intensity before and after prophylaxis**

No studies examining 0.2% chlorhexidine reported on duration of bacteraemia.

**Adverse events**

No studies examining 0.2% chlorhexidine reported on this outcome.

#### 2.8.3.3 0.5% chlorhexidine (grade table 163)

**Incidence of bacteraemia before and after prophylaxis**

Very low quality evidence from 1 RCT including 76 adolescents/adults showed that there may be a clinically important decrease in the incidence of bacteraemia at 30 to 60 seconds post extraction; however the uncertainty was high. The incidence of bacteraemia before prophylaxis was not reported for either group.

**Duration of bacteraemia**

No studies examining 0.5% chlorhexidine reported on this outcome.

**Bacteraemia levels/intensity before and after prophylaxis**

No studies examining 0.5% chlorhexidine reported on this outcome.

**Adverse events**

No studies examining 0.5% chlorhexidine reported on this outcome.

#### 2.8.3.4 1% chlorhexidine (grade table 164)

**Incidence of bacteraemia before and after prophylaxis**

Moderate quality evidence from 1 RCT including 40 adolescents/adults undergoing tooth extraction showed that there is a clinically important decrease in the incidence of bacteraemia at 30 seconds postextraction in those receiving chlorhexidine compared to normal saline placebo; this was a precise estimate. There were no positive blood cultures at before extraction (unclear if this is before prophylaxis) in either group.

**Duration of bacteraemia**

No studies examining 1% chlorhexidine reported on this outcome.

**Bacteraemia levels/intensity before and after prophylaxis**

No studies examining 1% chlorhexidine reported on this outcome.

**Adverse events**

1 No studies examining 1% chlorhexidine reported on this outcome.

### 2.8.42 Evidence to recommendations

| | Committee discussions |
|---|---|
| **Relative value of different outcomes** | For question 6b, the Committee discussed and agreed that the critical outcome for this review question was to establish whether there is a clear relationship between chlorhexidine prophylaxis and the incidence of IE in people undergoing interventional procedures who have pre-existing cardiac conditions. Therefore, the critical outcome is the measurement of such an association and the precision and certainty for these measurements reported in the included studies. In addition, the committee included adverse events as an outcome as this was an important factor for consideration if treatment with chlorhexidine was found to be clinically effective. In order for prophylaxis to be effective, a suitable regimen that gives a balance between side effects from prophylaxis and development of the disease would need to be considered.<br><br>For question 7b, the Committee discussed and agreed that the critical outcome for this review question was to establish whether there is a clear relationship between chlorhexidine prophylaxis and the the level and duration of bacteraemia in people undergoing interventional procedures regardless of whether they have pre-existing cardiac conditions. Bacteraemia, including the incidence, duration and intensity before and after prophylaxis were therefore considered to be the critical outcomes for the measurement of such association and furthermore, a surrogate outcome for IE as endocarditis usually follows bacteraemia. In addition, the committee included adverse events as an outcome. |
| **Quality of evidence** | The committee noted that no evidence was identified for Q6b which aimed to assess whether chlorhexidine prophylaxis reduces the incidence of IE when given before a defined interventional procedure. Furthermore, it was highlighted that oral chlorhexidine used as an oral rinse did not significantly reduce the level of bacteraemia following dental procedures.<br><br>The committee further discussed the evidence base and noted that:<br>• A power calculation was not reported in a number of studies<br>• A wide variation of chlorhexidine concentration was used across the studies<br>• The number of participants bacteraemic before prophylaxis was not reported in 4/10 studies and of some studies that did report this, it was unclear whether this was the number of participants bacteraemic before prophylaxis or just before the procedure<br>• The follow-up time points for post-procedure blood samples were very short (with most studies less than 60 min), making it difficult to establish the actual duration of bacteraemia<br>• The sample sizes of the included studies were small<br>• It was difficult to establish the association between chlorhexidine prophylaxis and bacteraemia because where multiple time points of blood samples were obtained, it was not clear whether the number positive for bacteraemia at different time points were from the same participants or not.<br>• All included studies gave chlorhexidine once to subjects under study – it was suggested that chlorhexidine is needed to be given over a longer period in order to be effective.<br>As with the antibiotic question, the committee noted that the assessment of imprecision using the GRADE default MIDs were not suitable for Q7b examining bacteraemia as the outcome given that clinical significance for bacteraemia, a surrogate outcome for IE, could not be defined due to uncertainty in the level that may be significant for the development of IE. |

| | Committee discussions |
|---|---|
| | Therefore, the committee are uncertain about the clinical significance of the evidence presented using GRADE methodology.<br><br>Overall, the Committee concluded that chlorhexidine prophylaxis did not significantly reduce the level of bacteraemia following dental procedures. The committee therefore concluded that the current recommendation indicating that oral chlorhexidine mouthwash should not be used for prophylaxis against IE should remain given that the evidence shows that it does not reduce the frequency of bacteraemia. |
| **Trade-off between benefits and harms** | Overall, the evidence suggested that oral chlorhexidine does not significantly reduce the level of bacteraema following dental procedures. The committee noted the lack of data on chlorhexidine prophylaxis to reduce incidence of IE and further noted that data on side effects from prophylaxis was lacking, however no major side effects are believed to exist. |
| **Trade-off between net health benefits and resource use** | Cost savings are available to the NHS by not administering an ineffective prophlyaxis. |
| **Other considerations** | There were no further issues highlighted by the committee. |

1

# 3 References

## 3.1 Overview of epidemiology

Bor DH, Woolhandler S, Nardin R et al. (2013) Infective endocarditis in the U.S., 1998-2009: a nationwide study. PLoS ONE [Electronic Resource] 8: e60033.

Correa de Sa DD, Tleyjeh IM, Anavekar NS et al. (2010) Epidemiological trends of infective endocarditis: a population-based study in Olmsted County, Minnesota.[Erratum appears in Mayo Clin Proc. 2010 Aug;85(8):772]. Mayo Clinic Proceedings 85: 422-6.

Dayer MJ, Jones S, Prendergast B et al. (2014) Incidence of infective endocarditis in England, 2000–13: a secular trend, interrupted time-series analysis. Lancet: DOI: http://dx.doi.org/10.1016/S0140-6736(14)62007-9

Fedeli U, Schievano E, Buonfrate D et al. (2011) Increasing incidence and mortality of infective endocarditis: a population-based study through a record-linkage system. BMC Infectious Diseases 11: 48.

Federspiel JJ, Stearns SC, Peppercorn AF et al. (2012) Increasing US rates of endocarditis with Staphylococcus aureus: 1999-2008. Archives of Internal Medicine 172: 363-5.

Lee CH, Tsai WC, Liu PY et al. (2007) Epidemiologic features of infective endocarditis in Taiwanese adults involving native valves. American Journal of Cardiology 100: 1282-5.

Pasquali SK, He X, Mohamad Z et al. (2012) Trends in endocarditis hospitalizations at US children's hospitals: impact of the 2007 American Heart Association Antibiotic Prophylaxis Guidelines. American Heart Journal 163: 894-9.

Ternhag A, Cederstrom A, Torner A et al. (2013) A nationwide cohort study of mortality risk and long-term prognosis in infective endocarditis in Sweden. PLoS ONE [Electronic Resource] 8: e67519.

## 3.2 Review question 1a and 1b

Alagna L, Park L, Nicholson B et al. (2014) Repeat endocarditis: analysis of risk factors based on the International collaboration of Endocarditis – Prospective Cohort Study. Clinical Microbiology and Infection. 20: 566-575.

Ammar W, El Aroussi W, El Mahy A et al. (2013) Case-Control study of potential culprit procedures for infective endocarditis in an Egyptian tertiary care centre. The Egyptian Heart Journal. 65, 153-157

Clemens JD, Horwitz RI, Jaffe CC, et al. (1982) A controlled evaluation of the risk of bacterial endocarditis in persons with mitral-valve prolapse. N Engl J Med 307: 776–81.

Hickey AJ, MacMahon SW, Wilcken DE, et al. (1985) Mitral valve prolapse and bacterial endocarditis: when is antibiotic prophylaxis necessary? American Heart Journal 109: 431–35.

Richet H, Casalta JP, Thuny F et al (2008). Development and assessment of a new early scoring system using non-specific clinical signs and biological results to identify children and adult patients with a high probability of infective endocarditis on admission. Journal of Antimicrobial Chemotherapy; 62:1434-1440.

Rushani D, Kaufman J, Ionescu-Ittu R. et al. (2013) Infective Endocarditis in Children with congenital heart disease. Cumulative incidence and predictors. Circulation. 128:1412-1419.

Strom BL, Abrutyn E, Berlin J et al (1998) Dental and cardiac risk factors for infective endocarditis: a population-based case-control study. Ann Int Med;129:761-9.

## 3.3 Review question 2

Aksoy O, Sexton D, Wang A et al (2007). Early surgery in patients with infective endocarditis: A propensity score analysis. Clinical Infectious diseases; 44:364-72.

Alagna L, Park L, Nicholson B et al (2014) Repeat endocarditis: analysis of risk factors based on the International collaboration of Endocarditis – Prospective Cohort Study. Clinical Microbiology and Infection. 20: 566-575.

Alonso-valle H, farinas-Alvarez C, Garcia-Palomo J. et al. (2010). Clinical course and predictors of death in prosthetic valve endocarditis over a 20-year period. The Journal of Thoracic and Cardiovascular Surgery. 139:4887-893

Bannay A, Hoen B, Duval X et al. (2011) The impact of valve surgery on short- and long-term mortality in left-sided infective endocarditis: do differences in methodological approaches explain previous conflicting results? European Heart Journal; 32, 2003-2015.

Da Costa M, Wollmann DR, Campos A et al. (2007) Risk index for death by infective endocarditis: a multivariate logistic model. Brazilian Journal of Cardiovascular Surgery. 22(2):192-200.

Delahaye F, Alla F, Beguinot I et al. (2007) In-hospital mortality of infective endocarditis: Prognostic factors and evaluation over an 8-year period. Scandinavian Journal of Infectious Diseases. 39:849-857.

Erbay AR, Erbay A, Canga A et al. (2010). Risk Factors for In-Hospital Mortality in Infective Endocarditis: Five years' Experience at a Tertiary Care Hospital in Turkey. Journal Heart Valve Disease; 19:2:216-224.

Fernandez Guerrero M, Goyenechea A, Verdejo C et al. (2007). Enterococcal endocarditis on native and prosthetic valves. A review of clinical and prognostic factors with emphasis on hospital-acquired infections as a major determinant of outcome. Medicine. 86:6:363-377

Fernandez Guerrero M, Alvarez B, Manzarbeitia F et al (2010) Left-sided Endocarditis caused by staphylococcus aureus. A comparison of clinical and prognostic factors of patients with native and prosthetic valve endocarditis. Infectious Diseases in Clinical Practice; 18:308-312.

Galvez-Acebal J, Rodriquez-Bano J, Martinez-Marcos F et al (2010). Prognostic factors in left-sided endocarditis: results from the Andalusian multicentre cohort. BMC Infectious diseases. 10:17.

Lin YT, Hsieh K, Chen, YS et al (2013) Infective endocarditis in children without underlying heart disease. Journal of Microbiology, Immunology and Infection. 46, 121-128.

Murakami T, Niwa K, Yoshinaga M et al (2012) Factors associated with surgery for active endocarditis in congenital heart disease. International Journal of Cardiology 157; 59-62.

Murdoch D, Corey G, Hoen B et al (2009). Clinical presentation, etiology, and outcome of Infective endocarditis in the 21st century. Archives of Internal Medicine; 169:5:463-473

San Roman J, Lopez J, Vilacosta I et al. (2007) Prognostic Stratification of patients with left sided endocarditis determined at admission. The American Journal of Medicine; 120, 369.e1-369.e7.

Smith MJ, So RR, Engel AM. (2007) Clinical predictors of mortality from infective endocarditis. International journal of Surgery. 5, 31-34.

Ternhag A, Cederstrom A, Torner A et al. (2013) A nationwide cohort study of mortality risk and long-term prognosis in infective endocarditis in Sweden. 8, 7, e67519.

Thuny F, Avierinos J, Tribouilloy C et al (2007) Impact of cerebrovascular complications on mortality and neurologic outcome during infective endocarditis: a prospective multicentre study. 28, 1155-1161.

Thuny F, Giorgi R, Habachi R et al. (2012) Excess mortality and morbidity in patients surviving infective endocarditis. Valvular and congenital heart disease. 164:94-101.

Tleyjeh IM, Anavekar N, Mirzoyev et al (2007) The impact of valve surgery on 6 month mortality in left-sided infective endocarditis. Circulation. 115:1721-1728.

Wang A, Athan E, Pappas PA et al. (2007) Contemporary clinical profile and outcome of prosthetic valve endocarditis 2926. JAMA: Journal of the American Medical Association 297: 1354-61

Wong CW, Porter G, Tisch J et al. (2009). Outcome and prognostic factors on 57 cases of infective endocarditis in a single centre. Journal of the New Zealand Medical Association. 122:1304:54-62.

Yoshinaga M, Niwa K, Niwa A et al. (2008) Risk factors for in-hospital mortality during infective endocarditis in patients with congenital heart disease. American Journal of Cardiology. 101:114-118.

## 3.4 Review question 3

Ammar W, El AW, El MA et al. (2013) Case - control study of potential culprit procedures for infective endocarditis in an Egyptian tertiary care center. Egyptian Heart Journal 65: 153-7.

Chen SJ, Liu CJ, Chao TF et al. (2013) Dental scaling and risk reduction in infective endocarditis: a nationwide population-based case-control study. The Canadian journal of cardiology 29: 429-33.

Duval X, Alla F, Hoen B et al. (2006) Estimated risk of endocarditis in adults with predisposing cardiac conditions undergoing dental procedures with or without antibiotic prophylaxis. Clinical Infectious Diseases 42: e102-e107.

Lacassin F, Hoen B, Leport C et al. (1995) Procedures associated with infective endocarditis in adults. A case control study. European Heart Journal 16: 1968-74.

Mohee AR, West R, Baig W et al. (2014) A case-control study: are urological procedures risk factors for the development of infective endocarditis? BJU international 114: 118-24.

Strom BL, Abrutyn E, Berlin JA et al. (2000) Risk factors for infective endocarditis: oral hygiene and nondental exposures. Circulation 102: 2842-8.

## 3.5 Review question 4

Assaf M, Yilmaz S, Kuru B et al. (2007) Effect of the diode laser on bacteremia associated with dental ultrasonic scaling: a clinical and microbiological study. Photomedicine and laser surgery 25: 250-6.

Barragan Casas JM, Hernandez Hernandez JM, Garcinuno Jimenez MA et al. (1999) Bacteremia cases by digestive system endoscopy. Revista Espanola de Enfermedades Digestivas 91: 111-6.

Cherry M, Daly CG, Mitchell D et al. (2007) Effect of rinsing with povidone-iodine on bacteraemia due to scaling: a randomized-controlled trial. Journal of clinical periodontology 34: 148-55.

Chun YJ, Yoon NR, Park JM et al. (2012) Prospective assessment of risk of bacteremia following colorectal stent placement. Digestive diseases and sciences 57: 1045-9.

Duval X, Delahaye F, Alla F et al. (2012) Temporal trends in infective endocarditis in the context of prophylaxis guideline modifications: Three successive population-based surveys. Journal of the American College of Cardiology 59: 1968-76.

El BS, Elassal G, Moustafa A et al. (2014) Bacteremia associated with bronchoscopy. Egyptian Journal of Chest Diseases and Tuberculosis 63: 701-4.

Ho H, Zuckerman MJ, Wassem C (1991) A prospective controlled study of the risk of bacteremia in emergency sclerotherapy of esophageal varices. Gastroenterology 101: 1642-8.

Kullman E, Borch K, Lindstrom E et al. (1992) Bacteremia following diagnostic and therapeutic ERCP. Gastrointestinal Endoscopy 38: 444-9.

Lockhart PB, Brennan MT, Sasser HC et al. (2008) Bacteremia associated with toothbrushing and dental extraction. Circulation 117: 3118-25.

London MT, Chapman BA, Faoagali JL et al. (1986) Colonoscopy and bacteraemia: an experience in 50 patients 952. New Zealand Medical Journal 99: 269-71.

Lucas VS, Omar J, Vieira A et al. (2002) The relationship between odontogenic bacteraemia and orthodontic treatment procedures. European Journal of Orthodontics 24: 301.

Melendez LJ, Chan KL, Cheung PK et al. (1991) Incidence of bacteremia in transesophageal echocardiography: a prospective study of 140 consecutive patients. Journal of the American College of Cardiology 18: 1650-4.

Min BH, Chang DK, Kim DU et al. (2008) Low frequency of bacteremia after an endoscopic resection for large colorectal tumors in spite of extensive submucosal exposure. Gastrointestinal endoscopy 68: 105-10.

Morozumi T, Kubota T, Abe D et al. (2010) Effects of irrigation with an antiseptic and oral administration of azithromycin on bacteremia caused by scaling and root planing. Journal of periodontology 81: 1555-63.

Pineiro A, Tomas I, Blanco J et al. (2010) Bacteraemia following dental implants' placement. Clinical oral implants research 21: 913-8.

Roberts GJ, Simmons NB, Longhurst P et al. (1998) Bacteraemia following local anaesthetic injections in children. British Dental Journal 185: 295-8.

Roberts GJ, Gardner P, Longhurst P et al. (2000) Intensity of bacteraemia associated with conservative dental procedures in children. British Dental Journal 188: 95-8.

Roberts GJ, Jaffray EC, Spratt DA et al. (2006) Duration, prevalence and intensity of bacteraemia after dental extractions in children. Heart 92: 1274-7.

Roudaut R, Lartigue MC, Texiermaugein J et al. (1993) Incidence of bacteremia or fever during transesophageal echocardiography - a prospective-study of 82 patients. European Heart Journal 14: 936-940.

Saayman AG, Findlay GP, Barnes RA et al. (2009) Bacteraemia following single-stage percutaneous dilatational tracheostomy. Intensive care medicine 35: 1970-3.

Sharif-Kashani B, Shahabi P, Behzadnia N et al. (2010) Incidence of fever and bacteriemia following flexible fiberoptic bronchoscopy: a prospective study. Acta medica Iranica 48: 385-8.

Shyu KG, Hwang JJ, Lin SC et al. (1992) Prospective study of blood culture during transesophageal echocardiography. American Heart Journal 124: 1541-4.

Sonbol H, Spratt D, Roberts GJ et al. (2009) Prevalence, intensity and identity of bacteraemia following conservative dental procedures in children. Oral microbiology and immunology 24: 177-82.

Tomas I, Alvarez M, Limeres J et al. (2007) Prevalence, duration and aetiology of bacteraemia following dental extractions. Oral Diseases 13: 56-62.

Tuna A, Delilbasi C, Arslan A et al. (2012) Do antibacterial mouthrinses affect bacteraemia in third molar surgery? A pilot study. Australian dental journal 57: 435-9.

Weickert U, Vetter S, Burkhardt U et al. (2006) Bacteremia after diagnostic conventional laparoscopy and minilaparoscopy: a prospective study in 100 patients. Journal of Clinical Gastroenterology 40: 701-4.

Yagci A, Uysal T, Demirsoy KK et al. (2013) Relationship between odontogenic bacteremia and orthodontic stripping. American journal of orthodontics and dentofacial orthopedics : official publication of the American Association of Orthodontists, its constituent societies, and the American Board of Orthodontics 144: 73-7.

Yildirim I, Okur E, Ciragil P et al. (2003) Bacteraemia during tonsillectomy. Journal of Laryngology & Otology 117: 619-23.

Yokoyama Y, Nishigaki E, Abe T et al. (2014) Randomized clinical trial of the effect of perioperative synbiotics versus no synbiotics on bacterial translocation after oesophagectomy. The British journal of surgery 101: 189-99.

Zhang W, Daly CG, Mitchell D et al. (2013) Incidence and magnitude of bacteraemia caused by flossing and by scaling and root planing. Journal of clinical periodontology 40: 41-52.

Zuccaro G Jr, Richter JE, Rice TW et al. (1998) Viridans streptococcal bacteremia after esophageal stricture dilation. Gastrointestinal Endoscopy 48: 568-73.

## 3.6 Review question 5

Bhanji S, Williams B, Sheller B, et al. (2002) Transient bacteremia induced by toothbrushing: a comparison of the Sonicare toothbrush with a conventional toothbrush. Pediatric Dentistry 24: 295–99.

Jones, DJ., Munro, CL., Grap, MJ., Kitten, T., Edmond, M. (2010). Oral care and bacteraemia risk in mechanically ventilated adults. Heart Lung. 39 (60): S57 –S65.

Lockhart, PB., Brennan, MT., Sasser, HC., Fox, PC., Paster, BJ., Bahrani-Mougeot, FK. (2008). Bacteremia associated with toothbrushing and dental extraction. Circulation. 117: 3118-3125.

Lucas V, Roberts GJ, Lucas V, Roberts GJ. Odontogenic bacteremia following tooth cleaning procedures in children 891. Pediatric dentistry 2000;22:96-100.

Lucas,VS., Gafan, G., Dewhurst, S., Roberts, GJ. (2008). Prevalence, intensity and nature of bacteraemia after toothbrushing. Journal of Dentistry. 36: 481-487.

Roberts GJ, Holzel HS, Sury MR, Simmons NA, Gardner P, Longhurst P. Dental bacteremia in children. SO: Pediatric cardiology 1997;18:24-7.

## 3.71 Review question 6a

2 Horstkotte D, Rosin H, Friedrichs W, Loogen F (1987) Contribution for choosing the optimal
3 prophylaxis of bacterial endocarditis. Eur Heart J. 8: 379–81.

4 Lacassin F, Hoen B, Leport C, Selton-Suty C, Delahaye F, Goulet V et al. Procedures
5 associated with infective endocarditis in adults. A case control study. European heart journal
6 1995;16:1968-74.

7 Van der Meer JT, van Wijk W, Thompson J, Vandenbroucke JP, Valkenburg HA, Michel MF.
8 Efficacy of antibiotic prophylaxis for prevention of native-valve endocarditis. Lancet
9 1992;339:135-9.

## 3.80 Review question 7a

11 Allan WR, Kumar A (1985) Prophylactic mezlocillin for transurethral prostatectomy. British
12 Journal of Urology 57: 46–49.

13 Bhattacharya S, Parkin DE, Reid TM et al. (1995) A prospective randomised study of the
14 effects of prophylactic antibiotics on the incidence of bacteraemia following hysteroscopic
15 surgery. European Journal of Obstetrics, Gynecology & Reproductive Biology 63: 37–40

16 Duvall, NB., Fisher, TD., Hensley, D. (2013). The comparative efficacy of 0.12%
17 chlorhexidine and amoxicillin to reduce the incidence and magnitude of bacteraemia during
18 third molar extractions. Oral surgery, oral medicine and oral pathology. 115 (6): 752-763

19 Diz DP, Tomas C, Limeres PJ, et al. (2006) Comparative efficacies of amoxicillin,
20 clindamycin, and moxifloxacin in prevention of bacteremia following dental extractions.
21 Antimicrobial Agents & Chemotherapy 50: 2996–3002.

22 Hall G, Hedstrom SA, Heimdahl A, Nord CE. Prophylactic administration of penicillins for
23 endocarditis does not reduce the incidence of postextraction bacteremia.[see comment].
24 Clinical Infectious Diseases 1993;17:188-94

25 Hall G, Heimdahl A, Nord CE. Effects of prophylactic administration of cefaclor on transient
26 bacteremia after dental extraction. European journal of clinical microbiology & infectious
27 diseases 1996; 15: 646–49

28 Harris A, Chan AC, Torres-Viera C et al. (1999) Meta-analysis of antibiotic prophylaxis in
29 endoscopic retrograde cholangiopancreatography (ERCP). Endoscopy 31: 718-24

30 Lockhart PB, Brennan MT, Kent ML, Norton HJ, Weinrib DA. Impact of amoxicillin
31 prophylaxis on the incidence, nature, and duration of bacteraemia in children after intubation
32 and dental procedures. Circulation 2004;109:2878-84

33 Lockhart, PB., Brennan, MT., Sasser, HC., Fox, PC., Paster, BJ., Bahrani-Mougeot, FK.
34 (2008). Bacteremia associated with toothbrushing and dental extraction. Circulation. 117:
35 3118-3125

36 Maharaj, B., Coovadia, Y., Vayej, AC. (2012). A comparative study of amoxicillin,
37 clindamycin and chlorhexidine in the prevention of post-extraction bacteraemia.
38 Cardiovascular journal of Africa. 23 (9): 491-494

39 Morozumi T, Kubota T, Abe D, Shimizu T. (2010) Effects of irrigation with an antiseptic and
40 oral administration of azithromycin on bacteraemia caused by scaling and root planning.
41 Journal of Periodontology 81 (11): 1555-1563

Qiang W, Jianchen W, MacDonald R et al. (2005) Antibiotic prophylaxis for transurethral prostatic resection in men with preoperative urine containing less than 100,000 bacteria per ml: a systematic review. [Review] [40 refs]. Journal of Urology 173: 1175-81

Roberts GJ, Radford P, Holt R. Prophylaxis of dental bacteraemia with oral amoxycillin in children. British Dental Journal 1987;162:179-82.

Rolando N, Gimson A, Philpott-Howard J et al. (1993) Infectious sequelae after endoscopic sclerotherapy of oesophageal varices: role of antibiotic prophylaxis. Journal of Hepatology 18: 290-4

Sanchez-Carrion, S., Prim, MP., De Diego, JI., Sastre, N., Pena-Garcia, P. (2006). Utility of prophylactic antibiotics in pediatric adenoidectomy. International journal of pediatric otorhinolaryngology. 70 (7): 1275 -1281

Selby WS, Norton ID, Pokorny CS et al. (1994) Bacteremia and bacterascites after endoscopic sclerotherapy for bleeding esophageal varices and prevention by intravenous cefotaxime: a randomized trial. Gastrointestinal Endoscopy 40: 680-4

Shanson DC, Akash S, Harris M, Tadayon M. Erythromycin stearate, 1.5 g, for the oral prophylaxis of streptococcal bacteraemia in patients undergoing dental extraction: efficacy and tolerance. Journal of Antimicrobial Chemotherapy 1985;15:83-90

Wahlmann U, Al Nawas B, Jutte M, Wagner W. Clinical and microbiological efficacy of single dose cefuroxime prophylaxis for dental surgical procedures. International Journal of Antimicrobial Agents 1999;12:253-6

## 3.9 Review question 7b

Brown AR, Papasian CJ, Shultz P, et al (1998) Bacteremia and intraoral suture removal: can an antimicrobial rinse help? Journal of the American Dental Association 129: 1455–61.

Duvall, NB., Fisher, TD., Hensley, D. (2013). The comparative efficacy of 0.12% chlorhexidine and amoxicillin to reduce the incidence and magnitude of bacteraemia during third molar extractions. Oral surgery, oral medicine and oral pathology. 115 (6): 752-763.

Jokinen MA. Prevention of postextraction bacteremia by local prophylaxis. International Journal of Oral Surgery 1978;7:450-2.

Lockhart PB. An analysis of bacteremias during dental extractions. A double-blind, placebo-controlled study of chlorhexidine. Archives of Internal Medicine 1996;156:513-20.

MacFarlane TW, Ferguson MM, Mulgrew CJ. Post-extraction bacteremia : role of antiseptics and antibiotics. Br Dent J 1984;156:179-81.

Maharaj, B., Coovadia, Y., Vayej, AC. (2012). A comparative study of amoxicillin, clindamycin and chlorhexidine in the prevention of post-extraction bacteraemia. Cardiovascular journal of Africa. 23 (9): 491-494.

Pineiro, A., Tomas, I., Blanco, J., Alvarez, M. (2010). Bacteraemia following dental implants' placement. Clinical oral implants research. 21: 913-918.

Rahn R, Schneider S, Diehl O, Schafer V, Shah PM. Preventing post-treatment bacteremia: comparing topical povidone-iodine and chlorhexidine.[see comment]. Journal of the American Dental Association 1995;126:1145-9.

Tomas I, Alvarez M, Limeres J, Tomas M, Medina J, Otero JL et al. Effect of a chlorhexidine mouthwash on the risk of postextraction bacteremia. Infection Control & Hospital Epidemiology 2007;28:577-82.

1 Tuna, A., Delilbasi, C., Arslan, A., Gurol, Y., Tekkanat, ZT. (2012). Do antibacterial
2 mouthrinses affect bacteraemia in third molar surgery? A pilot study. Australian dental
3 journal. 57: 435-439.

# 41 Glossary and abbreviations

2 Please refer to the NICE glossary.

# 1 Appendices

# 2 Appendix A: Standing Committee 3 members and NICE teams

## A.1 4 Core members

| Name | Role |
|---|---|
| Damien Longson (Chair) | Consultant Liaison Psychiatrist, Manchester Mental Health and Social Care Trust |
| Catherine Briggs | GP Principal, Bracondale Medical Centre, Stockport |
| John Cape | Director of Psychological Therapies Programme, University College London |
| Alun Davies | Professor of Vascular Surgery and Honorary Consultant Surgeon, Charing Cross & St Mary's Hospital & Imperial College NHS Trust |
| Alison Eastwood | Senior Research Fellow, Centre for Reviews and Dissemination, University of York |
| Sarah Fishburn | Lay Member |
| Jim Gray | Consultant Medical Microbiologist, The Birmingham Children's Hospital NHS Foundation Trust |
| Kath Nuttall | Director, Lancashire & South Cumbria Cancer Network (- April 2013) |
| Tilly Pillay | Consultant Neonatologist, Staffordshire, Shropshire and Black Country Newborn Network, Royal Wolverhampton Hospitals Trust |
| Nick Screaton | Radiologist, Papworth Hospital NHS Foundation Trust |
| Lindsay Smith | Principal in General Medical Practice, Somerset |
| Philippa Williams | Lay Member |
| Sophie Wilne | Paediatric Oncologist, Nottingham Children's Hospital |

## A.2 5 Topic expert Committee members

| Name | Role |
|---|---|
| Richard Balmer | Paediatric Dentist, University of Leeds |
| Mark Dayer (Non-voting expert witness) | Consultant Cardiologist, Taunton & Somerset NHS Trust |
| Valentina Gallo | Epidemiologist, University of London |
| Alison Loescher | Dentist, University of Sheffield |
| Suzannah Power | Lay Member |
| Craig Ramsay (Non-voting expert witness) | Professor of Healthcare Assessment, University of Aberdeen |
| Jon Sandoe | Consultant Microbiologist, Leeds Teaching Hospital NHS Trust |
| Richard Watkin | Consultant Cardiologist, Good Hope Hosptial, Birmingham |

## A.3 6 NICE project team

| Name | Role |
|---|---|
| Catharine Baden-Daintree | Editor |
| Mark Baker | Clinical Adviser |
| Christine Carson | Guideline Lead |

| | |
|---|---|
| Joy Carvill | Guideline Co-ordinator |
| Jessica Fielding | Public Involvement Adviser |
| Bhash Naidoo | Technical Lead (Health Economics) |
| Beth Shaw | Technical Lead |
| Louise Shires | Guideline Commissioning Manager |

## A.41 Clinical guidelines update team

| Name | Role |
|---|---|
| Phil Alderson | Clinical Adviser |
| Emma Banks | Co-ordinator |
| Paul Crosland | Health Economist |
| Nicole Elliott | Associate Director |
| Sarah Glover | Information Specialist |
| Cheryl Hookway | Technical Analyst |
| Susannah Moon | Programme Manager |
| Rebecca Parsons | Project Manager |
| Nitara Prasannan | Technical Analyst |
| Charlotte Purves | Administrator |
| Toni Tan | Technical Adviser |
| Allan Wailoo | Professor of Health Economics and Director of NICE Decision Support Unit, University of Sheffield |

2

3

# Appendix B: Declarations of interest

| Standing Committee | Interest Declared | Type of Interest | Decision |
|---|---|---|---|
| Damien Longson | Family member employee of NICE. | Personal family non-specific | Declare and participate |
| Damien Longson | Director of Research & Innovation, Manchester Mental Health & Social Care NHS Trust. | Personal non-specific financial | Declare and participate |
| Catherine Briggs | Husband is a consultant anaesthetist at the University Hospital of South Manchester. | Personal family non-specific | Declare and participate |
| Catherine Briggs | Member of the Royal College of Surgeons, the Royal College of General Practitioners, the Faculty of Sexual and Reproductive Health and the BMA. | Personal non-specific financial | Declare and participate |
| John Cape | Trustee of the Anna Freud Centre, a child and family mental health charity which applies for and receives grants from the department of health and the national institute for health research. | Personal non-specific non-financial | Declare and participate |
| John Cape | Member of British Psychological Society & British Association for Behaviour & Cognitive Psychotherapists who seek to influence policy towards psychology & psychological therapies. | Personal non-specific non-financial | Declare and participate |
| John Cape | Clinical Services Lead half-day a week to Big Health, a digital health company that has one commercial product; an online CBT self-help programme for insomnia with online support | Personal non-specific financial | Declare and participate |
| Alun Davies | Research grant funding – commercial: Vascular Insights; | Personal non-specific financial | Declare and participate |

| Standing Committee | Interest Declared | Type of Interest | Decision |
|---|---|---|---|
| | Acergy Ltd; Firstkind; URGO laboratoire; Sapheon Inc (terminated 2013). All administered by Imperial College London as Sponsor and Professor Davies as CI. | | |
| Alun Davies | Research grant funding – non-commercial:<br>National Institute for Health Research, British Heart Foundation, Royal College of Surgeons, Circulation Foundation, European Venous Forum. | Personal non-specific financial | Declare and participate |
| Alun Davies | Non-commercial:<br>Attendance at numerous national & international meetings as an invited guest to lecture where the organising groups receive funding from numerous sources including device and pharmaceutical manufacturers. Organising groups pay expenses and occasionally honoraria - the exact source of funding is often not known. | Personal non-specific financial | Declare and participate |
| Alison Eastwood | Member of an independent academic team at Centre for Review & Dissemination, University of York commissioned by NICE through NIHR to undertake technology assessment reviews. | Non-personal non-specific financial | Declare and participate |
| Sarah Fishburn | Organises workshops for physiotherapists treating pelvic girdle pain. Paid for this work. | Personal non-specific financial | Declare and participate |
| Sarah Fishburn | Receives payment and expenses from the Nursing and Midwifery Council as a lay panellist of the Fitness | Personal non-specific financial | Declare and participate |

| Standing Committee | Interest Declared | Type of Interest | Decision |
|---|---|---|---|
| | to Practise Investigating Committee. | | |
| Sarah Fishburn | Lay reviewed with the Local Supervising Authority auditing supervision of midwives - receives payment and expenses for this work. | Personal non-specific financial | Declare and participate |
| Sarah Fishburn | Lay reviewer for the National Institute for Health Research; has reviewed a number of research proposals being considered for funding. Paid for carrying out these reviews. | Personal non-specific financial | Declare and participate |
| Sarah Fishburn | Chair of the Pelvic Partnership, a support group for women with pregnancy-related pelvic girdle pain. This is a voluntary position. | Personal non-specific financial | Declare and participate |
| Sarah Fishburn | Trained as a chartered physiotherapist and qualified in 1988 but have not been in clinical practice since 1997. Remains a non-practicing member of the Chartered Society of Physiotherapy. | Personal non-specific financial | Declare and participate |
| Sarah Fishburn | Appointed by Mott MacDonald to carry out reviews as a lay reviewer on behalf to the Nursing and Midwifery Council of Local Supervising Authorities and Universities providing courses for nurses and midwives. This is paid work. | Personal non-specific financial | Declare and participate |
| Jim Gray | Deputy Editor, Journal of Hospital Infection, funded by the Healthcare Infection Society (HIS pay the hospital for my time) | Personal financial non-specific | Declare and participate |
| Jim Gray | Co-investigator in four major trials (3 HTA-funded; 1 British Council funded. Two trials are about antibiotic prophylaxis | Non-personal financial non-specific | Declare and participate |

| Standing Committee | Interest Declared | Type of Interest | Decision |
|---|---|---|---|
| | on obstetrics and gynaecology to prevent pelvic infections, one is comparing different suture materials and the fourth is a diagnostic test accuracy study for use in woman in labour). | | |
| Jim Gray | Associate Editor, International Journal of Antimicrobial Agents. | Non-personal financial non-specific | Declare and participate |
| Jim Gray | Associate Editor Journal of Pediatric Infectious Diseases. | Non-personal financial non-specific | Declare and participate |
| Jim Gray | Expert Advisor, British National Formulary for Children. | Non-personal financial non-specific | Declare and participate |
| Jim Gray | My Department is in receipt of an Educational Grant from Pfizer Ltd to develop improved diagnosis of invasive fungal infections in immunocompromised children | Non-personal financial non-specific | Declare and participate |
| Kath Nuttall | None | | No action |
| Tilly Pillay | None | | No action |
| Nick Screaton | Attended Thorax meeting – travel expenses paid. | Non-specific personal financial | Declare and participate |
| Nick Screaton | Clinical Commissioning Group stakeholder member | Non-specific personal non-financial | Declare and participate |
| Nick Screaton | Senior Editor British Journal of Radiology | Non-specific personal non-financial | Declare and participate |
| Nick Screaton | Advisory Editor Clinical Radiology | Non-specific personal non-financial | Declare and participate |
| Nick Screaton | Chair East of England British Institute of Radiology | Non-specific personal non-financial | Declare and participate |
| Nick Screaton | Director – Cambridge Clinical Imaging LTD | Non-specific personal financial | Declare and participate |
| Nick Screaton | British Thoracic Society Bronchiectasis Guidelines Group | Non-specific personal non-financial | Declare and participate |
| Nick Screaton | Specialised Imaging Clinical Commissioning Group stakeholder member | Non-specific personal non-financial | Declare and participate |
| Lindsay Smith | None | | Declare and participate |
| Philippa Williams | None | | Declare and |

| Standing Committee | Interest Declared | Type of Interest | Decision |
|---|---|---|---|
| | | | participate |
| Sophie Wilne | Recipient of NHS Innovation Challenge Award for clinical awareness campaign to reduce delays in diagnosis of brain tumours in children & young adults. Award will be used to develop the campaign. | Personal non-specific non-financial | Declare and participate |
| Sophie Wilne | Co-investigator for RFPB grant to undertake systematic reviews in childhood brain tumours. | Personal non-specific non-financial | Declare and participate |
| Sophie Wilne | Co-investigator for grant awards from charity to evaluate impact of brain tumour awareness campaign. | Personal non-specific non-financial | Declare and participate |
| Sophie Wilne | Funding for travel and accommodation from Novartis to attend a conference on the management of tuberous sclerosis | Personal non-specific financial | Declare and participate |
| **Topic Expert** | **Interest declared** | **Type of interest** | **Decision** |
| Richard Balmer | Co-author: Hollis A, Willcoxon F, Smith A, Balmer R. An investigation into dental anxiety amongst paediatric cardiology patients. International Journal of Paediatric Dentistry. Article first published online | Specific personal non-financial | Declare and participate |
| Richard Balmer | Committee member (representing British Society Paediatric Dentistry) on specialist advisory committee for paediatric dentistry. | Specific personal non-financial | Declare and participate |
| Mark Dayer (non-voting expert) | Fees and expenses paid as a member of an advisory board to RESMED (developers, manufacturers and distributors of medical equipment for sleep-disordered breathing and other respiratory disorders). | Non-specific personal financial | Declare and participate |

| Standing Committee | Interest Declared | Type of Interest | Decision |
|---|---|---|---|
| Mark Dayer (non-voting expert) | Fees paid by Pfizer/Bristol Myers Squibb, for presentations on the diagnosis and management of atrial fibrillation. | Non-specific personal financial | Declare and participate |
| Mark Dayer (non-voting expert) | Fees paid by Boehringer-Ingelheim, for presentations on the diagnosis and management of atrial fibrillation. | Non-specific personal financial | Declare and participate |
| Mark Dayer (non-voting expert) | Fee paid by Roche, for presentations on the diagnosis and management of heart failure. | Non-specific personal financial | Declare and participate |
| Mark Dayer (non-voting expert) | Expenses paid by Sorin for educational support to attend “New Horizons in Heart Failure” conference in London. | Non-specific personal financial | Declare and participate |
| Mark Dayer (non-voting expert) | Commercial trial sponsored by Novartis (PARAGON: heart failure) undertaken by department | Non-specific non-personal financial | Declare and participate |
| Mark Dayer (non-voting expert) | Commercial trial sponsored by Novartis (CANTOS: coronary artery disease) undertaken by department | Non-specific non-personal financial | Declare and participate |
| Mark Dayer (non-voting expert) | Commercial trial sponsored by Boehringer-Ingelheim (GLORIA AF: atrial fibrillation) undertaken by department | Non-specific non-personal financial | Declare and participate |
| Mark Dayer (non-voting expert) | Commercial trial sponsored by Bristol Myers Squibb (AEGEAN: atrial fibrillation) undertaken by department | Non-specific non-personal financial | Declare and participate |
| Mark Dayer (non-voting expert) | Commercial trial sponsored by Biotronik (MATRIX: device registry) undertaken by department | Non-specific non-personal financial | Declare and participate |

| Standing Committee | Interest Declared | Type of Interest | Decision |
|---|---|---|---|
| | | | |
| Mark Dayer (non-voting expert) | Commercial trial sponsored by Astra Zeneca (TIGRIS: coronary artery disease) undertaken by department | Non-specific non-personal financial | Declare and participate |
| Mark Dayer (non-voting expert) | Lead author of a publication in The Lancet that has in part led to the review of the PIE update. | Specific personal non-financial | Declare and leave prior to the recommendations being made (non-voting expert) |
| Suzannah Power | None | | Declare and participate |
| Craig Ramsay (non-voting expert) | None | | Declare and leave (non-voting expert) |
| Jon Sandoe | Registration for 24th European Congress of Clinical Microbiology and Infectious Diseases in Barcelona provided by Abbott | Specific personal financial | Declare and participate |
| Jon Sandoe | Accommodation/travel/ subsistence for 24th European Congress of Clinical Microbiology and Infectious Diseases in Barcelona funded by Eumedica | Specific personal financial | Declare and participate |
| Jon Sandoe | Honoraria paid by Astellas to a Leeds Charitable Trust Account for lecturing on the 7 point summary and implementation of AMR (antimicrobial resistance) Strategy | Non-specific non-personal financial | Declare and participate |
| Jon Sandoe | Advisor board: Cubicin (medication used to treat serious bacterial infections) | Specific personal Non-financial | Declare and participate |
| Jon Sandoe | Chairman of the British Society for Antimicrobial Chemotherapy endocarditis working party. | Non-specific personal non-financial | Declare and participate |
| Jon Sandoe | Member of a British Heart Valve Society valve disease working party | Non-specific personal non-financial | Declare and participate |
| Richard Watkin | Expenses paid to attend Medtronic sponsored EURO PCR | Non-specific personal financial | Declare and participate |

| Standing Committee | Interest Declared | Type of Interest | Decision |
|---|---|---|---|
| | meeting (technological advances in complex cardiovascular interventions) | | |
| Richard Watkin | Expenses paid to attend 2015 Medtronic sponsored BCIS advanced coronary intervention meeting | Personal financial non-specific | Declare and participate |
| Valentina Gallo | None | | Declare and participate |
| Alison Loescher | None | | Declare and participate |

1

# 1 Appendix C: Review protocol

## C.1 2 Review questions 1a, 1b and 2

| | Details |
|---|---|
| **Review question 1a/1b/2** | Q1a) What pre-existing cardiac conditions, in adults and children increase the risk of developing infective endocarditis (IE)?<br>Q1b) What pre-existing cardiac conditions are not associated with increased risk of developing IE?<br>Q2) Which pre-existing cardiac conditions are associated with relatively poorer outcomes from IE? |
| **Background/Objectives** | Patients with certain cardiac conditions are known to be at risk of developing IE. Guidelines and discussion on prophylaxis against IE start from the principle that it is possible to classify those with underlying cardiac conditions into those who are at increased risk and those whose risk is considered to be the same as, or little greater than, the general population. We therefore ought to review which underlying cardiac conditions affect a person's risk of developing IE/outcome of IE because it will influence decisions made about offering prophylaxis. |
| **Original review questions (if relevant)** | Same as above |
| **Type of review question** | Clinical prediction and risk identification review |
| **Language** | English language only |
| **Study design** | Cohort studies (prospective/retrospective), case-control and cross sectional studies |
| **Status** | Published studies (full text only) since 2008 |
| **Population** | Adults and children with known underlying cardiac conditions<br>Adults and children who have previously had IE (irrespective of whether they have a known underlying cardiac condition)<br><br>*Subgroups: adults vs children (if data allows for this) |
| **Intervention** | For i.) above - prevalence of IE in those with underlying cardiac conditions<br>For ii.) above - prevalence of cardiac conditions in those with IE |
| **Comparator** | For i.) above - prevalence of IE in those without underlying cardiac conditions<br>For ii.) above - prevalence of cardiac conditions in those without IE |
| **Outcomes** | For all 3 review questions stated above:<br>*Relative risks/odds ratios<br><br>For Q2) poorer outcomes chosen by the TSM include:<br>1) mortality<br>2) cardiac surgery<br>3) stroke/systemic embolism<br>4) length of stay<br>5) recurrent attacks of IE<br>6) acute kidney injury |
| **Other criteria for inclusion / exclusion of studies** | For exclusion:<br>*Single case report and qualitative studies<br>*Case series<br>*People at increased risk of IE who do not have underlying cardiac conditions (such as intravenous drug users) |

| | Details |
|---|---|
| | *Non-infective and fungal causes of IE. The guideline defines IE as bacterial endocarditis (including the HACEK group bacteria).<br>*Rhythmic disorders |
| **Review strategies** | *A list of excluded studies will be provided following sifting of the database<br>*Data on all included studies will be extracted into evidence tables<br>*Where statistically possible, a meta-analytical approach will be used to give an overall summary effect<br>*For intervention question, all critical and important outcomes from evidence will be presented in GRADE profiles (where appropriate) and further summarized in evidence statements. For epidemiology question, narrative summary with indication of quality (using checklist from Developing NICE guidelines - the Manual2014) will be used to summarise the evidence, and then further summarized in evidence statements.<br>*Distinctions between relapse and recurrent IE to be made clear in the evidence tables<br>*The bacteria reported in the study to be specified in the evidence tables. |

## C.21 Review questions 3

| | Details |
|---|---|
| **Review question 3** | Q3) Which dental and other interventional procedures are associated with increased incidence of IE in those considered at risk of IE? |
| **Background/Objectives** | IE is a rare condition and therefore it is difficult to determine which interventional procedures may be associated with an increased incidence of IE in those with defined pre-existing cardiac conditions. It has been suggested that some interventional procedures can cause bacteraemia which in healthy people, eliminates naturally. However those with certain other conditions may be at risk of this bacteraemia leading to the development of IE. It is hence important to consider any evidence of significant postprocedure bacteraemia that may be contributing to the risk of developing IE. |
| **Original review questions (if relevant)** | Same as above |
| **Type of review question** | Clinical prediction and early identification review |
| **Language** | English language only |
| **Study design** | Cohort studies (prospective/retrospective), case-control and cross sectional studies |
| **Status** | Published studies (full text only) since 2008 |
| **Population** | i.) Adults and children undergoing interventional procedures (with underlying cardiac condition); dental, upper and lower gastrointestinal tract, genitourinary tract (this includes urological, gynaecological and obstetric procedures including childbirth), upper and lower respiratory tract (includes ear nose and throat and bronchoscopy procedures).<br>ii.) Adults and children who have previously had IE (with underlying cardiac condition)<br><br>*Subgroups: adults vs children (if data allows for this) |
| **Intervention** | For i.) above: prevalence of IE in those undergoing interventional |

| | Details |
|---|---|
| | procedures (one or more procedures)<br>For ii.) above: prevalence of interventional procedures in adults and children who had IE |
| **Comparator** | For i.) above: prevalence of IE in those not undergoing interventional procedures<br>For ii.) above: prevalence of interventional procedures in those without IE |
| **Outcomes** | *Relative risks/odds ratios |
| **Other criteria for inclusion / exclusion of studies** | Criteria for exclusion:<br>*Single case report and qualitative studies<br>*Case series<br>*People at increased risk of IE who do not have structural cardiac defects (such as intravenous drug users)<br>*Non-infective and fungal causes of IE will not be considered. The guideline defines IE as bacterial endocarditis (including the HACEK group bacteria).<br>*All other interventional procedures not listed above |
| **Review strategies** | *A list of excluded studies will be provided following sifting of the database<br>*Although an explicit timeframe between undergoing the procedure and onset of IE could not be defined, if reported in the study, the time period needs to be noted in the evidence tables<br>*Data on all included studies will be extracted into evidence tables<br>*Where statistically possible, a meta-analytical approach will be used to give an overall summary effect<br>*For intervention question, all critical and important outcomes from evidence will be presented in GRADE profiles (where appropriate) and further summarized in evidence statements. For epidemiology question, narrative summary with indication of quality (using checklist from Developing NICE guidelines - the Manual 2014) will be used to summarise the evidence, and then further summarized in evidence statements.<br>* The bacteria reported in the study to be specified in the evidence tables. |

## C.51 Review question 4 and 5

| | Details |
|---|---|
| **Review question 4/5** | Q4) What levels of bacteraemia are associated with interventional procedures, both pre and post-procedure (including consideration of what is considered significant bacteraemia)?<br>Q5) What levels of bacteraemia are associated with everyday activities (toothbrushing/chewing/urination/defecation)? |
| **Background/Objectives** | The basis for many of the decisions which have been made regarding which procedures merit antibiotic prophylaxis is the assumption that the bacteraemia that arises following interventional procedures is a key part of the causative process in the development of IE. The aim of this review is to identify what levels of bacteraemia are associated with interventional procedures (dental and non-dental) and everyday activities. |
| **Original review questions (if relevant)** | Same as above |
| **Type of review question** | Clinical prediction |

| | Details |
|---|---|
| **Language** | English language only |
| **Study design** | RCTs, cohort studies, case-control studies and cross-sectional studies |
| **Status** | Published studies (full text only) since 2008 |
| **Population** | Adults and children undergoing interventional procedures (both dental and non-dental)/everyday activities irrespective of whether they have an underlying cardiac condition |
| **Intervention** | Level/duration of bacteraemia after procedure or everyday activity, incidence/odds of having positive blood samples after procedure or activity |
| **Comparator** | Level/duration of bacteraemia at baseline/during procedure or activity, incidence/odds of having positive blood sample at baseline/during procedure or activity |
| **Outcomes** | *Bacteraemia levels/intensity/bacterial counts per unit volume at one or more timepoints following the procedure/everyday activity (definition of intensity may vary by study)<br>*Duration of bacteraemia following a procedure/everyday activity<br>*Number/incidence/odds of having positive blood samples before and after procedure/everyday activity<br>For all of the above, studies may report p values comparing before procedure/activity versus after procedure/activity. 95% CIs will be calculated if possible. |
| **Other criteria for inclusion / exclusion of studies** | Criteria for inclusion:<br>*Sequential blood sampling is needed to determine the duration of bacteraemia. You can quantify bacteria in a single blood sample. Therefore, to measure the duration of bacteraemia there must be sequential sampling and to quantify bacteraemia a test must be used that measures the number of bacteria (any test measuring numbers of bacteria can be included as there is no gold standard). |
| **Criteria for exclusion:** | *Single case report and qualitative studies<br>*Case series<br>*Bacteraemia means bacteria in the blood so measurement of bacteria in any other body fluid is not relevant for this question. |
| **Review strategies** | *A list of excluded studies will be provided following sifting of the database<br>*Data on all included studies will be extracted into evidence tables<br>*Where statistically possible, a meta-analytical approach will be used to give an overall summary effect<br>*For intervention question, all critical and important outcomes from evidence will be presented in GRADE profiles (where appropriate) and further summarized in evidence statements. For epidemiology question, narrative summary with indication of quality (using checklist from Developing NICE guidelines - the Manual 2014) will be used to summarise the evidence, and then further summarized in evidence statements<br>*Definitions/terminology used in the studies (bacteraemia vs sepsis vs inflammatory response) to be extracted as term bacteraemia may be used incorrectly.<br>*Level/intensity of bacteraemia and definition of significant bacteraemia may vary in studies - any variation will be noted in evidence tables.<br>*The method for measuring number and duration of bacteraemia (mean/median) should be extracted into the evidence tables. Also state if sequential or not. |

# C.6.1 Review question 6a and 7a

| | Details |
|---|---|
| **Review question 6a/7a** | Q6a) Does antibiotic prophylaxis in those at risk of developing IE reduce the incidence of IE when given before a defined Interventional Procedure?<br>Q7a) Does antibiotic prophylaxis given to those undergoing Interventional Procedures reduce the level and duration of bacteraemia? |
| **Background/Objectives** | Since 1955, antibiotic prophylaxis that aims to prevent endocarditis has been used in at-risk patients. The rationale for prophylaxis against IE is that endocarditis usually follows bacteraemia, certain interventional procedures cause bacteraemia with organisms that can cause endocarditis and these bacteria are usually sensitive to antibiotics; therefore, antibiotics should be given to patients with predisposing heart conditions before procedures that may cause bacteraemia. The aim of these 2 reviews is to assess whether antibiotic prophylaxis in those at risk of IE/undergoing interventional procedures reduces the risk of IE and the level and duration of bacteraemia. |
| **Original review questions (if relevant)** | Same as above |
| **Type of review question** | Intervention |
| **Language** | English language only |
| **Study design** | Systematic review of RCTs, RCTs, case-control, cohort studies |
| **Status** | Published studies (full text only) since 2008 |
| **Population** | For Q6a) adults and children with known underlying structural cardiac defects undergoing interventional procedures<br>For Q7a) adults and children undergoing interventional procedures (both dental and non-dental) irrespective of whether they have an underlying cardiac condition<br>Subgroups: adults vs children if data allows for this |
| **Intervention** | Antibiotic prophylaxis (all types) |
| **Comparator** | No antibiotic prophylaxis or placebo (if non-active placebo) |
| **Outcomes** | For Q6a) *Incidence/odds of developing IE in those receiving prophylaxis compared to those not receiving prophylaxis, incidence of adverse effects including anaphylaxis<br>For Q7a) *bacteraemia levels/intensity/bacterial counts per unit volume at one or more timepoints following prophylaxis versus before prophylaxis (definition of intensity may vary by study)<br>*Duration of bacteraemia following prophylaxis versus before<br>*Number/incidence/odds of having positive blood samples following prophylaxis versus before<br><br>For all of the above, studies may report p values comparing before prophylaxis versus after prophylaxis but where possible, 95% confidence intervals will be calculated |
| **Other criteria for inclusion / exclusion of studies** | Criteria for exclusion:<br>*Single case report and qualitative studies<br>*Case series<br>*People at increased risk of IE who do not have structural cardiac defects (such as intravenous drug users)<br>*Non-infective and fungal causes of IE will not be considered. The guideline defines IE as bacterial endocarditis (including the HACEK group bacteria). |
| **Review strategies** | *A list of excluded studies will be provided following sifting of the |

| | Details |
|---|---|
| | database<br>*Data on all included studies will be extracted into evidence tables<br>*Although a specific route of administration/timing of administration for antibiotics could not be specified, it was noted that any variation in studies (in particular, the number of doses and whether prophylaxis continues after the interventional procedure) should be extracted into the evidence tables<br>*Where statistically possible, a meta-analytical approach will be used to give an overall summary effect<br>*All critical and important outcomes from evidence will be presented in GRADE profiles and further summarized in evidence statements |

## C.71 Review question 6b and 7b

| | Details |
|---|---|
| **Review question 6b/7b** | Q6b) Does oral chlorhexidine prophylaxis in those at risk of developing IE reduce the risk of developing IE when given before a defined Interventional Procedure?<br>Q7b) Does oral chlorhexidine prophylaxis given to those undergoing Interventional Procedures reduce the level and duration of bacteraemia? |
| **Background/Objectives** | Chlorhexidine is often used as an active ingredient in mouthwash designed to reduce dental plaque and oral bacteria. The aim of this review is to assess whether oral chlorhexidine prophylaxis in those at risk of IE reduces the risk of developing IE and the level and duration of bacteraemia when given before an interventional procedure. |
| **Original review questions (if relevant)** | Same as above |
| **Type of review question** | Intervention |
| **Language** | English language only |
| **Study design** | Systematic review of RCTs, RCTs, case-control and cohort studies |
| **Status** | Published studies (full text only) since 2008 |
| **Population** | For Q6b) adults and children with known underlying structural cardiac defects undergoing interventional procedures<br>For Q7b) adults and children undergoing interventional procedures (both dental and non-dental) irrespective of whether they have an underlying cardiac condition<br>Subgroups: adults vs children if data allows for this |
| **Intervention** | Chlorhexidine prophylaxis (any concentration) |
| **Comparator** | No chlorhexidine prophylaxis or placebo (if non-active placebo) |
| **Outcomes** | For Q6b) *Incidence/odds of developing IE in those receiving prophylaxis compared to those not receiving prophylaxis, incidence of adverse effects including anaphylaxis<br>For Q7b) *bacteraemia levels/intensity at one or more timepoints following prophylaxis versus before prophylaxis (definition of intensity may vary by study)<br>*Duration of bacteraemia following prophylaxis versus before<br>*Number/incidence/odds of having positive blood samples following prophylaxis versus before<br><br>For all of the above, studies may report p values comparing before prophylaxis versus after prophylaxis |
| **Other criteria for inclusion / exclusion of** | Criteria for exclusion:<br>*Single case report and qualitative studies |

| | Details |
|---|---|
| **studies** | *Case series<br>*People at increased risk of IE who do not have structural cardiac conditions (such as intravenous drug users)<br>*Non-infective and fungal causes of IE will not be considered. The guideline defines IE as bacterial endocarditis (including the HACEK group bacteria). |
| **Review strategies** | *A list of excluded studies will be provided following sifting of the database<br>*Data on all included studies will be extracted into evidence tables<br>*Concentration of chlorhexidine in formulation needs to be documented in evidence tables as well as any other ingredients.<br>*Where statistically possible, a meta-analytical approach will be used to give an overall summary effect<br>*All critical and important outcomes from evidence will be presented in GRADE profiles and further summarized in evidence statements |

1

# Appendix D: Search strategy

Databases that were searched, together with the number of articles retrieved from each database for each question are shown in tables 20, 22, 24, 26, 28 and 30. The search strategy for each question is shown in table 21, 23, 25, 27, 29 and 31. The same strategy was translated for the other databases listed.

## D.1 Overview of epidemiology

**Table 21: Clinical search summary (overview of epidemiology)**

| Database | Date searched | Number retrieved |
|---|---|---|
| MEDLINE (Ovid) | 12/02/2015 | 2845 |

**Table 22: Clinical search terms (overview of epidemiology)**

| Line number | Search term | Number retrieved |
|---|---|---|
| | MEDLINE (Ovid) | |
| 1 | exp Endocarditis/ (23944) | 23944 |
| 2 | endocardit$.tw. (25238) | 25238 |
| 3 | 1 or 2 (30535) | 30535 |
| 4 | incidence/ (180952) | 180952 |
| 5 | incidence*.tw. (498625) | 498625 |
| 6 | epidemiology/ (11592) | 11592 |
| 7 | pharmacoepidemiology/ (1285) | 1285 |
| 8 | epidemiol*.tw. (250400) | 250400 |
| 9 | epidemiology.fs. (1224547) | 1224547 |
| 10 | Epidemiologic Studies/ (6084) | 6084 |
| 11 | prevalence/ (197503) | 197503 |
| 12 | prevalenc*.tw. (367263) | 367263 |
| 13 | trends.fs. (291107) | 291107 |
| 14 | trend*.tw. (229895) | 229895 |
| 15 | or/4-14 (2195239) | 2195239 |
| 16 | 3 and 15 (4638) | 4638 |
| 17 | animals/ not humans/ (3890800) | 3890800 |
| 18 | 16 not 17 (4525) | 4525 |
| 19 | limit 18 to english language (3637) | 3637 |
| 20 | limit 19 to yr="1990 -Current" (2845) | 2845 |

## D.2 Review question 1 and 2

**Table 23: Clinical search summary (review question 1 & 2)**

| Database | Date searched | Number retrieved |
|---|---|---|
| MEDLINE (Ovid) | 20/11/2014 | 2223 |
| MEDLINE IN PROCESS (Ovid) | 20/11/2014 | 124 |
| EMBASE (Ovid) | 20/11/2014 | 3204 |
| CDSR (Wiley) | 20/11/2014 | 4 |

| Database | Date searched | Number retrieved |
|---|---|---|
| Database of Abstracts of Reviews of Effects – DARE (Wiley) | 20/11/2014 | 77 |
| HTA database (Wiley) | 20/11/2014 | 6 |
| CENTRAL (Wiley) | 20/11/2014 | 1 |

1 **Table 24: Clinical search terms (review question 1 & 2)**

| Line number / Search term | Number retrieved |
|---|---|
| MEDLINE OVID<br>1 exp Endocarditis/ (24453)<br>2 endocardit$.tw. (25708)<br>3 1 or 2 (31159)<br>4 Observational Study as Topic/ (497)<br>5 Observational Study/ (6239)<br>6 Epidemiologic Studies/ (6267)<br>7 exp Case-Control Studies/ (710179)<br>8 exp Cohort Studies/ (1438148)<br>9 Cross-Sectional Studies/ (192723)<br>10 Comparative Study.pt. (1730486)<br>11 case control$.tw. (80639)<br>12 case series.tw. (35292)<br>13 (cohort adj (study or studies)).tw. (89735)<br>14 cohort analy$.tw. (3823)<br>15 (follow up adj (study or studies)).tw. (37500)<br>16 (observational adj (study or studies)).tw. (44307)<br>17 longitudinal.tw. (141448)<br>18 prospective.tw. (354362)<br>19 retrospective.tw. (271969)<br>20 cross sectional.tw. (166880)<br>21 or/4-20 (3436224)<br>22 Meta-Analysis.pt. (54493)<br>23 Meta-Analysis as Topic/ (14587)<br>24 Review.pt. (1963157)<br>25 exp Review Literature as Topic/ (8125)<br>26 (metaanaly$ or metanaly$ or (meta adj3 analy$)).tw. (64401)<br>27 (review$ or overview$).ti. (278689)<br>28 (systematic$ adj5 (review$ or overview$)).tw. (59139)<br>29 ((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw. (4589)<br>30 ((studies or trial$) adj2 (review$ or overview$)).tw. (26231)<br>31 (integrat$ adj3 (research or review$ or literature)).tw. (5738)<br>32 (pool$ adj2 (analy$ or data)).tw. (15001)<br>33 (handsearch$ or (hand adj3 search$)).tw. (5666)<br>34 (manual$ adj3 search$).tw. (3290)<br>35 or/22-34 (2129806)<br>36 animals/ not humans/ (3998169)<br>37 35 not 36 (1991468)<br>38 Randomized Controlled Trial.pt. (399610)<br>39 Controlled Clinical Trial.pt. (90639)<br>40 Clinical Trial.pt. (500856) | Please see number in the bracket at the end of each line. |

| Line number / Search term | Number retrieved |
|---|---|
| 41 exp Clinical Trials as Topic/ (294593) | |
| 42 Placebos/ (34004) | |
| 43 Random Allocation/ (84070) | |
| 44 Double-Blind Method/ (132421) | |
| 45 Single-Blind Method/ (20589) | |
| 46 Cross-Over Studies/ (36201) | |
| 47 ((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw. (775730) | |
| 48 (random$ adj3 allocat$).tw. (21548) | |
| 49 placebo$.tw. (159726) | |
| 50 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (129984) | |
| 51 (crossover$ or (cross adj over$)).tw. (58906) | |
| 52 or/38-51 (1442998) | |
| 53 animals/ not humans/ (3998169) | |
| 54 52 not 53 (1345397) | |
| 55 21 or 37 or 54 (5841865) | |
| 56 3 and 55 (10268) | |
| 57 animals/ not humans/ (3998169) | |
| 58 56 not 57 (10049) | |
| 59 limit 58 to english language (7904) | |
| 60 limit 59 to ed=20070529-20141120 (2223) | |
| | |
| Ovid MEDLINE(R) | |
| 1 exp Endocarditis/ (0) | |
| 2 endocardit$.tw. (1431) | |
| 3 1 or 2 (1431) | |
| 4 Observational Study as Topic/ (0) | |
| 5 Observational Study/ (9) | |
| 6 Epidemiologic Studies/ (0) | |
| 7 exp Case-Control Studies/ (3) | |
| 8 exp Cohort Studies/ (6) | |
| 9 Cross-Sectional Studies/ (0) | |
| 10 Comparative Study.pt. (173) | |
| 11 case control$.tw. (6943) | |
| 12 case series.tw. (4660) | |
| 13 (cohort adj (study or studies)).tw. (9916) | |
| 14 cohort analy$.tw. (385) | |
| 15 (follow up adj (study or studies)).tw. (1882) | |
| 16 (observational adj (study or studies)).tw. (6571) | |
| 17 longitudinal.tw. (14373) | |
| 18 prospective.tw. (27851) | |
| 19 retrospective.tw. (27666) | |
| 20 cross sectional.tw. (22291) | |
| 21 or/4-20 (101280) | |
| 22 Meta-Analysis.pt. (45) | |
| 23 Meta-Analysis as Topic/ (0) | |
| 24 Review.pt. (15815) | |
| 25 exp Review Literature as Topic/ (0) | |
| 26 (metaanaly$ or metanaly$ or (meta adj3 analy$)).tw. (9610) | |
| 27 (review$ or overview$).ti. (33748) | |
| 28 (systematic$ adj5 (review$ or overview$)).tw. (10832) | |

| Line number / Search term | | Number retrieved |
|---|---|---|
| 29 | ((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw. (674) | |
| 30 | ((studies or trial$) adj2 (review$ or overview$)).tw. (2965) | |
| 31 | (integrat$ adj3 (research or review$ or literature)).tw. (841) | |
| 32 | (pool$ adj2 (analy$ or data)).tw. (1597) | |
| 33 | (handsearch$ or (hand adj3 search$)).tw. (659) | |
| 34 | (manual$ adj3 search$).tw. (458) | |
| 35 | or/22-34 (59928) | |
| 36 | animals/ not humans/ (5) | |
| 37 | 35 not 36 (59928) | |
| 38 | Randomized Controlled Trial.pt. (390) | |
| 39 | Controlled Clinical Trial.pt. (28) | |
| 40 | Clinical Trial.pt. (390) | |
| 41 | exp Clinical Trials as Topic/ (5) | |
| 42 | Placebos/ (0) | |
| 43 | Random Allocation/ (0) | |
| 44 | Double-Blind Method/ (2) | |
| 45 | Single-Blind Method/ (0) | |
| 46 | Cross-Over Studies/ (0) | |
| 47 | ((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw. (64709) | |
| 48 | (random$ adj3 allocat$).tw. (2061) | |
| 49 | placebo$.tw. (9497) | |
| 50 | ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (7112) | |
| 51 | (crossover$ or (cross adj over$)).tw. (6246) | |
| 52 | or/38-51 (74224) | |
| 53 | animals/ not humans/ (5) | |
| 54 | 52 not 53 (74224) | |
| 55 | 21 or 37 or 54 (202085) | |
| 56 | 3 and 55 (261) | |
| 57 | animals/ not humans/ (5) | |
| 58 | 56 not 57 (261) | |
| 59 | limit 58 to english language (246) | |
| 60 | limit 59 to ed=20070529-20141120 (124) | |

# D.3 Review question 3

Note: review question 3 overlapped with both review question 1 and review question 4, hence, both searches for review question 1 and review question 4 have been sifted for review question 3 as well. For search strategies, please see review question 1 and review question 4.

# D.4 Review question 4

**Table 25: Clinical search summary (review question 4)**

| Database | Date searched | Number retrieved |
|---|---|---|
| MEDLINE (Ovid) | 1/12/2014 | 718 |
| MEDLINE IN PROCESS (Ovid) | 1/12/2014 | 36 |
| EMBASE (Ovid) | 1/12/2014 | 605 |
| CDSR (Wiley) | 1/12/2014 | 52 |
| Database of Abstracts of Reviews of Effects – DARE (Wiley) | 1/12/2014 | 0 |
| HTA database (Wiley) | 1/12/2014 | 0 |
| CENTRAL (Wiley) | 1/12/2014 | 208 |

**Table 26: Clinical search terms (review question 4)**

| Line number | Search term | Number retrieved |
|---|---|---|
| | MEDLINE (Ovid) | Please see number in the bracket at the end of each line. |
| 1 | exp Dentistry, Operative/ (43172) | |
| 2 | exp Dental Prophylaxis/ (6702) | |
| 3 | ((dent$ or tooth$ or teeth$ or peridont$ or orthodont$) adj4 (prophyla$ or debridement)).tw. (1395) | |
| 4 | (crown adj4 length$).tw. (2643) | |
| 5 | exp Endodontics/ (23721) | |
| 6 | endodontic$.tw. (12546) | |
| 7 | Apicoectom$.tw. (436) | |
| 8 | (pulp$ adj4 cap$).tw. (1149) | |
| 9 | (pulpectom$ or pulpotom$).tw. (1063) | |
| 10 | exp Oral Surgical Procedures/ (53252) | |
| 11 | (gingivectom$ or gingivoplast$ or glossectom$).tw. (1068) | |
| 12 | mucoperio$ flap$.tw. (521) | |
| 13 | (tartar adj4 remov$).tw. (24) | |
| 14 | Sialography/ (1521) | |
| 15 | (sialograph$ or radiosialograph$).tw. (1080) | |
| 16 | (root adj4 canal adj4 (therap$ or treat$)).tw. (2619) | |
| 17 | ((dent$ or oral$ or tooth$ or teeth or peridont$ or orthodont$ or root$) adj4 (restorat$ or implant$ or replant$ or reimplant$ or re-implant$ or extract$ or remov$ or scal$ or polish$ or fill$ or irrigat$ or separat$ or expos$ or bond$ or band$ or prob$ or investigat$ or rubber dam$ or wedg$ or lining$ or liner$ or planing$)).tw. (94312) | |
| 18 | ((dent$ or oral$ or tooth$ or teeth$ or peridont$ or orthodont$ or root$ canal$) adj4 (surg$ or procedure$ or endoscop$ or operat$ or incis$ or excis$ or intervention$ or invasiv$ or biops$ or inject$)).tw. (42084) | |
| 19 | or/1-18 (210506) | |

| Line number | Search term | Number retrieved |
|---|---|---|
| 20 | exp Digestive System Surgical Procedures/ (284006) | |
| 21 | ((digestive or gastro$) adj4 (surg$ or operati$)).tw. (10530) | |
| 22 | (roux-en-y or appendectom$).tw. (12144) | |
| 23 | (Bili$ adj4 (bypas$ or divers$ or surg$)).tw. (5805) | |
| 24 | (cholecystectom$ or cholecystostom$ or choledochostom$).tw. (21956) | |
| 25 | (gallbladder adj4 remov$).tw. (662) | |
| 26 | (portoenterostom$ or sphincterotom$ or sphincteroplast$ or papillotom$).tw. (6915) | |
| 27 | (colectom$ or proctocolectom$ or coloproctectom$).tw. (9909) | |
| 28 | (laparotom$ or endoscop$ or colonoscop$).tw. (184236) | |
| 29 | (duodenoscop$ or gastroscop$ or proctoscop$).tw. (6748) | |
| 30 | Cholangiopancreatograph$.tw. (6766) | |
| 31 | (ercp or esophagoscop$ or esophagogastroduodenoscop$).tw. (10077) | |
| 32 | (oesophagoscop$ or oesophagogastroduodenoscop$).tw. (598) | |
| 33 | Echocardiography, Transesophageal/ (15719) | |
| 34 | Echocardiography/ (68982) | |
| 35 | ((trans?esophag$ or trans-esophag or trans-oesophag) adj4 echo$).tw. (13261) | |
| 36 | ((esophag$ or oesophag$) adj4 echo$).tw. (468) | |
| 37 | (tee or toe).tw. (14555) | |
| 38 | ((esophag$ or oesophag$) adj4 dilat$).tw. (2170) | |
| 39 | exp Lithotripsy/ (9116) | |
| 40 | (lithotrip$ or litholapax$ or ESWL or ESWLS).tw. (8847) | |
| 41 | (enterostom$ or cecostom$ or colostom$).tw. (7665) | |
| 42 | (duodenostom$ or ileostom$ or jejunostom$).tw. (7280) | |
| 43 | (esophagectom$ or oesophagectom$).tw. (6552) | |
| 44 | (esophagoplast$ or oesophagoplast$).tw. (783) | |
| 45 | (esophagostom$ or oesophagostom$).tw. (1252) | |
| 46 | (fundoplicat$ or nissen or billroth).tw. (7335) | |
| 47 | (gastrectom$ or gastroenterostom$ or gastrojejunostom$).tw. (19512) | |
| 48 | (Gast$ adj4 Bypass).tw. (6227) | |
| 49 | (gastroplast$ or gastrostom$ or hepatectom$ or hemorrhoidectom$).tw. (24524) | |
| 50 | ((jejunoileal or jejuno-ileal or ileojejunal or intestin$) adj4 bypass).tw. (1592) | |
| 51 | ((liver or hepat$ or pancrea$) adj4 (transplant$ or graft$)).tw. (56852) | |
| 52 | Pancreatectom$.tw. (6447) | |
| 53 | (pancrea$ adj4 remov$).tw. (973) | |
| 54 | (pancreaticoduodenectom$ or duodenopancreatectom$ or pancreatoduodenectom$ or pancreaticojejunostom$).tw. (6422) | |
| 55 | ((periton$ or leveen) adj4 shunt$).tw. (2294) | |
| 56 | ((digest$ or gastr$ or intestin$ or gi or oesophag$ or esophag$ or stomach or bowel$ or colon$ or liver or hepat$ or bili$ or duoden$ or gall$ or pancrea$ or append$ or abdom$ or anal or anus or sphinct$) adj4 (surg$ or procedure$ or operat$ or incis$ or excis$ or intervention$ or invasiv$ or biops$ or endoscop$ or sclerotherap$ or diversion$)).tw. (208685) | |
| 57 | or/20-56 (659400) | |
| 58 | exp Urogenital Surgical Procedures/ (270819) | |
| 59 | (colposcop$ or colpotom$ or culdoscop$ or endometrial ablation$).tw. | |

| Line number | Search term | Number retrieved |
|---|---|---|
| | (8043) | |
| 60 | ((dilatation or vacuum) adj4 curettage).tw. (1138) | |
| 61 | (hysterectom$ or hysteroscop$ or uterine myomectom$).tw. (29793) | |
| 62 | (uter$ adj4 endoscop$).tw. (114) | |
| 63 | (ovariectom$ or oophorectom$ or salpingostom$).tw. (30264) | |
| 64 | ((reproduct$ or tub$) adj4 sterili$).tw. (2380) | |
| 65 | (tub$ adj4 ligat$).tw. (2054) | |
| 66 | aldridge.tw. (54) | |
| 67 | (tub$ adj4 occlu$).tw. (1976) | |
| 68 | cooke.tw. (321) | |
| 69 | (cornual adj4 coagulat$).tw. (2) | |
| 70 | fimbriectom$.tw. (76) | |
| 71 | (irving or kroener or madlener or pomeroy).tw. (594) | |
| 72 | (tub$ adj4 (excis$ or ring$)).tw. (1197) | |
| 73 | (uchida or vasectom$ or salpingectom$).tw. (5458) | |
| 74 | (cystectom$ or cystoscop$ or cysto?tom$).tw. (17072) | |
| 75 | (kidney$ adj4 (transplant$ or graft$)).tw. (35238) | |
| 76 | (nephrectom$ or vesicotom$ or ureteroscop$).tw. (28194) | |
| 77 | (Urin$ adj4 Diver$).tw. (5004) | |
| 78 | (nephrostom$ or nephroli$).tw. (8869) | |
| 79 | (ureterostom$ or orchiectom$).tw. (5307) | |
| 80 | (Pen$ adj4 Implant$).tw. (1313) | |
| 81 | Prostatectom$.tw. (20532) | |
| 82 | Trans?uret$.tw. (13240) | |
| 83 | Trans?rect$.tw. (7494) | |
| 84 | (vasovasostom$ or castrat$ or circumci$).tw. (25193) | |
| 85 | (uret$ adj4 (catheter$ or dilatat$)).tw. (5010) | |
| 86 | exp Obstetric Surgical Procedures/ (107928) | |
| 87 | (abortion$ or embryotom$ or cerclage).tw. (48693) | |
| 88 | ((obstetr$ or abdom$) adj4 deliver$).tw. (2469) | |
| 89 | C?esarean.tw. (40409) | |
| 90 | Episiotom$.tw. (1888) | |
| 91 | (Obstetr$ adj4 extract$).tw. (245) | |
| 92 | (Induc$ adj4 (labor$ or labour$)).tw. (8675) | |
| 93 | Parturition/ (3604) | |
| 94 | (parturit$ or childbirth$ or birth$).tw. (252670) | |
| 95 | (vagina$ adj4 deliver$).tw. (12130) | |
| 96 | ((fet$ or cepha$) adj4 version$).tw. (562) | |
| 97 | Fetoscop$.tw. (887) | |
| 98 | Intrauterine Devices/ (7990) | |
| 99 | (Intra?uterine adj4 device$).tw. (5317) | |
| 100 | iud.tw. (6060) | |
| 101 | Vaginal Smears/ (20355) | |
| 102 | ((vagina$ or cervi$ or papanicolaou) adj4 smear$).tw. (8697) | |
| 103 | ((genit$ or urin$ or uro$ or uret$ or endometr$ or ovar$ or ooph$ or uter$ or bladder or vagina$ or cervi$ or gyn$ or obstet$ or prostat$ or reproduct$) adj4 (surg$ or procedure$ or operat$ or incis$ or excis$ or intervention$ or invasiv$ or biops$ or endoscop$)).tw. (106657) | |
| 104 | or/58-103 (801009) | |
| 105 | exp Pulmonary Surgical Procedures/ (57243) | |
| 106 | (pulmonary adj4 (surg* or operati*)).tw. (10089) | |

| Line number | Search term | Number retrieved |
|---|---|---|
| 107 | (Collapse adj4 Therap$).tw. (431) | |
| 108 | (pneumonolys$ or pneumothora$).tw. (16038) | |
| 109 | Bronchoscopy/ (20952) | |
| 110 | Bronchoscopes/ (2035) | |
| 111 | bronchoscop$.tw. (19032) | |
| 112 | thyroidectomy/ or adenoidectomy/ or laryngoplasty/ or laryngectomy/ or laryngoscopy/ or neck dissection/ or pharyngectomy/ or pharyngostomy/ or rhinoplasty/ or tonsillectomy/ or tracheostomy/ or tracheotomy/ (68513) | |
| 113 | (thyroidectom$ or adenoidectom$).tw. (15189) | |
| 114 | (laryngectom$ or laryngoscop$ or laryngoplast$).tw. (14170) | |
| 115 | neck dissect$.tw. (6297) | |
| 116 | (pharyngectom$ or pharyngostom$).tw. (411) | |
| 117 | rhinoplast$.tw. (3965) | |
| 118 | tonsillectom$.tw. (6389) | |
| 119 | tracheo?tom$.tw. (14393) | |
| 120 | (nasal adj4 pack$).tw. (806) | |
| 121 | Pneumonectomy/ (21682) | |
| 122 | Pneumonectom$.tw. (6678) | |
| 123 | (lung$ adj4 (transplant$ or graft$ or reduct$)).tw. (17321) | |
| 124 | ((nasal or sinus$ or rhino$ or rhina$ or pharyn$ or laryn$ or trache$ or bronch$ or lung$ or pulmonar$ or respirat$) adj4 (surg$ or procedure$ or endoscop$ or operat$ or incis$ or excis$ or intervention$ or invasiv$ or biops$)).tw. (80249) | |
| 125 | or/105-124 (228071) | |
| 126 | 19 or 57 or 104 or 125 (1814014) | |
| 127 | (bacter$ adj6 (level$ or rate$ or incidence$ or prevalence$ or duration$ or cumulat$ or transient or translocat$ or trans-locat$ or transfer$)).tw. (34586) | |
| 128 | (streptococ$ adj6 (level$ or rate$ or incidence$ or prevalence$ or duration$ or cumulat$ or transient or translocat$ or trans-locat$ or transfer$)).tw. (3730) | |
| 129 | (staphylococ$ adj6 (level$ or rate$ or incidence$ or prevalence$ or duration$ or cumulat$ or transient or translocat$ or trans-locat$ or transfer$)).tw. (4149) | |
| 130 | (enterococ$ adj6 (level$ or rate$ or incidence$ or prevalence$ or duration$ or cumulat$ or transient or translocat$ or trans-locat$ or transfer$)).tw. (1635) | |
| 131 | or/127-130 (42760) | |
| 132 | 126 and 131 (4196) | |
| 133 | Observational Study as Topic/ (501) | |
| 134 | Observational Study/ (6356) | |
| 135 | Epidemiologic Studies/ (6272) | |
| 136 | exp Case-Control Studies/ (711198) | |
| 137 | exp Cohort Studies/ (1439568) | |
| 138 | Cross-Sectional Studies/ (193002) | |
| 139 | Comparative Study.pt. (1731142) | |
| 140 | case control$.tw. (80732) | |
| 141 | case series.tw. (35347) | |
| 142 | (cohort adj (study or studies)).tw. (89864) | |
| 143 | cohort analy$.tw. (3830) | |
| 144 | (follow up adj (study or studies)).tw. (37517) | |
| 145 | | |

| Line number | Search term | Number retrieved |
|---|---|---|
| 146 | (observational adj (study or studies)).tw. (44392) | |
| 147 | longitudinal.tw. (141606) | |
| 148 | prospective.tw. (354704) | |
| 149 | retrospective.tw. (272363) | |
| 150 | cross sectional.tw. (167096) | |
| 151 | or/133-149 (3438792) | |
| 152 | Meta-Analysis.pt. (54585) | |
| 153 | Meta-Analysis as Topic/ (14595) | |
| 154 | Review.pt. (1964534) | |
| 155 | exp Review Literature as Topic/ (8135) | |
| 156 | (metaanaly$ or metanaly$ or (meta adj3 analy$)).tw. (64511) | |
| 157 | (review$ or overview$).ti. (278949) | |
| 158 | (systematic$ adj5 (review$ or overview$)).tw. (59256) | |
| 159 | ((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw. (4592) | |
| 160 | ((studies or trial$) adj2 (review$ or overview$)).tw. (26255) | |
| 161 | (integrat$ adj3 (research or review$ or literature)).tw. (5748) | |
| 162 | (pool$ adj2 (analy$ or data)).tw. (15021) | |
| 163 | (handsearch$ or (hand adj3 search$)).tw. (5670) | |
| 164 | (manual$ adj3 search$).tw. (3296) | |
| 165 | or/151-163 (2131312) | |
| 166 | animals/ not humans/ (4000367) | |
| 167 | 164 not 165 (1992913) | |
| 168 | Randomized Controlled Trial.pt. (399960) | |
| 169 | Controlled Clinical Trial.pt. (90666) | |
| 170 | Clinical Trial.pt. (501003) | |
| 171 | exp Clinical Trials as Topic/ (294731) | |
| 172 | Placebos/ (34008) | |
| 173 | Random Allocation/ (84113) | |
| 174 | Double-Blind Method/ (132489) | |
| 175 | Single-Blind Method/ (20614) | |
| 176 | Cross-Over Studies/ (36229) | |
| 177 | ((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw. (776483) | |
| 178 | (random$ adj3 allocat$).tw. (21567) | |
| 179 | placebo$.tw. (159821) | |
| 180 | ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (130057) | |
| 181 | (crossover$ or (cross adj over$)).tw. (58948) | |
| 182 | or/167-180 (1444186) | |
| 183 | animals/ not humans/ (4000367) | |
| 184 | 181 not 182 (1346509) | |
| 185 | 150 or 166 or 183 (5846186) | |
| 186 | 132 and 184 (2358) | |
| 187 | animals/ not humans/ (4000367) | |
| 188 | 185 not 186 (2265) | |
| 189 | limit 187 to english language (2018) | |
| | limit 188 to ed=20070831-20141201 (718) | |

# D.5 Review question 5

**Table 27: Clinical search summary (review question 5)**

| Databases | Date searched | No. retrieved |
|---|---|---|
| MEDLINE (Ovid) | 26/11/2014 | 201 |
| MEDLINE IN PROCESS (Ovid) | 26/11/2014 | 12 |
| EMBASE (Ovid) | 26/11/2014 | 108 |
| CDSR (Wiley) | 26/11/2014 | 28 |
| Database of Abstracts of Reviews of Effects – DARE (Wiley) | 26/11/2014 | 1 |
| CENTRAL (Wiley) | 26/11/2014 | 76 |
| HTA database (Wiley) | 26/11/2014 | 0 |

**Table 28: Clinical search terms (review question 5)**

| Line number | Search terms | No retrieved |
|---|---|---|
| | Ovid MEDLINE | Please see brackets at end of each line for numbers. retrieved |
| 1 | Oral Hygiene/ (10647) | |
| 2 | ((oral$ or dent$ or mouth$) adj4 hyg$).tw. (12867) | |
| 3 | Toothbrushing/ (6264) | |
| 4 | (toothbrush$ or tooth-brush$).tw. (4686) | |
| 5 | ((tooth$ or teeth) adj4 (brush$ or clean$ or pick$)).tw. (3665) | |
| 6 | (tongue$ adj4 (brush$ or scrap$ or clean$)).tw. (182) | |
| 7 | Dental Devices, Home Care/ (1759) | |
| 8 | floss$.tw. (957) | |
| 9 | Mastication/ (8301) | |
| 10 | (masticat$ or chew$).tw. (19420) | |
| 11 | or/1-10 (47303) | |
| 12 | exp Exercise/ (127628) | |
| 13 | exercis*.tw. (195111) | |
| 14 | (physical$ adj4 (activit$ or effort$)).tw. (63019) | |
| 15 | exp Sports/ (134852) | |
| 16 | sport$.tw. (40291) | |
| 17 | (workout$ or work$ out$).tw. (8111) | |
| 18 | Physical exertion/ (53902) | |
| 19 | exertion$.tw. (14526) | |
| 20 | Physical Fitness/ (22953) | |
| 21 | fit$.tw. (191367) | |
| 22 | or/12-21 (572788) | |
| 23 | Defecation/ (5905) | |
| 24 | (defecat$ or defaecat$).tw. (6508) | |
| 25 | ((void$ or pass$ or excret$ or evac$ or discharg$ or empt$ or mov$ or motion$ or open$) adj4 bowel$).tw. (3867) | |

| Line number | Search terms | No retrieved |
|---|---|---|
| 26 | laxation.tw. (123) | |
| 27 | ((void$ or pass$ or discharg$ or excret$) adj4 (excreta or stool$ or feces or fecal or faec$)).tw. (10873) | |
| 28 | or/23-27 (23844) | |
| 29 | Urination/ (8534) | |
| 30 | (urinat$ or micturit$).tw. (8945) | |
| 31 | ((void$ or pass$ or excret$ or evac$ or discharg$ or empt$) adj4 (bladder or urin$)).tw. (72741) | |
| 32 | ((pass$ or mak$) adj3 water$).tw. (2128) | |
| 33 | or/29-32 (87879) | |
| 34 | 11 or 22 or 28 or 33 (723634) | |
| 35 | (bacter$ adj6 (level$ or rate$ or incidence$ or prevalence$ or duration$ or cumulat$ or transient or translocat$ or trans-locat$ or transfer$)).tw. (34586) | |
| 36 | (streptococ$ adj6 (level$ or rate$ or incidence$ or prevalence$ or duration$ or cumulat$ or transient or translocat$ or trans-locat$ or transfer$)).tw. (3730) | |
| 37 | (staphylococ$ adj6 (level$ or rate$ or incidence$ or prevalence$ or duration$ or cumulat$ or transient or translocat$ or trans-locat$ or transfer$)).tw. (4149) | |
| 38 | (enterococ$ adj6 (level$ or rate$ or incidence$ or prevalence$ or duration$ or cumulat$ or transient or translocat$ or trans-locat$ or transfer$)).tw. (1635) | |
| 39 | or/35-38 (42760) | |
| 40 | 34 and 39 (1346) | |
| 41 | limit 40 to english language (1212) | |
| 42 | animals/ not humans/ (4000367) | |
| 43 | 41 not 42 (1022) | |
| 44 | limit 43 to ed=20070809-20141126 (447) | |
| 45 | Observational Study as Topic/ (501) | |
| 46 | Observational Study/ (6356) | |
| 47 | Epidemiologic Studies/ (6272) | |
| 48 | exp Case-Control Studies/ (711198) | |
| 49 | exp Cohort Studies/ (1439568) | |
| 50 | Cross-Sectional Studies/ (193002) | |
| 51 | Comparative Study.pt. (1731142) | |
| 52 | case control$.tw. (80732) | |
| 53 | case series.tw. (35347) | |
| 54 | (cohort adj (study or studies)).tw. (89864) | |
| 55 | cohort analy$.tw. (3830) | |
| 56 | (follow up adj (study or studies)).tw. (37517) | |
| 57 | (observational adj (study or studies)).tw. (44392) | |
| 58 | longitudinal.tw. (141606) | |
| 59 | prospective.tw. (354704) | |
| 60 | retrospective.tw. (272363) | |
| 61 | cross sectional.tw. (167096) | |

| Line number | Search terms | No retrieved |
|---|---|---|
| 62 | or/45-61 (3438792) | |
| 63 | Meta-Analysis.pt. (54585) | |
| 64 | Meta-Analysis as Topic/ (14595) | |
| 65 | Review.pt. (1964534) | |
| 66 | exp Review Literature as Topic/ (8135) | |
| 67 | (metaanaly$ or metanaly$ or (meta adj3 analy$)).tw. (64511) | |
| 68 | (review$ or overview$).ti. (278949) | |
| 69 | (systematic$ adj5 (review$ or overview$)).tw. (59256) | |
| 70 | ((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw. (4592) | |
| 71 | ((studies or trial$) adj2 (review$ or overview$)).tw. (26255) | |
| 72 | (integrat$ adj3 (research or review$ or literature)).tw. (5748) | |
| 73 | (pool$ adj2 (analy$ or data)).tw. (15021) | |
| 74 | (handsearch$ or (hand adj3 search$)).tw. (5670) | |
| 75 | (manual$ adj3 search$).tw. (3296) | |
| 76 | or/63-75 (2131312) | |
| 77 | animals/ not humans/ (4000367) | |
| 78 | 76 not 77 (1992913) | |
| 79 | Randomized Controlled Trial.pt. (399960) | |
| 80 | Controlled Clinical Trial.pt. (90666) | |
| 81 | Clinical Trial.pt. (501003) | |
| 82 | exp Clinical Trials as Topic/ (294731) | |
| 83 | Placebos/ (34008) | |
| 84 | Random Allocation/ (84113) | |
| 85 | Double-Blind Method/ (132489) | |
| 86 | Single-Blind Method/ (20614) | |
| 87 | Cross-Over Studies/ (36229) | |
| 88 | ((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw. (776483) | |
| 89 | (random$ adj3 allocat$).tw. (21567) | |
| 90 | placebo$.tw. (159821) | |
| 91 | ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (130057) | |
| 92 | (crossover$ or (cross adj over$)).tw. (58948) | |
| 93 | or/79-92 (1444186) | |
| 94 | animals/ not humans/ (4000367) | |
| 95 | 93 not 94 (1346509) | |
| 96 | 62 or 78 or 95 (5846186) | |
| 97 | 44 and 96 (201) | |

# D.61 Review question 6a and 7a

2 **Table 29: Clinical search summary (review question 6a and 7a)**

| Databases | Date searched | No. retrieved |
|---|---|---|

| Databases | Date searched | No. retrieved |
|---|---|---|
| MEDLINE (Ovid) | 02/12/2014 | 801 |
| MEDLINE In-Process (Ovid) | 02/12/2014 | 55 |
| EMBASE (Ovid) | 02/12/2014 | 801 |
| CDSR (Ovid, Wiley)* | 02/12/2014 | 89 |
| Database of Abstracts of Reviews of Effects – DARE (CRD, Ovid, Wiley)* | 02/12/2014 | 34 |
| CENTRAL (Ovid, Wiley)* | 02/12/2014 | 366 |
| HTA database (CRD, Ovid, Wiley)* | 02/12/2014 | 6 |
| NHS Economic Evaluation Database - NHS EED (CRD, Ovid, Wiley)* | 02/12/2014 | 15 |

1 **Table 30: Clinical search terms (review question 6a and 7a)**

| Line number | Search terms | Number retrieved |
|---|---|---|
| | Ovid MEDLINE(R) | Please see number in brackets for each line |
| 1 | exp Dentistry, Operative/ (43182) | |
| 2 | exp Dental Prophylaxis/ (6703) | |
| 3 | ((dent$ or tooth$ or teeth$ or peridont$ or orthodont$) adj4 (prophyla$ or debrid$)).tw. (1413) | |
| 4 | (crown adj4 length$).tw. (2646) | |
| 5 | exp Endodontics/ (23730) | |
| 6 | endodontic$.tw. (12554) | |
| 7 | Apicoectom$.tw. (436) | |
| 8 | ((pulp$ adj4 cap$).tw. (1149) | |
| 9 | (pulpectom$ or pulpotom$).tw. (1063) | |
| 10 | exp Oral Surgical Procedures/ (53293) | |
| 11 | (gingivectom$ or gingivoplast$ or glossectom$).tw. (1068) | |
| 12 | mucoperio$ flap$.tw. (522) | |
| 13 | (tartar adj4 remov$).tw. (24) | |
| 14 | Sialography/ (1521) | |
| 15 | (sialograph$ or radiosialograph$).tw. (1080) | |
| 16 | (root adj4 canal adj4 (therap$ or treat$)).tw. (2619) | |
| 17 | ((dent$ or oral$ or tooth$ or teeth or peridont$ or orthodont$ or root$) adj4 (restorat$ or implant$ or replant$ or reimplant$ or re-implant$ or extract$ or remov$ or scal$ or polish$ or fill$ or irrigat$ or separat$ or expos$ or bond$ or band$ or prob$ or investigat$ or rubber dam$ or wedg$ or lining$ or liner$ or planing$)).tw. (94397) | |
| 18 | ((dent$ or oral$ or tooth$ or teeth$ or peridont$ or orthodont$ or root$ canal$) adj4 (surg$ or procedure$ or endoscop$ or operat$ or incis$ or excis$ or intervention$ or invasiv$ or biops$ or inject$)).tw. (42156) | |
| 19 | or/1-18 (210674) | |
| 20 | exp Digestive System Surgical Procedures/ (284321) | |
| 21 | ((digestive or gastro$) adj4 (surg$ or operati$)).tw. (10539) | |
| 22 | (roux-en-y or appendectom$).tw. (12163) | |
| 23 | (Bili$ adj4 (bypas$ or divers$ or surg$)).tw. (5812) | |

| Line number | Search terms | Number retrieved |
|---|---|---|
| 24 | (cholecystectom$ or cholecystostom$ or choledochostom$).tw. (21972) | |
| 25 | (gallbladder adj4 remov$).tw. (662) | |
| 26 | (portoenterostom$ or sphincterotom$ or sphincteroplast$ or papillotom$).tw. (6918) | |
| 27 | (colectom$ or proctocolectom$ or coloproctectom$).tw. (9919) | |
| 28 | (laparotom$ or endoscop$ or colonoscop$).tw. (184414) | |
| 29 | (duodenoscop$ or gastroscop$ or proctoscop$).tw. (6753) | |
| 30 | Cholangiopancreatograph$.tw. (6774) | |
| 31 | (ercp or esophagoscop$ or esophagogastroduodenoscop$).tw. (10087) | |
| 32 | (oesophagoscop$ or oesophagogastroduodenoscop$).tw. (598) | |
| 33 | Echocardiography, Transesophageal/ (15730) | |
| 34 | Echocardiography/ (69032) | |
| 35 | ((trans?esophag$ or trans-esophag or trans-oesophag) adj4 echo$).tw. (13269) | |
| 36 | ((esophag$ or oesophag$) adj4 echo$).tw. (468) | |
| 37 | (tee or toe).tw. (14573) | |
| 38 | ((esophag$ or oesophag$) adj4 dilat$).tw. (2171) | |
| 39 | exp Lithotripsy/ (9123) | |
| 40 | (lithotrip$ or litholapax$ or ESWL or ESWLS).tw. (8854) | |
| 41 | (enterostom$ or cecostom$ or colostom$).tw. (7669) | |
| 42 | (duodenostom$ or ileostom$ or jejunostom$).tw. (7282) | |
| 43 | (esophagectom$ or oesophagectom$).tw. (6560) | |
| 44 | (esophagoplast$ or oesophagoplast$).tw. (783) | |
| 45 | (esophagostom$ or oesophagostom$).tw. (1252) | |
| 46 | (fundoplicat$ or nissen or billroth).tw. (7343) | |
| 47 | (gastrectom$ or gastroenterostom$ or gastrojejunostom$).tw. (19535) | |
| 48 | (Gast$ adj4 Bypass).tw. (6242) | |
| 49 | (gastroplast$ or gastrostom$ or hepatectom$ or hemorrhoidectom$).tw. (24548) | |
| 50 | ((jejunoileal or jejuno-ileal or ileojejunal or intestin$) adj4 bypass).tw. (1592) | |
| 51 | ((liver or hepat$ or pancrea$) adj4 (transplant$ or graft$)).tw. (56910) | |
| 52 | Pancreatectom$.tw. (6460) | |
| 53 | (pancrea$ adj4 remov$).tw. (977) | |
| 54 | (pancreaticoduodenectom$ or duodenopancreatectom$ or pancreatoduodenectom$ or pancreaticojejunostom$).tw. (6441) | |
| 55 | ((periton$ or leveen) adj4 shunt$).tw. (2294) | |
| 56 | ((digest$ or gastr$ or intestin$ or gi or oesophag$ or esophag$ or stomach or bowel$ or colon$ or liver or hepat$ or bili$ or duoden$ or gall$ or pancrea$ or append$ or abdom$ or anal or anus or sphinct$) adj4 (surg$ or procedure$ or operat$ or incis$ or excis$ or intervention$ or invasiv$ or biops$ or endoscop$ or sclerotherap$ or diversion$)).tw. (208872) | |
| 57 | or/20-56 (659975) | |
| 58 | exp Urogenital Surgical Procedures/ (271012) | |

| Line number | Search terms | Number retrieved |
|---|---|---|
| 59 | (colposcop$ or colpotom$ or culdoscop$ or endometrial ablation$).tw. (8050) | |
| 60 | ((dilatation or vacuum) adj4 curettage).tw. (1138) | |
| 61 | (hysterectom$ or hysteroscop$ or uterine myomectom$).tw. (29808) | |
| 62 | (uter$ adj4 endoscop$).tw. (114) | |
| 63 | (ovariectom$ or oophorectom$ or salpingostom$).tw. (30281) | |
| 64 | ((reproduct$ or tub$) adj4 sterili$).tw. (2380) | |
| 65 | (tub$ adj4 ligat$).tw. (2055) | |
| 66 | aldridge.tw. (54) | |
| 67 | (tub$ adj4 occlu$).tw. (1976) | |
| 68 | cooke.tw. (321) | |
| 69 | (cornual adj4 coagulat$).tw. (2) | |
| 70 | fimbriectom$.tw. (76) | |
| 71 | (irving or kroener or madlener or pomeroy).tw. (594) | |
| 72 | (tub$ adj4 (excis$ or ring$)).tw. (1198) | |
| 73 | (uchida or vasectom$ or salpingectom$).tw. (5460) | |
| 74 | (cystectom$ or cystoscop$ or cysto?tom$).tw. (17097) | |
| 75 | (kidney$ adj4 (transplant$ or graft$)).tw. (35254) | |
| 76 | (nephrectom$ or vesicotom$ or ureteroscop$).tw. (28214) | |
| 77 | (Urin$ adj4 Diver$).tw. (5008) | |
| 78 | (nephrostom$ or nephroli$).tw. (8876) | |
| 79 | (ureterostom$ or orchiectom$).tw. (5315) | |
| 80 | (Pen$ adj4 Implant$).tw. (1315) | |
| 81 | Prostatectom$.tw. (20581) | |
| 82 | Trans?uret$.tw. (13258) | |
| 83 | Trans?rect$.tw. (7510) | |
| 84 | (vasovasostom$ or castrat$ or circumci$).tw. (25216) | |
| 85 | (uret$ adj4 (catheter$ or dilatat$)).tw. (5016) | |
| 86 | exp Obstetric Surgical Procedures/ (107992) | |
| 87 | (abortion$ or embryotom$ or cerclage).tw. (48699) | |
| 88 | ((obstetr$ or abdom$) adj4 deliver$).tw. (2473) | |
| 89 | C?esarean.tw. (40438) | |
| 90 | Episiotom$.tw. (1891) | |
| 91 | (Obstetr$ adj4 extract$).tw. (245) | |
| 92 | (Induc$ adj4 (labor$ or labour$)).tw. (8680) | |
| 93 | Parturition/ (3610) | |
| 94 | (parturit$ or childbirth$ or birth$).tw. (252872) | |
| 95 | (vagina$ adj4 deliver$).tw. (12148) | |
| 96 | ((fet$ or cepha$) adj4 version$).tw. (562) | |
| 97 | Fetoscop$.tw. (890) | |
| 98 | Intrauterine Devices/ (7992) | |
| 99 | (Intra?uterine adj4 device$).tw. (5318) | |
| 100 | iud.tw. (6060) | |
| 101 | Vaginal Smears/ (20361) | |
| 102 | ((vagina$ or cervi$ or papanicolaou) adj4 smear$).tw. (8698) | |

| Line number | Search terms | Number retrieved |
|---|---|---|
| 103 | ((genit$ or urin$ or uro$ or uret$ or endometr$ or ovar$ or ooph$ or uter$ or bladder or vagina$ or cervi$ or gyn$ or obstet$ or prostat$ or reproduct$) adj4 (surg$ or procedure$ or operat$ or incis$ or excis$ or intervention$ or invasiv$ or biops$ or endoscop$)).tw. (106763) | |
| 104 | or/58-103 (801574) | |
| 105 | exp Pulmonary Surgical Procedures/ (57266) | |
| 106 | (pulmonary adj4 (surg* or operati*)).tw. (10095) | |
| 107 | (Collapse adj4 Therap$).tw. (431) | |
| 108 | (pneumonolys$ or pneumothora$).tw. (16053) | |
| 109 | Bronchoscopy/ (20962) | |
| 110 | Bronchoscopes/ (2036) | |
| 111 | bronchoscop$.tw. (19041) | |
| 112 | thyroidectomy/ or adenoidectomy/ or laryngoplasty/ or laryngectomy/ or laryngoscopy/ or neck dissection/ or pharyngectomy/ or pharyngostomy/ or rhinoplasty/ or tonsillectomy/ or tracheostomy/ or tracheotomy/ (68569) | |
| 113 | (thyroidectom$ or adenoidectom$).tw. (15206) | |
| 114 | (laryngectom$ or laryngoscop$ or laryngoplast$).tw. (14178) | |
| 115 | neck dissect$.tw. (6308) | |
| 116 | (pharyngectom$ or pharyngostom$).tw. (411) | |
| 117 | rhinoplast$.tw. (3971) | |
| 118 | tonsillectom$.tw. (6392) | |
| 119 | tracheo?tom$.tw. (14400) | |
| 120 | (nasal adj4 pack$).tw. (808) | |
| 121 | Pneumonectomy/ (21686) | |
| 122 | Pneumonectom$.tw. (6681) | |
| 123 | (lung$ adj4 (transplant$ or graft$ or reduct$)).tw. (17339) | |
| 124 | ((nasal or sinus$ or rhino$ or rhina$ or pharyn$ or laryn$ or trache$ or bronch$ or lung$ or pulmonar$ or respirat$) adj4 (surg$ or procedure$ or endoscop$ or operat$ or incis$ or excis$ or intervention$ or invasiv$ or biops$)).tw. (80300) | |
| 125 | or/105-124 (228216) | |
| 126 | 19 or 57 or 104 or 125 (1815407) | |
| 127 | exp Chemoprevention/ (13624) | |
| 128 | (chemoprevent$ or chemo-prevent$).tw. (16449) | |
| 129 | (prophyla$ or chemoprophyla$ or chemo-prophyla$).tw. (123271) | |
| 130 | exp anti-infective agents/ (1306763) | |
| 131 | exp Penicillins/ (70946) | |
| 132 | penicillin$.tw. (44607) | |
| 133 | "pen v".tw. (19) | |
| 134 | "pen g".tw. (43) | |
| 135 | (antibiot$ or anti-biot$).tw. (223952) | |
| 136 | (antibacter$ or anti-bacter$).tw. (43572) | |
| 137 | (antimycobacter$ or anti-mycobacter$).tw. (3359) | |
| 138 | bacteriocid$.tw. (518) | |
| 139 | (microbicid$ or antimicrob$ or anti-microb$).tw. (96075) | |
| 140 | (anti-infect$ or antiinfect$).tw. (4084) | |

| Line number | Search terms | Number retrieved |
|---|---|---|
| 141 | exp Gentamicins/ (17561) | |
| 142 | (gentam?cin$ or cidomycin$ or garam?cin$).tw. (21303) | |
| 143 | (gentacycol$ or gentavet$ or genticin$).tw. (17) | |
| 144 | Glycopeptides/ (7994) | |
| 145 | (teicoplanin$ or teichom?cin$ or targocid$).tw. (2820) | |
| 146 | exp Clindamycin/ (5013) | |
| 147 | (clindam?cin$ or dalacin c).tw. (7777) | |
| 148 | (deoxylincomycin$ or chlo?lincocin$ or cleocin$).tw. (46) | |
| 149 | exp Ceftriaxone/ (4774) | |
| 150 | (cef?triaxon$ or rocephin).tw. (7266) | |
| 151 | exp Cephalexin/ (3180) | |
| 152 | (cephalexin$ or cefalexin$).tw. (2372) | |
| 153 | (ceporex or Keflex).tw. (30) | |
| 154 | exp Azithromycin/ (3792) | |
| 155 | (az?throm?cin$ or zithromax).tw. (5100) | |
| 156 | exp Clarithromycin/ (5208) | |
| 157 | clar?throm?cin$.tw. (6670) | |
| 158 | (clarosip or klaricid).tw. (10) | |
| 159 | exp Vancomycin/ (10687) | |
| 160 | (vancom?cin$ or vancocin$).tw. (17807) | |
| 161 | exp Cefuroxime/ (1958) | |
| 162 | (cefuroxime or cephuroxime).tw. (3437) | |
| 163 | (zinacef or zinnat).tw. (49) | |
| 164 | exp Ampicillin/ (24218) | |
| 165 | (ampicillin$ or penbritin or amcill).tw. (18058) | |
| 166 | (aminobenzylpenicillin$ or aminobenzyl-penicillin$).tw. (118) | |
| 167 | (benzylpenicillin$ or benzyl-penicillin$).tw. (2350) | |
| 168 | (omnipen or pentrexyl or polycillin$ or ukapen).tw. (9) | |
| 169 | xp Amoxicillin/ (9522) | |
| 170 | (augmentin$ or amox?cillin$).tw. (21506) | |
| 171 | (co-amox$ or coamox$).tw. (473) | |
| 172 | hydroxyampicillin$.tw. (1) | |
| 173 | (actimoxi$ or amoxil$ or amoyl$).tw. (61) | |
| 174 | (clamoxyl or penamox or polymox).tw. (20) | |
| 175 | (trimox or wymox).tw. (2) | |
| 176 | exp Floxacillin/ (619) | |
| 177 | (flucloxacillin$ or floxacillin$).tw. (632) | |
| 178 | (fluorochloroxacillin or floxapen).tw. (3) | |
| 179 | exp Cefazolin/ (2437) | |
| 180 | (cefazolin$ or cephazolin$).tw. (3564) | |
| 181 | (cefamedin$ or cefamezine$ or gramaxin$).tw. (11) | |
| 182 | or/127-181 (1559034) | |
| 183 | ((bacter$ or staphylococ$ or streptococ$ or enterococ$) adj5 eliminat$ or prevent$ or reduc$ or decreas$ or lower$)).tw. (37313) | |
| 184 | 126 and 182 and 183 (1858) | |

| Line number | Search terms | Number retrieved |
|---|---|---|
| 185 | (chemoprevent$ or chemo-prevent$).ti. (4898) | |
| 186 | (chemoprophyla$ or chemo-prophyla$).ti. (1887) | |
| 187 | (antibiot$ and prophyla$).ti. (4134) | |
| 188 | (anti-biot$ and prophyla$).ti. (0) | |
| 189 | (antimicrob$ and prophyla$).ti. (806) | |
| 190 | (anti-microb$ and prophyla$).ti. (3) | |
| 191 | (antibacter$ and prophyla$).ti. (143) | |
| 192 | (anti-bacter$ and prophyla$).ti. (4) | |
| 193 | (antibiot$ and premedi$).ti. (8) | |
| 194 | (anti-biot$ and premedi$).ti. (0) | |
| 195 | (antimicrob$ and premedi$).ti. (0) | |
| 196 | (anti-microb$ and premedi$).ti. (0) | |
| 197 | (antibacter$ and premedi$).ti. (0) | |
| 198 | (anti-bacter$ and premedi$).ti. (0) | |
| 199 | (antibiot$ and prevent$).ti. (1493) | |
| 200 | (anti-biot$ and prevent$).ti. (1) | |
| 201 | antimicrob$ and prevent$).ti. (385) | |
| 202 | (anti-microb$ and prevent$).ti. (2) | |
| 203 | (antibacter$ and prevent$).ti. (109) | |
| 204 | (anti-bacter$ and prevent$).ti. (7) | |
| 205 | or/185-204 (13551) | |
| 206 | 126 and 205 (2934) | |
| 207 | 184 or 206 (4643) | |
| 208 | Observational Study as Topic/ (508) | |
| 209 | Observational Study/ (6505) | |
| 210 | Epidemiologic Studies/ (6277) | |
| 211 | exp Case-Control Studies/ (712372) | |
| 212 | exp Cohort Studies/ (1441303) | |
| 213 | Cross-Sectional Studies/ (193365) | |
| 214 | Comparative Study.pt. (1731817) | |
| 215 | case control$.tw. (80825) | |
| 216 | case series.tw. (35413) | |
| 217 | (cohort adj (study or studies)).tw. (90024) | |
| 218 | cohort analy$.tw. (3836) | |
| 219 | (follow up adj (study or studies)).tw. (37541) | |
| 220 | (observational adj (study or studies)).tw. (44485) | |
| 221 | longitudinal.tw. (141799) | |
| 222 | prospective.tw. (355138) | |
| 223 | retrospective.tw. (272845) | |
| 224 | cross sectional.tw. (167433) | |
| 225 | or/208-224 (3441792) | |
| 226 | Meta-Analysis.pt. (54725) | |
| 227 | Meta-Analysis as Topic/ (14604) | |
| 228 | Review.pt. (1966250) | |
| 229 | exp Review Literature as Topic/ (8137) | |

| Line number | Search terms | Number retrieved |
|---|---|---|
| 230 | (metaanaly$ or metanaly$ or (meta adj3 analy$)).tw. (64666) | |
| 231 | (review$ or overview$).ti. (279292) | |
| 232 | (systematic$ adj5 (review$ or overview$)).tw. (59439) | |
| 233 | ((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw. (4602) | |
| 234 | ((studies or trial$) adj2 (review$ or overview$)).tw. (26283) | |
| 235 | (integrat$ adj3 (research or review$ or literature)).tw. (5767) | |
| 236 | (pool$ adj2 (analy$ or data)).tw. (15049) | |
| 237 | (handsearch$ or (hand adj3 search$)).tw. (5677) | |
| 238 | (manual$ adj3 search$).tw. (3301) | |
| 239 | or/226-238 (2133166) | |
| 240 | animals/ not humans/ (4001991) | |
| 241 | 239 not 240 (1994683) | |
| 242 | Randomized Controlled Trial.pt. (400332) | |
| 243 | Controlled Clinical Trial.pt. (90710) | |
| 244 | Clinical Trial.pt. (501127) | |
| 245 | exp Clinical Trials as Topic/ (294922) | |
| 246 | Placebos/ (34020) | |
| 247 | Random Allocation/ (84147) | |
| 248 | Double-Blind Method/ (132581) | |
| 249 | Single-Blind Method/ (20647) | |
| 250 | Cross-Over Studies/ (36257) | |
| 251 | ((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw. (777356) | |
| 252 | (random$ adj3 allocat$).tw. (21589) | |
| 253 | placebo$.tw. (159942) | |
| 254 | ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (130155) | |
| 255 | (crossover$ or (cross adj over$)).tw. (58984) | |
| 256 | or/242-255 (1445480) | |
| 257 | animals/ not humans/ (4001991) | |
| 258 | 256 not 257 (1347733) | |
| 259 | 225 or 241 or 258 (5851229) | |
| 260 | 207 and 259 (3052) | |
| 261 | Animals/ not Humans/ (4001991) | |
| 262 | 260 not 261 (2989) | |
| 263 | limit 262 to ed=20070907-20141202 (878) | |
| 264 | limit 263 to english language (801) | |

# D.7 Review question 6b and 7b

**Table 31: Clinical search summary (review question 6b and 7b)**

| Databases | Date searched | No. retrieved |
|---|---|---|
| MEDLINE (Ovid) | 01/12/2014 | 389 |
| MEDLINE In-Process (Ovid) | 01/12/2014 | 26 |
| EMBASE (Ovid) | 01/12/2014 | 222 |
| CDSR (Wiley) | 01/12/2014 | 33 |

| Databases | Date searched | No. retrieved |
|---|---|---|
| Database of Abstracts of Reviews of Effects – DARE (Wiley) | 01/12/2014 | 9 |
| CENTRAL (Wiley) | 01/12/2014 | 206 |
| HTA Database (Wiley) | 01/12/2014 | 1 |

1 **Table 32: Clinical search terms (review question 6b and 7b)**

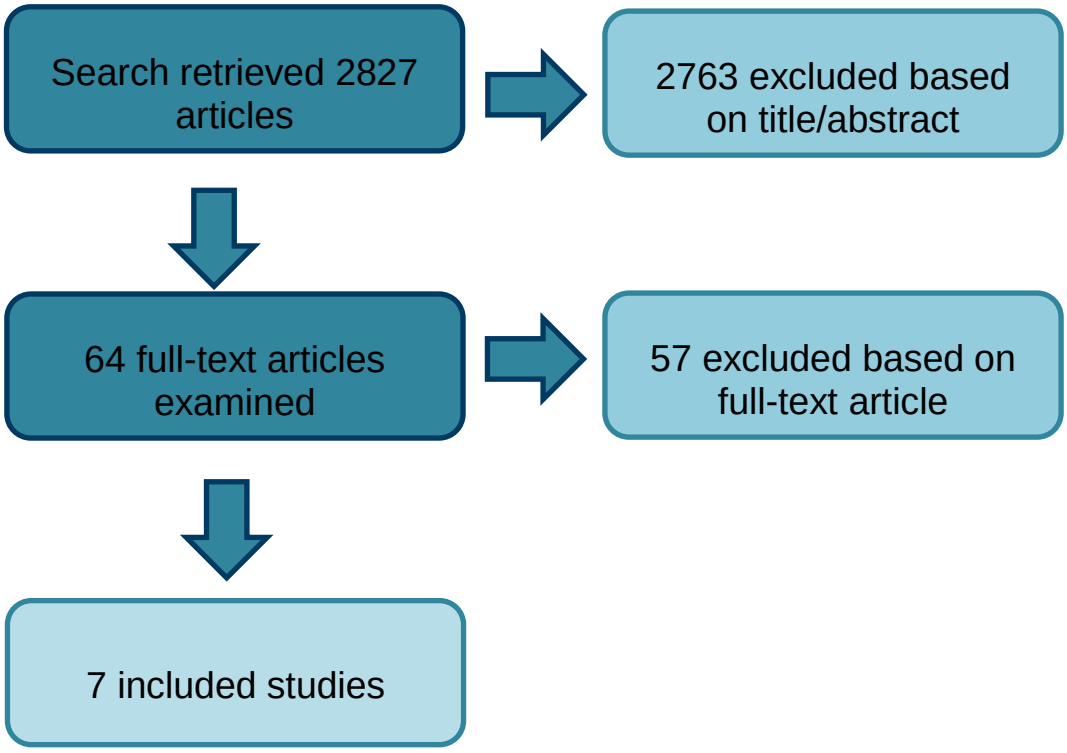
| Line number | Search terms | No. retrieved |
|---|---|---|
| | Ovid MEDLINE | Please see number in brakcets for each line |
| 1 | exp Dentistry, Operative/ (43172) | |
| 2 | exp Dental Prophylaxis/ (6702) | |
| 3 | ((dent$ or tooth$ or teeth or peridont$ or orthodont$) adj4 (prophyla$ or debrid$)).tw. (1413) | |
| 4 | (crown adj4 length$).tw. (2643) | |
| 5 | exp Endodontics/ (23721) | |
| 6 | endodontic$.tw. (12546) | |
| 7 | Apicoectom$.tw. (436) | |
| 8 | (pulp$ adj4 cap$).tw. (1149) | |
| 9 | (pulpectom$ or pulpotom$).tw. (1063) | |
| 10 | exp Oral Surgical Procedures/ (53252) | |
| 11 | (gingivectom$ or gingivoplast$ or glossectom$).tw. (1068) | |
| 12 | mucoperio$ flap$.tw. (521) | |
| 13 | (tartar adj4 remov$).tw. (24) | |
| 14 | Sialography/ (1521) | |
| 15 | (sialograph$ or radiosialograph$).tw. (1080) | |
| 16 | (root adj4 canal adj4 (therap$ or treat$)).tw. (2619) | |
| 17 | ((dent$ or oral$ or tooth$ or teeth or peridont$ or orthodont$ or root$) adj4 (restorat$ or implant$ or replant$ or reimplant$ or re-implant$ or extract$ or remov$ or scal$ or polish$ or fill$ or irrigat$ or separat$ or expos$ or bond$ or band$ or prob$ or investigat$ or rubber dam$ or wedg$ or lining$ or liner$ or planing$)).tw. (94312) | |
| 18 | ((dent$ or oral$ or tooth$ or teeth$ or peridont$ or orthodont$ or root$ canal$) adj4 (surg$ or procedure$ or endoscop$ or operat$ or incis$ or excis$ or intervention$ or invasiv$ or biops$ or inject$)).tw. (42084) | |
| 19 | or/1-18 (210511) | |
| 20 | Mouthwashes/ (4487) | |
| 21 | Dentifrices/ (3458) | |
| 22 | (mouthwash$ or mouth wash$ or dentifrice$ or toothpaste$).tw. (6212) | |
| 23 | Chlorobenzenes/ (2496) | |
| 24 | chlorobenzene$.tw. (1116) | |
| 25 | Biguanides/ (2822) | |
| 26 | biguanide$.tw. (2078) | |
| 27 | Chlorhexidine/ (6430) | |
| 28 | chlor?hex$.tw. (6767) | |
| 29 | (corsodyl or eludril or tubulicid).tw. (89) | |

| Line number | Search terms | No. retrieved |
|---|---|---|
| 30 | ((cavit$ or oral or dent$ or mouth$ or endodontic$ or orthodontic$ or peridont$) adj4 (antibiot$ or anti-biot$ or antimicrob$ or anti-microb$ or anti-bacter$ or antibacter$ or anti-mycobacter$ or antimycobacter$ or bacteriocid$ or microbicid$ or anti-infect$ or antiinfect$ or anti-sept$ or antisept$ or disinfect$ or dis-infect$ or prophyla$ or chemoprophyla$ or chemo-prophyla$ or irrigant$)).tw. (11944) | |
| 31 | or/20-30 (34259) | |
| 32 | exp Bacteria/ (1106581) | |
| 33 | Bacterial Infections/ (61532) | |
| 34 | exp Bacteremia/ (22201) | |
| 35 | exp Endotoxemia/ (3565) | |
| 36 | (bacter$ or eubacter$ or endotox?emia$).tw. (583926) | |
| 37 | (enterococ$ or streptococ$ or staphylococ$).tw. (178823) | |
| 38 | or/32-37 (1378332) | |
| 39 | 19 and 31 and 38 (1859) | |
| 40 | Animals/ not Humans/ (4000367) | |
| 41 | 39 not 40 (1759) | |
| 42 | meta-analysis.pt. (54585) | |
| 43 | review.pt. (1964534) | |
| 44 | exp review literature/ (1968883) | |
| 45 | meta-analysis/ (54585) | |
| 46 | (metaanaly$ or metanaly$ or (meta adj2 analy$)).tw. (64437) | |
| 47 | (review$ or overview$).ti. (278949) | |
| 48 | (systematic$ adj4 (review$ or overview$)).tw. (58934) | |
| 49 | ((quantitative$ or qualitative$) adj4 (review$ or overview$)).tw. (4010) | |
| 50 | ((studies or trial$) adj1 (review$ or overview$)).tw. (7967) | |
| 51 | (integrat$ adj2 (research or review$ or literature)).tw. (3984) | |
| 52 | (pool$ adj1 (analy$ or data)).tw. (10184) | |
| 53 | (handsearch$ or (hand adj2 search$)).tw. (5614) | |
| 54 | (manual$ adj2 search$).tw. (3136) | |
| 55 | or/42-54 (2121198) | |
| 56 | randomized controlled trial.pt. (399960) | |
| 57 | controlled clinical trial.pt. (90666) | |
| 58 | clinical trial.pt. (501003) | |
| 59 | exp clinical trial/ (816374) | |
| 60 | placebos/ (34008) | |
| 61 | random allocation/ (84113) | |
| 62 | double-blind method/ (132489) | |
| 63 | single-blind method/ (20614) | |
| 64 | cross-over studies/ (36229) | |
| 65 | ((random$ or control$ or clinical$) adj2 (trial$ or stud$)).tw. (675952) | |
| 66 | (random$ adj2 allocat$).tw. (20999) | |
| 67 | placebo$.tw. (159821) | |

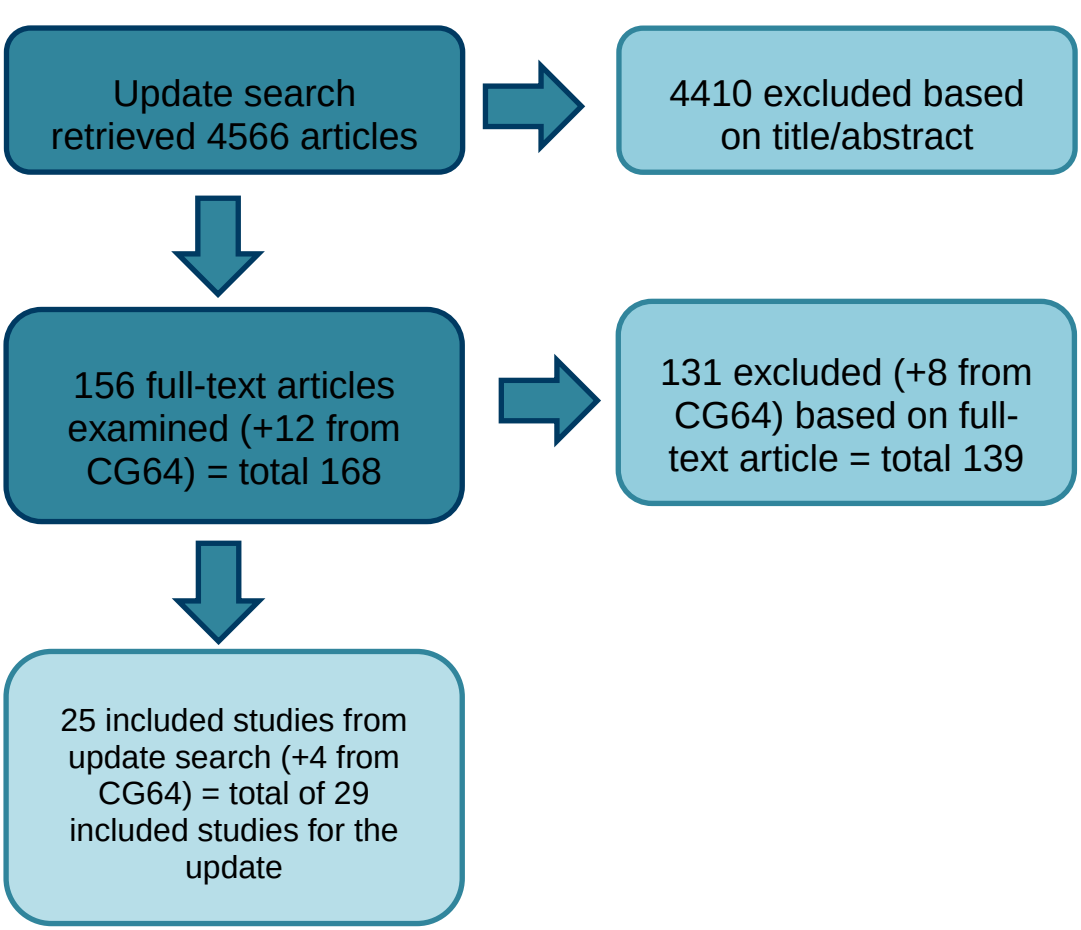
| Line number | Search terms | No. retrieved |
|---|---|---|
| 68 | ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (130057) | |
| 69 | (crossover$ or (cross adj over$)).tw. (58948) | |
| 70 | or/56-69 (1376504) | |
| 71 | Epidemiologic Studies/ (6272) | |
| 72 | exp Case-Control Studies/ (711198) | |
| 73 | exp Cohort Studies/ (1439568) | |
| 74 | Cross-Sectional Studies/ (193002) | |
| 75 | Comparative Study.pt. (1731142) | |
| 76 | case control$.tw. (80732) | |
| 77 | case series.tw. (35347) | |
| 78 | (cohort adj (study or studies)).tw. (89864) | |
| 79 | cohort analy$.tw. (3830) | |
| 80 | (follow up adj (study or studies)).tw. (37517) | |
| 81 | (observational adj (study or studies)).tw. (44392) | |
| 82 | longitudinal.tw. (141606) | |
| 83 | prospective.tw. (354704) | |
| 84 | retrospective.tw. (272363) | |
| 85 | cross sectional.tw. (167096) | |
| 86 | or/71-85 (3438039) | |
| 87 | 55 or 70 or 86 (5994621) | |
| 88 | Animals/ not Humans/ (4000367) | |
| 89 | 87 not 88 (5345098) | |
| 90 | 41 and 89 (1093) | |
| 91 | limit 90 to ed=20070904-20141201 (407) | |
| 92 | limit 91 to english language (389) | |

# Appendix E: Review flowchart

## E.1 Overview of epidemiology

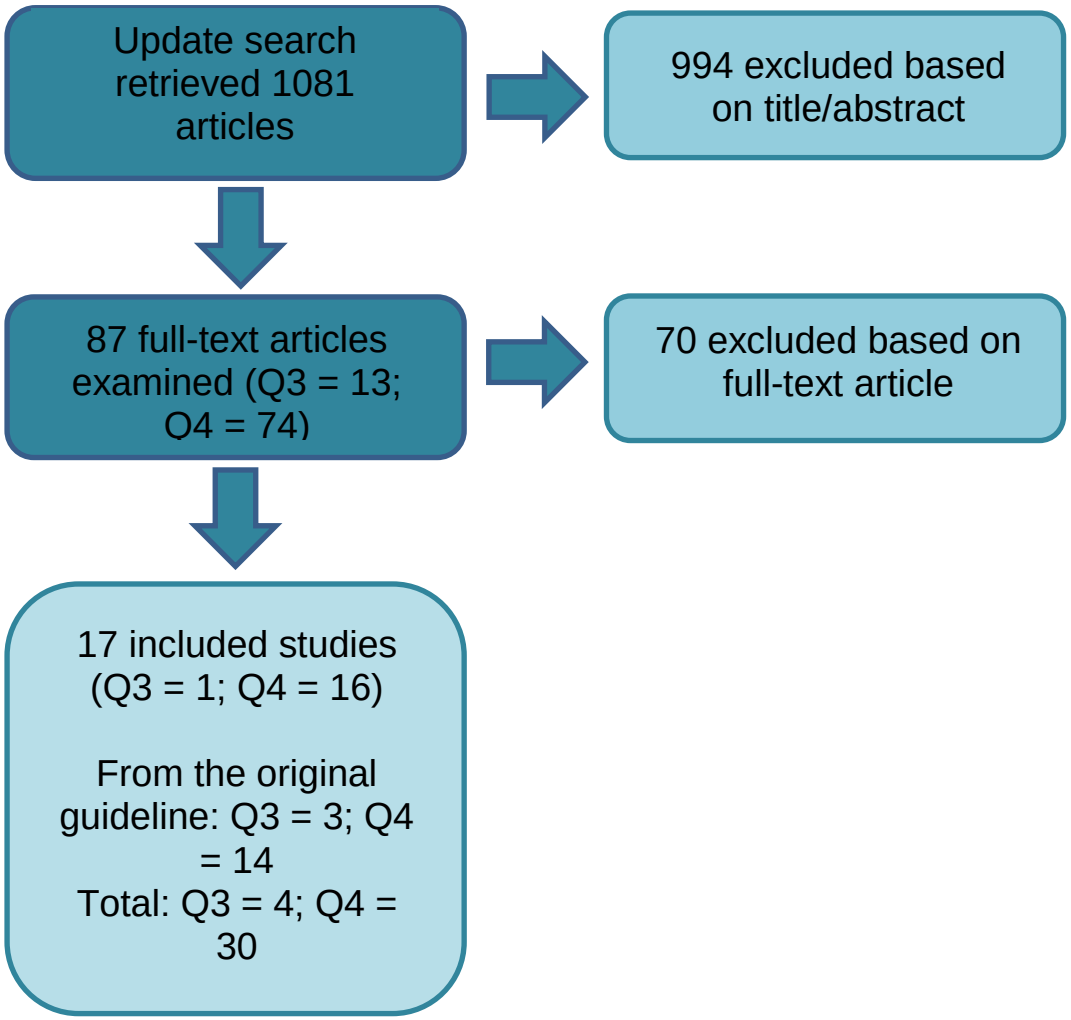



## E.2 Review questions 1a 1b and 2

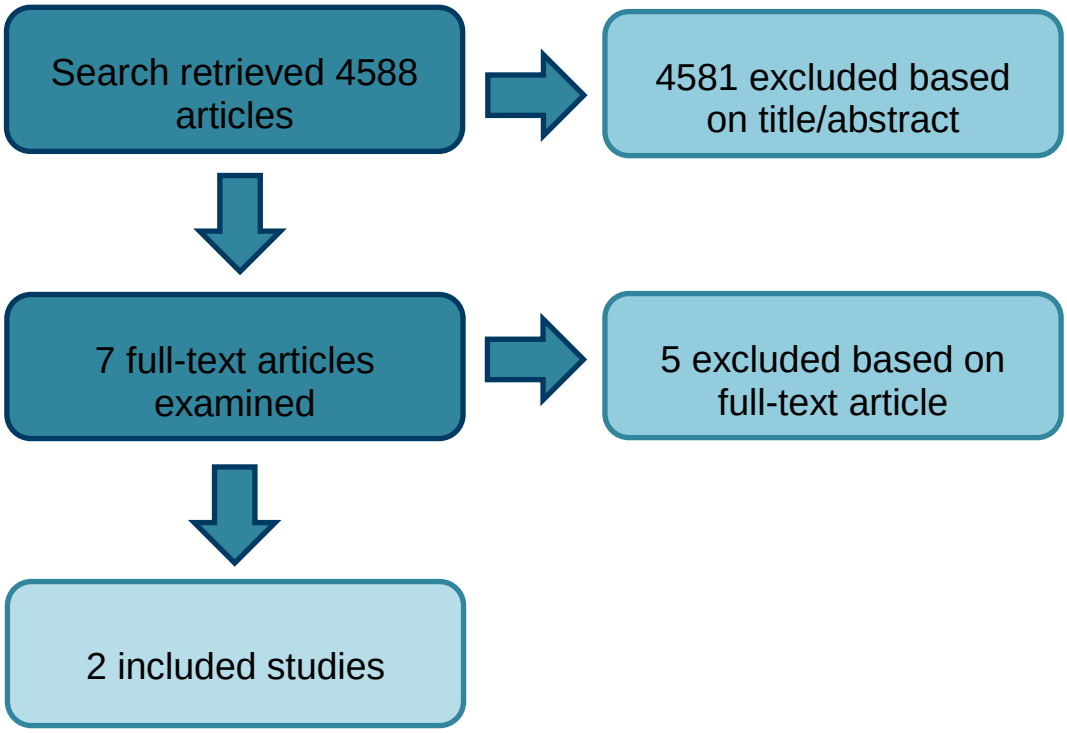


## E.3 Review questions 3 and 4

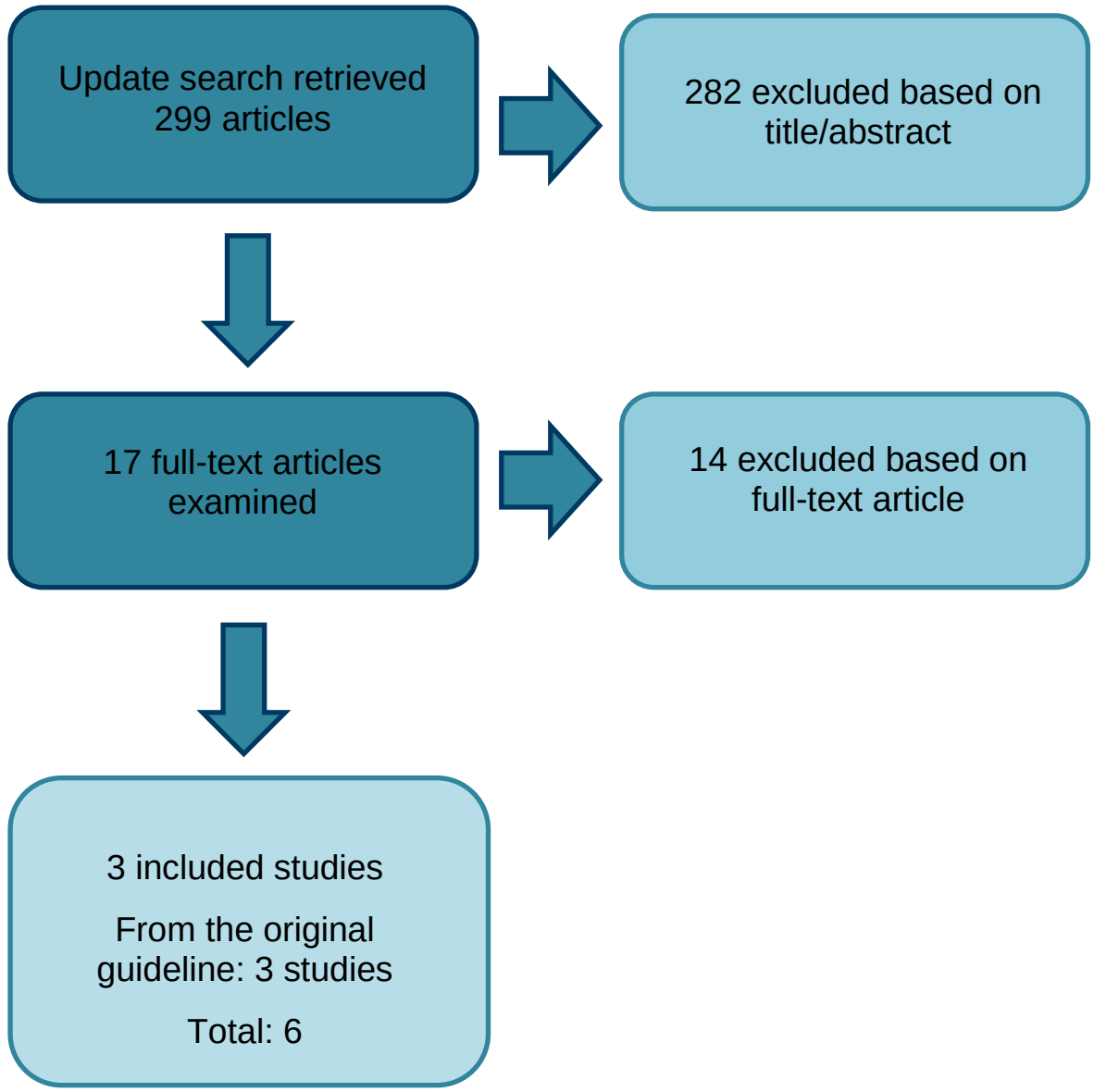
Update search for question 3 and 4 was conducted under one search



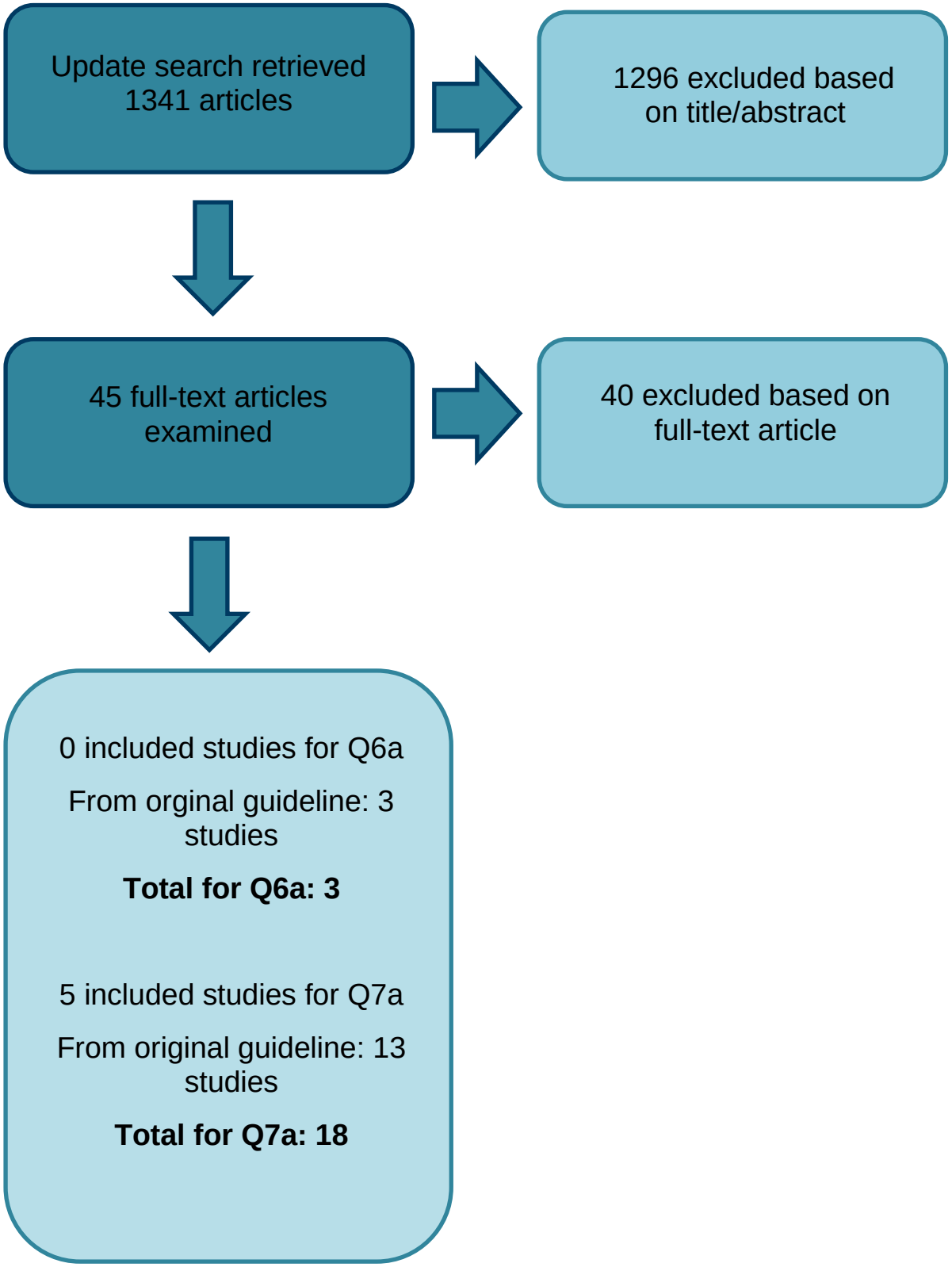
Additional broad search for review question 3:



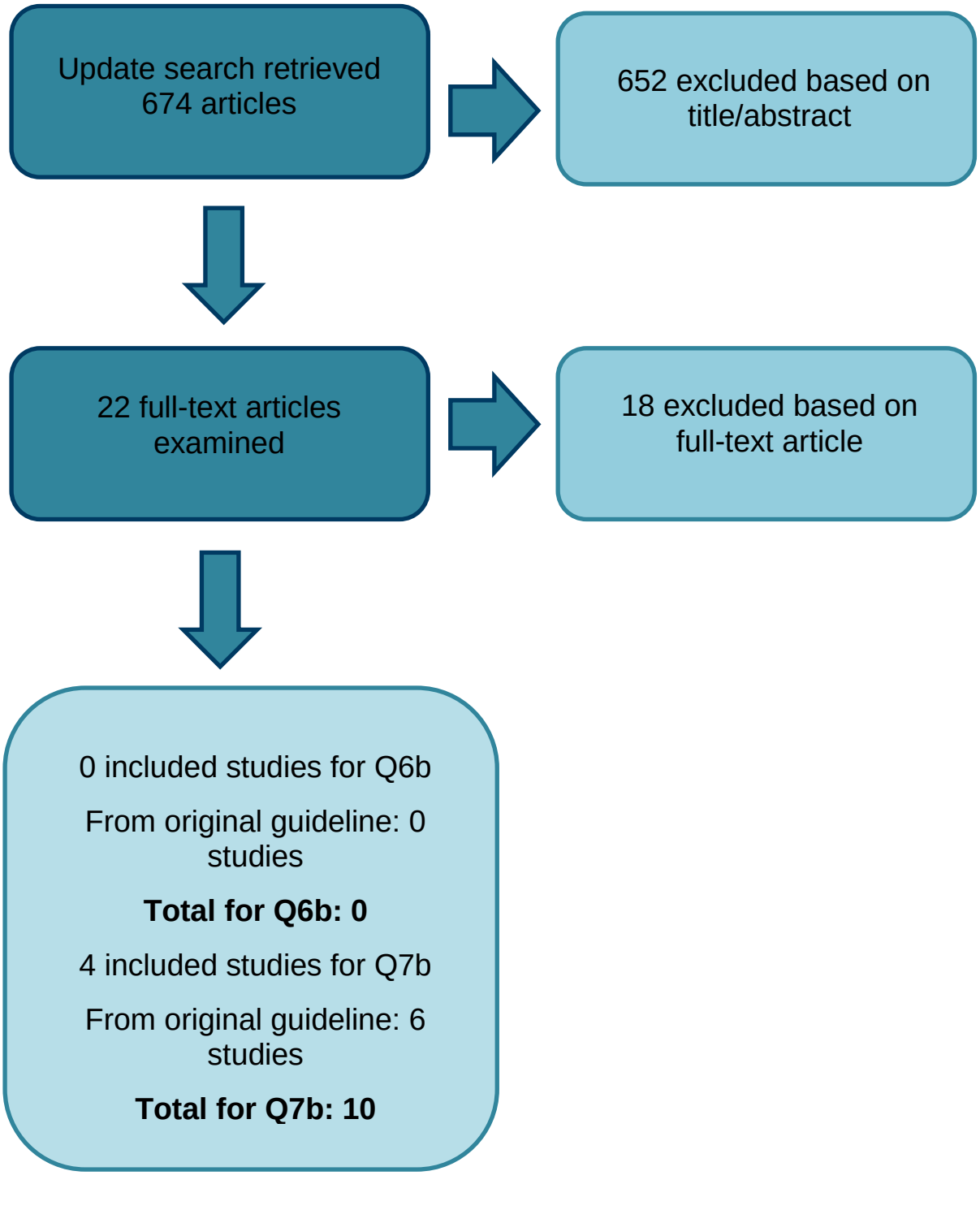
## E.4 Review question 5



## E.5 Review question 6a and 7a



## E.6 Review question 6b and 7b



# 1 Appendix F: Excluded studies

## F.1 2 Overview of epidemiology

| Reference | Reason for exclusion |
|---|---|
| Alestig K, Hogevik H, Olaison L (2000) Infective endocarditis: a diagnostic and therapeutic challenge for the new millennium. [Review] [89 refs]. Scandinavian Journal of Infectious Diseases 32: 343-56. | Not relevant – about diagnostics. |
| Allen KD, Vardhan MS (2000) Epidemiology of infective endocarditis. Journal of Infection 40: 99-100. | Letter only. |
| Bashore TM, Cabell C, Fowler V, Jr. (2006) Update on infective endocarditis. [Review] [234 refs]. Current Problems in Cardiology 31: 274-352. | Not relevant – general overview of the condition only. |
| Baskerville CA, Hanrahan BB, Burke AJ et al. (2012) Infective endocarditis and rheumatic heart disease in the north of Australia. Heart, Lung & Circulation 21: 36-41. | Distribution of clinical features data only, no trend of incidence. |
| Berlin JA, Abrutyn E, Strom BL et al. (1995) Incidence of infective endocarditis in the Delaware Valley, 1988-1990. American Journal of Cardiology 76: 933-6. | Distribution of clinical features data only, no trend of incidence. |
| Cecchi E, Imazio M, De Rosa FG et al. (2008) Infective endocarditis in the real world: the Italian Registry of Infective Endocarditis (Registro Italiano Endocardite Infettiva - RIEI). Journal of Cardiovascular Medicine 9: 508-14. | Distribution of clinical features data only, no trend of incidence. |
| Cecchi E, De Rosa FG, Chirillo F et al. (2010) The prophylaxis of infective endocarditis: a joint position study of the Italian Federation of Cardiologists and the Italian Society of Infectious and Tropical Diseases. [Review] [23 refs]. Journal of Cardiovascular Medicine 11: 419-25. | Commentary on the guideline, no data on the impact of the guideline. |
| Chen SJ, Liu CJ, Chao TF et al. (2013) Dental scaling and risk reduction in infective endocarditis: a nationwide population-based case-control study. Canadian Journal of Cardiology 29: 429-33. | Not relevant – about risk, not about trend of incidence. |
| Chirouze C, Hoen B, Duval X (2012) Infective endocarditis prophylaxis: moving from dental prophylaxis to global prevention?. [Review]. European Journal of Clinical Microbiology & Infectious Diseases 31: 2089-95. | Narrative review/commentary |
| Chirouze C, Athan E, Alla F et al. (2013) Enterococcal endocarditis in the beginning of the 21st century: analysis from the International Collaboration on Endocarditis-Prospective Cohort Study. Clinical Microbiology & Infection 19: 1140-7. | Single hospital study only, not population-based. |
| Chopra T, Kaatz GW (2010) Treatment strategies for infective endocarditis. [Review] [98 refs]. Expert Opinion on Pharmacotherapy 11: 345-60. | Not relevant – about treatment. |
| Chugh TD (2004) Pathogenesis of infective endocarditis. [Review] [31 refs]. Indian Journal of Pathology & Microbiology 47: 163-7. | Not relevant – no data on trend of incidence. |
| Cicalini S, Puro V, Angeletti C et al. (2006) Profile of infective endocarditis in a referral hospital over the last 24 years. Journal of Infection 52: 140-6. | Single hospital study only, not population-based. |
| Curlier E, Hoen B, Alla F et al. (2014) Relationships between sex, early valve surgery and mortality in patients with left-sided infective endocarditis analysed in a population-based cohort study. Heart 100: 1173-8. | Distribution of clinical features data only, no trend of incidence. |
| Delahaye F, Alla F, Beguinot I et al. (2007) In-hospital mortality of infective endocarditis: prognostic factors and evolution over an 8-year | Not relevant – about prognosis. |

| Reference | Reason for exclusion |
|---|---|
| period. Scandinavian Journal of Infectious Diseases 39: 849-57. | |
| DeSimone DC, Tleyjeh IM, Correa de Sa DD et al. (2012) Incidence of infective endocarditis caused by viridans group streptococci before and after publication of the 2007 American Heart Association's endocarditis prevention guidelines. Circulation 126: 60-4. | Analysis between 2007 to 2010 were only based on 3 cases of IE. |
| DeSimone DC, Tleyjeh IM, Correa de Sa DD et al. (2013) Response to letter regarding article, "Incidence of infective endocarditis due to viridans group streptococci before and after publication of the 2007 American Heart Association's endocarditis prevention guidelines". Circulation 127: e521. | Letter only. |
| Di FS (2012) Prophylaxis of infective endocarditis in patients with congenital heart disease in the context of recent modified guidelines. [Review]. Archives of cardiovascular diseases 105: 454-60. | Narrative review/commentary |
| Duval X, Alla F, Hoen B (2013) Letter by Duval et al regarding article, "Incidence of Infective endocarditis caused by viridans group streptococci before and after publication of the 2007 American Heart Association's endocarditis prevention guidelines". Circulation 127: e520. | Letter only. |
| Dzupova O, Machala L, Baloun R et al. (2012) Incidence, predisposing factors, and aetiology of infective endocarditis in the Czech Republic. Scandinavian Journal of Infectious Diseases 44: 250-5. | Distribution of clinical features data only, no trend of incidence. |
| Erwin JP, Otto CM (2014) Infective endocarditis: old problem, new guidelines and still much to learn. Heart 100: 996-8. | Narrative review/commentary |
| Fernandez-Hidalgo N, Almirante B, Tornos P et al. (2012) Immediate and long-term outcome of left-sided infective endocarditis. A 12-year prospective study from a contemporary cohort in a referral hospital. Clinical Microbiology & Infection 18: E522-E530. | Single hospital study only, not population-based. |
| Ferreira JP, Gomes F, Rodrigues P et al. (2013) Left-sided infective endocarditis: analysis of in-hospital and medium-term outcome and predictors of mortality. Revista Portuguesa de Cardiologia 32: 777-84. | Two hospitals study only, not population-based. |
| Ferreiros E, Nacinovich F, Casabe JH et al. (2006) Epidemiologic, clinical, and microbiologic profile of infective endocarditis in Argentina: a national survey. The Endocarditis Infecciosa en la Republica Argentina-2 (EIRA-2) Study. American Heart Journal 151: 545-52. | Distribution of clinical features data only, no trend of incidence. |
| Fonager K, Lindberg J, Thulstrup AM et al. (2003) Incidence and short-term prognosis of infective endocarditis in Denmark, 1980-1997. Scandinavian Journal of Infectious Diseases 35: 27-30. | Not relevant – data too old (only between 1980 to 1997), 18 years gap to be deemed as current trend. |
| Galvez-Acebal J, Rodriguez-Bano J, Martinez-Marcos FJ et al. (2010) Prognostic factors in left-sided endocarditis: results from the Andalusian multicenter cohort. BMC Infectious Diseases 10: 17. | Not relevant – about prognosis. |
| Giannitsioti E, Skiadas I, Antoniadou A et al. (2007) Nosocomial vs. community-acquired infective endocarditis in Greece: changing epidemiological profile and mortality risk. Clinical Microbiology & Infection 13: 763-9. | Distribution of clinical features data only, no trend of incidence. |
| Hill EE, Herijgers P, Herregods MC et al. (2006) Evolving trends in infective endocarditis. [Review] [58 refs]. Clinical Microbiology & Infection 12: 5-12. | Narrative review/commentary |
| Hill EE, Herijgers P, Claus P et al. (2007) Infective endocarditis: changing epidemiology and predictors of 6-month mortality: a prospective cohort study. European Heart Journal 28: 196-203. | Single hospital study only, not population-based. |
| Hoen B (2006) Epidemiology and antibiotic treatment of infective | Not relevant – about |

| Reference | Reason for exclusion |
|---|---|
| endocarditis: an update. [Review] [36 refs]. Heart 92: 1694-700. | treatment. |
| Hogevik H, Olaison L, Andersson R et al. (1995) Epidemiologic aspects of infective endocarditis in an urban population. A 5-year prospective study. [Review] [69 refs]. Medicine 74: 324-39. | Distribution of clinical features data only, no trend of incidence. |
| Hricak V, Liska B, Kovackova J et al. (2007) Trends in risk factors and etiology of 606 cases of infective endocarditis over 23 years (1984-2006) in slovakia. Journal of Chemotherapy 19: 198-202. | About risk factors only, no trend of incidence. |
| Kerr A, Williams M (2014) Infective endocarditis: trends in the disease and how we study them. New Zealand Medical Journal 127: 10-2. | Narrative review/commentary |
| Kohli V (2002) Infective endocarditis. [Review] [13 refs]. Indian Journal of Pediatrics 69: 333-9. | Narrative review/commentary |
| Krcmery V, Hricak V, Demitrovicova A et al. (2009) Infective endocarditis in elderly patients. Scandinavian Journal of Infectious Diseases 41: 623-4. | Letter only. |
| Leone S, Ravasio V, Durante-Mangoni E et al. (2012) Epidemiology, characteristics, and outcome of infective endocarditis in Italy: the Italian Study on Endocarditis. Infection 40: 527-35. | Distribution of clinical features data only, no trend of incidence. |
| Letaief A, Boughzala E, Kaabia N et al. (2007) Epidemiology of infective endocarditis in Tunisia: a 10-year multicenter retrospective study. International Journal of Infectious Diseases 11: 430-3. | Distribution of clinical features data only, no trend of incidence. |
| Loupa C, Mavroidi N, Boutsikakis I et al. (2004) Infective endocarditis in Greece: a changing profile. Epidemiological, microbiological and therapeutic data. Clinical Microbiology & Infection 10: 556-61. | Distribution of clinical features data only, no trend of incidence. |
| Mokhles MM, Ciampichetti I, van DR et al. (2012) Infective endocarditis in a tertiary referral hospital: long-term follow up. Journal of Heart Valve Disease 21: 118-24. | Single hospital study only, not population-based. |
| Nishimura RA, Carabello BA, Faxon DP et al. (2008) ACC/AHA 2008 Guideline update on valvular heart disease: focused update on infective endocarditis: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Journal of the American College of Cardiology 52: 676-85. | Commentary on the guideline, no data on the impact of the guideline. |
| Pachirat O, Chetchotisakd P, Klungboonkrong V et al. (2002) Infective endocarditis: prevalence, characteristics and mortality in Khon Kaen, 1990-1999. Journal of the Medical Association of Thailand 85: 1-10. | Distribution of clinical features data only, no trend of incidence. |
| Prendergast BD (2006) The changing face of infective endocarditis. [Review] [46 refs]. Heart 92: 879-85. | Narrative review/commentary |
| Rushani D, Kaufman JS, Ionescu-Ittu R et al. (2013) Infective endocarditis in children with congenital heart disease: cumulative incidence and predictors. Circulation 128: 1412-9. | Distribution of clinical features data only, no trend of incidence. |
| Seto TB (2007) The case for infectious endocarditis prophylaxis: time to move forward. [Review] [42 refs]. Archives of Internal Medicine 167: 327-30. | Narrative review/commentary |
| Shanson D (2008) New British and American guidelines for the antibiotic prophylaxis of infective endocarditis: do the changes make sense? A critical review. [Review] [55 refs]. Current Opinion in Infectious Diseases 21: 191-9. | Narrative review/commentary |
| Singh J, Straznicky I, Avent M et al. (2005) Antibiotic prophylaxis for endocarditis: time to reconsider. [Review] [56 refs]. Australian Dental Journal 50: Suppl-8. | Narrative review/commentary |
| Slipczuk L, Codolosa JN, Davila CD et al. (2013) Infective | Distribution of clinical |

| Reference | Reason for exclusion |
|---|---|
| endocarditis epidemiology over five decades: a systematic review. [Review]. PLoS ONE [Electronic Resource] 8: e82665. | features data only, no trend of incidence. |
| Sousa C, Botelho C, Rodrigues D et al. (2012) Infective endocarditis in intravenous drug abusers: an update. [Review]. European Journal of Clinical Microbiology & Infectious Diseases 31: 2905-10. | Narrative review/commentary |
| Tak T, Reed KD, Haselby RC et al. (2002) An update on the epidemiology, pathogenesis and management of infective endocarditis with emphasis on Staphylococcus aureus. [Review] [51 refs]. WMJ 101: 24-33. | Distribution of clinical features data only, no trend of incidence. |
| Thanavaro KL, Nixon JV (2014) Endocarditis 2014: an update. [Review]. Heart & Lung 43: 334-7. | Narrative review/commentary |
| Thornhill MH, Dayer MJ, Forde JM et al. (2011) Impact of the NICE guideline recommending cessation of antibiotic prophylaxis for prevention of infective endocarditis: before and after study. BMJ 342: d2392. | Part of Thornhill et al (2014) paper |
| Thornhill MH (2012) Infective endocarditis: the impact of the NICE guidelines for antibiotic prophylaxis. Dental Update 39: 6-10. | Part of Thornhill et al (2014) paper |
| Tornos P, Iung B, Permanyer-Miralda G et al. (2005) Infective endocarditis in Europe: lessons from the Euro heart survey. Heart 91: 571-5. | Distribution of clinical features data only, no trend of incidence. |
| Tornos P, Gonzalez-Alujas T, Thuny F et al. (2011) Infective endocarditis: the European viewpoint. [Review]. Current Problems in Cardiology 36: 175-222. | Narrative review/commentary |
| Tseng WC, Chiu SN, Shao PL et al. (2014) Changing spectrum of infective endocarditis in children: a 30 years experiences from a tertiary care center in Taiwan. Pediatric Infectious Disease Journal 33: 467-71. | Single centre study, clinical features data only, no trend of incidence. |
| Walls G, McBride S, Raymond N et al. (2014) Infective endocarditis in New Zealand: data from the International Collaboration on Endocarditis Prospective Cohort Study. New Zealand Medical Journal 127: 38-51. | Single centre study, clinical features data only, no trend of incidence. |
| Wang W, Sun H, Lv T et al. (2014) Retrospective studies on pediatric infective endocarditis over 40 years in a mid-west area of China. Cardiology 128: 88-91. | Distribution of clinical features data only, no trend of incidence. |

## F.21 Review questions 1a, 1b and 2

| Reference | Reason for exclusion |
|---|---|
| Alsmady,M.M., Ennab,R.M., Hassuneh,S.S., et al. (2010) Early and mid-term evaluation of mechanical heart valve replacement, Kuwait Medical JournalKuwait Med.J., 42, 55-59. | Case series |
| Alsoufi,Bahaaldin, Al-Halees,Zohair, Fadel,Bahaa et al. (2010) Simultaneous aortic and mitral valve replacement in children: time-related outcomes and risk factors, The Journal of heart valve diseaseJ Heart Valve Dis, 19, 341-348. | Does not answer research question. Case series |
| Anderson,D.J., Olaison,L., Mcdonald,J.R. et al. (2005) Enterococcal prosthetic valve infective endocarditis: report of 45 episodes from the International Collaboration on Endocarditis-merged database, Eur J Clin Microbiol Infect Dis, 24, 665-70, | Analysis between types of IE only |
| Ardal,H, Toker,M E, Rabus, M.B. (2006) Does aortic root enlargement impair the outcome of patients with small aortic root? Journal of cardiac surgeryJ Card Surg, 21, 449-453. | Does not answer research question |
| Ariyaratne,Thathya V., Billah,Baki, Yap,Cheng Hon et al (2011) An Australian risk prediction model for determining early mortality following aortic valve replacement, European journal of cardio- | Does not answer research question |

| Reference | Reason for exclusion |
|---|---|
| thoracic surgery : official journal of the European Association for Cardio-thoracic SurgeryEur J Cardiothorac Surg, 39, 815-821. | |
| Assiri,Abdullah S., (2011) Clinical and microbiological profiles of infective endocarditis in a tertiary hospital in Aseer region, Saudi Arabia, Journal of the Saudi Heart AssociationJ.Saudi Heart Assoc., 23, 207-211. | Case series |
| Athan, Eugene, Chu, Vivian H., Tattevin, Pierre et al. (2012) ICE-PCS,Investigators, Clinical characteristics and outcome of infective endocarditis involving implantable cardiac devices, JAMA : the journal of the American Medical Association, 307, 1727-1735. | No data on parameters for comparison group |
| Aydin,Ebuzer, Yapici,Fikri, (2013) A retrospective analysis of factors influencing re-operation in patients undergoing mechanical valve replacement, Cardiovascular journal of AfricaCardiovasc.j.Afr., 24, 251-254. | Case series |
| Bachour,Khaled, Zmily,Hammam, Kizilbash,Mohammad et al. (2009) Valvular perforation in left-sided native valve infective endocarditis, Clinical cardiologyClin Cardiol, 32, E55-E62. | Does not answer research question |
| Barker,Gregory M., O'Brien,Sean M., Welke,Karl F et al. (2010) Major infection after pediatric cardiac surgery: a risk estimation model, The Annals of thoracic surgeryAnn Thorac Surg, 89, 843-850. | 1) infection after acute surgery 2) IE is grouped with another infection (data not separated) |
| Barsic,Bruno, Dickerman,Stuart, Krajinovic,Vladimir et al. (2013) International Collaboration on Endocarditis-Prospective Cohort Study Investigators, Influence of the timing of cardiac surgery on the outcome of patients with infective endocarditis and stroke, Clinical infectious diseases : an official publication of the Infectious Diseases Society of AmericaClin Infect Dis, 56, 209-217. | Does not answer research question. Population IE and stroke not reported by cardiac conditions. |
| Baskerville, Catherine A. Hanrahan, Brendan B. Burke, Andrew J. et al. (2012) Infective endocarditis and Rheumatic Heart Disease in the North of Australia. Heart, Lung and Circulation 21:36-41. | No comparison group |
| Baumgartner,H. (2011) Infective endocarditis in adults with congenital heart disease: Is it time to change our approach to prophylaxis based on new insights into risk prediction?, European heart journalEur Heart J, 32, 1835-1837. | Editorial |
| Benito,Natividad, Miro,Jose M., de Lazzari,Elisa et al. (2009) ICE-PCS (International Collaboration on Endocarditis Prospective Cohort Study) Investigators, Health care-associated native valve endocarditis: importance of non-nosocomial acquisition, Annals of internal medicineAnn Intern Med, 150, 586-594. | Does not answer research question |
| Bernhardt,Alexander M.J., Treede,Hendrik, Rybczynski,Meike et al. (2011) Comparison of aortic root replacement in patients with Marfan syndrome, European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic SurgeryEur J Cardiothorac Surg, 40, 1052-1057. | Not relevant - no comparator |
| Bin Abdulhak,A.A., Baddour,L.M., Erwin,P.J. et al (2014) Global and regional burden of infective endocarditis, 1990-2010: A systematic review of the literature, Global HeartGlo.Heart, 9, 131-143. | Does not report on incidences of IE in pre-existing cardiac conditions. |
| Brennan,J.Matthew, Edwards,Fred H., Zhao,Yue et al. (2013) DEcIDE AVR (Developing Evidence to Inform Decisions about Effectiveness-Aortic Valve Replacement) Research Team, Long-term safety and effectiveness of mechanical versus biologic aortic valve prostheses in older patients: results from the Society of Thoracic Surgeons Adult Cardiac Surgery National Database, Circulation, 127, 1647-1655. | Does not answer research question |
| Brown,Morgan L., Dearani,Joseph A., Danielson,Gordon K. et al. (2009) Comparison of the outcome of porcine bioprosthetic versus | Cardiac procedure |

| Reference | Reason for exclusion |
|---|---|
| mechanical prosthetic replacement of the tricuspid valve in the Ebstein anomaly, The American journal of cardiologyAm J Cardiol, 103, 555-561, | |
| Chirouze,C., Athan,E., Alla,F. et al. (2013) International Collaboration on Endocarditis Study Group, Enterococcal endocarditis in the beginning of the 21st century: analysis from the International Collaboration on Endocarditis-Prospective Cohort Study, Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious DiseasesClin Microbiol Infect, 19, 1140-1147. | Not relevant |
| Danchin,N., Voiriot,P., Briancon,S. et al. (1989) Mitral valve prolapse as a risk factor for infective endocarditis, The Lancet,1,743-5. | Evaluating the risk of mitral valve prolapse in people with mitral value endocarditis |
| Chu,V.H., Miro,J.M., Hoen,B., Cabell,C.H. et al. (2009) International Collaboration on Endocarditis-Prospective Cohort Study Group, Coagulase-negative staphylococcal prosthetic valve endocarditis--a contemporary update based on the International Collaboration on Endocarditis: prospective cohort study, Heart (British Cardiac Society)Heart, 95, 570-576. | Outcomes don't match protocol. |
| d'Alessandro,Cosimo, Vistarini,Nicola, Aubert,Stephane, et al. (2007) European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic SurgeryEur J Cardiothorac Surg, 32, 596-603. | IE reported as outcome but data not reported by group therefore no comparison possible |
| Deharo,Jean Claude, Quatre,Amandine, Mancini,Julien et al. (2012) Long-term outcomes following infection of cardiac implantable electronic devices: a prospective matched cohort study, Heart (British Cardiac Society)Heart, 98, 724-731. | Inappropriate study population |
| Desai,Nimesh D., McCarthy,Fenton, Moser,William et al. (2011) Durability of porcine bioroots in younger patients with aortic root pathology: a propensity-matched comparison with composite mechanical roots, The Annals of thoracic surgeryAnn Thorac Surg, 92, 2054-1. | Cardiac procedure |
| Dhawan,V.K., (2003) Infective Endocarditis in Elderly Patients, Curr.Infect.Dis.Rep., 5, 285-292. | Review article |
| Doss,Mirko, Wood,Jeffrey P., Kiessling,Arndt H. et al (2011) Comparative evaluation of left ventricular mass regression after aortic valve replacement: a prospective randomized analysis, Journal of cardiothoracic surgeryJ Cardiothorac Surg, 6, 136-, | Does not answer research question |
| Dzupova,Olga, Machala,Ladislav, Baloun,Rudolf et al. (2012) Incidence, predisposing factors, and aetiology of infective endocarditis in the Czech Republic, Scandinavian journal of infectious diseasesScand J Infect Dis, 44, 250-255. | Case series |
| Emery,R.W., Krogh,C.C., Jones,D.J. et al. (2004) Five-year follow up of the ATS mechanical heart valve, Journal of Heart Valve DiseaseJ.Heart Valve Dis., 13, 231-238. | Not relevant. Single case of IE |
| Emery,Robert W., Krogh,Christopher C., McAdams,Sean et al. (2010) Long-term follow up of patients undergoing reoperative surgery with aortic or mitral valve replacement using a St. Jude Medical prosthesis, The Journal of heart valve diseaseJ Heart Valve Dis, 19, 473-484. | Reoperative open heart surgery |
| Englberger,L., Carrel,T., Schaff,H.V. et al (2001) Differences in heart valve procedures between North American and European centers: A report from the artificial valve endocarditis reduction trial (AVERT), Journal of Heart Valve DiseaseJ.Heart Valve Dis., 10, 562-571. | Does not answer research question |
| Ennker,Juergen A.C., Albert,Alexander A., Rosendahl,Ulrich P. et al. | Outcomes not reported by |

| Reference | Reason for exclusion |
|---|---|
| (2008) Ten-year experience with stentless aortic valves: full-root versus subcoronary implantation, The Annals of thoracic surgeryAnn Thorac Surg, 85, 445-3. | cardiac condition |
| Fedoruk,Lynn M., Jamieson,W.R.E., Ling,Hilton et al (2009) Predictors of recurrence and reoperation for prosthetic valve endocarditis after valve replacement surgery for native valve endocarditis, The Journal of thoracic and cardiovascular surgeryJ Thorac Cardiovasc Surg, 137, 326-333. | Does not answer research question |
| Feringa,H.H.H., Shaw,L.J., Poldermans,D. et al (2007) Mitral Valve Repair and Replacement in Endocarditis: A Systematic Review of Literature, Annals of Thoracic SurgeryAnn.Thorac.Surg. 83, 564-570. | Does not answer research question |
| Fernandez Guerrero,Manuel L., Gonzalez Lopez,Julio J., Goyenechea,Ana et al (2009) Endocarditis caused by Staphylococcus aureus: A reappraisal of the epidemiologic, clinical, and pathologic manifestations with analysis of factors determining outcome, MedicineMedicine (Baltimore), 88, 1-22. | Inadequate comparison group |
| Fernandez-Hidalgo,N., Almirante,B., Tornos,P. et al (2012) Immediate and long-term outcome of left-sided infective endocarditis. A 12-year prospective study from a contemporary cohort in a referral hospital, Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious DiseasesClin Microbiol Infect, 18, E522-E530. | Indirect population. Hospital vs community acquired. No extractable data, only types of IE |
| Fernandez-Hidalgo,Nuria, Almirante,Benito, Tornos,Pilar, et al (2008) Contemporary epidemiology and prognosis of health care-associated infective endocarditis, Clinical infectious diseases : an official publication of the Infectious Diseases Society of AmericaClin Infect Dis, 47, 1287-1297. | Indirect population. Hospital vs community aquired |
| Finkelstein, R. et al (2012). Incidence and risk factors for endocarditis among patients with health care-associated Staphylococcus aureus bacteraemia. Scandinavian Journal of Infectious Diseases.44:934-940. | Population is peole with s.aureus bacteraemia who get IE (inapprorpriate population for comparison). Pre-existing cardiac conditions is a composite risk factor that include pace-makers. |
| Fisher,M.C. (2001) Changing Risk Factors for Pediatric Infective Endocarditis, Curr.Infect.Dis.Rep., 3, 333-336. | Narrative article |
| Fitzmaurice,Gerard J., McKenna,Adrian J., Murphy,Jamie et al. (2014) Streptococcus bovis bacteraemia: an evaluation of the long-term effect on cardiac outcomes, General thoracic and cardiovascular surgeryGen Thorac Cardiovasc Surg, 62, 142-148. | Could not tease out the number of different cardiac outcomes |
| Forcillo,Jessica, El Hamamsy,Ismail, Stevens,Louis Mathieu et al (2014) The perimount valve in the aortic position: twenty-year experience with patients under 60 years old, The Annals of thoracic surgeryAnn Thorac Surg, 97, 1526-1532. | Does not answer research question |
| Fortun,J., Centella,T., Martin-Davila,P., Lamas,M.J. et al (2013) Infective endocarditis in congenital heart disease: a frequent community-acquired complication, Infection, 41, 167-174. | Case series |
| Gaca,Jeffrey G., Sheng,Shubin, Daneshmand,Mani A. et al (2011) Outcomes for endocarditis surgery in North America: a simplified risk scoring system, The Journal of thoracic and cardiovascular surgeryJ Thorac Cardiovasc Surg, 141, 98-2. | Does not answer research question |
| Gamez,Antonio, Castillo,Juan C., Bonilla,Juan L. et al (2011) Infective endocarditis after the Ross procedure, International journal of cardiologyInt J Cardiol, 147, e53-e54. | Case report |
| Garcia,Mercedes A., Alarcon,Graciela S., Boggio,Gabriela, et al | Does not answer research |

| Reference | Reason for exclusion |
|---|---|
| (2014) Grupo Latino Americano de Estudio del Lupus Eritematoso (GLADEL), Primary cardiac disease in systemic lupus erythematosus patients: protective and risk factors--data from a multi-ethnic Latin American cohort, Rheumatology (Oxford, England)Rheumatology (Oxford), 53, 1431-1438. | question |
| Gersony,W.M., Hayes ,C.J., Driscoll,D.J. et al (1993) Bacterial endocarditis in patients with aortic stenosis, pulmonary stenosis, or ventricular septal defect, Circulation, 87, I-121-I-126. | Prevalence data only, no comparisons. |
| Girdauskas,Evaldas, Rouman,Mina, Borger,Michael A. et al (2013) Comparison of aortic media changes in patients with bicuspid aortic valve stenosis versus bicuspid valve insufficiency and proximal aortic aneurysm, Interactive cardiovascular and thoracic surgeryInteract Cardiovasc Thorac Surg, 17, 931-936. | Does not answer research question |
| Gregor,P. (2013) What's new in the prevention of infective endocarditis?, Cor et VasaCor Vasa, 55, e520-e524. | Narrative article |
| Habib,Ammar, Le,Katherine Y., Baddour,Larry M. et al. (2013) Mayo Cardiovascular Infections Study Group, Predictors of mortality in patients with cardiovascular implantable electronic device infections, The American journal of cardiologyAm J Cardiol, 111, 874-879. | Outcomes not reported by cardiac condition |
| Hanai,Makoto, Hashimoto,Kazuhiro, Mashiko,Kenoh et al. (2008) Active infective endocarditis: management and risk analysis of hospital death from 24 years' experience, Circulation journal : official journal of the Japanese Circulation SocietyCirc J, 72, 2062-2068. | Outcomes not reported according to pre-existing cardiac condition |
| Hill E.E., Vanderschueren, S. Verhaegen, J.  Herugers, P et al. (2007) Risk Factors for Infective Endocarditis and Outcome of Patients with Staphylococcus aureus Bacteremia.  Mayo Clin Proc. 82(10):1165-1169. | Population inadequate (all patients had bacteremia) and comparison was therefore inappropriate. |
| Holden,E., Bashir,A., Das,I. et al (2014) Staphylococcus aureus bacteraemia in a UK tertiary referral centre: A 'transoesophageal echocardiogram for all' policy, Journal of Antimicrobial ChemotherapyJ.Antimicrob.Chemother., 69, 1960-1965. | Does not answer research question |
| Jang,W.S., Kim,W.-H., Choi,K. et al (2013) What factors predict long-term survival and valve durability in patients with atrioventricular valve regurgitation in single-ventricle physiology?, Pediatric cardiologyPediatr Cardiol, 34, 1366-1373. | Does not answer research question |
| Jaussaud,Nicolas, Gariboldi,Vlad, Giorgi,Roch et al (2009) Risk of reoperation for aortic bioprosthesis dysfunction, The Journal of heart valve diseaseJ Heart Valve Dis, 18, 256-261. | Does not answer research question |
| Johnson,Jennifer A., Boyce,Thomas G., Cetta,Frank, et al (2012) Infective endocarditis in the pediatric patient: a 60-year single-institution review, Mayo Clinic proceedings.Mayo Clinic, 87, 629-635. | Comparison of 2 case series at different time points |
| Jokinen,Janne J., Hippelainen,Mikko J., Pitkanen,Otto A. et al (2007) Mitral valve replacement versus repair: propensity-adjusted survival and quality-of-life analysis, The Annals of thoracic surgeryAnn Thorac Surg, 84, 451-458. | No report of IE by cardiac risk factors |
| Kim,H.J., Kim,J.B., Jung,S.-H. et al (2014) Valve replacement surgery for older individuals with preoperative atrial fibrillation: The effect of prosthetic valve choice and surgical ablation, Journal of Thoracic and Cardiovascular SurgeryJ.Thorac.Cardiovasc.Surg., 147, 1907-1917. | Population - AF only and report on cause of death only |
| Klein,Isabelle, Iung,Bernard, Labreuche,Julien et al (2009) IMAGE Study Group, Cerebral microbleeds are frequent in infective endocarditis: a case-control study, Stroke; a journal of cerebral circulationStroke, 40, 3461-3465. | Risk factors for cerebral microbleeds, did not include pre-existing conditions. |
| Klieverik,Loes M.A., Bekkers,Jos A., Roos,Jolien W. (2008) Autograft or allograft aortic valve replacement in young adult patients with | Does not answer research question |

| Reference | Reason for exclusion |
|---|---|
| congenital aortic valve disease, European heart journalEur Heart J, 29, 1446-1453. | |
| Klug,Didier, Balde,Mamadou, Pavin,Dominique et al (2007) PEOPLE Study Group, Risk factors related to infections of implanted pacemakers and cardioverter-defibrillators: results of a large prospective study, Circulation, 116, 1349-1355. | Pacemaker infections |
| Koolbergen,D.R., Manshanden,J.S., Bouma,B.J. et al (2014) Valve-sparing aortic root replacement, Eur.J.Cardiothorac Surg., 8 January 348-54. | Case series |
| Kratz,J.M., Toole,J.M., (2010) Pacemaker and internal cardioverter defibrillator lead extraction: A safe and effective surgical approach, Annals of Thoracic SurgeryAnn.Thorac.Surg., 90, 1411-1417. | Does not answer research question |
| Kulik,A., Lam,B.-K., Rubens,F.D. et al (2009) Gender differences in the long-term outcomes after valve replacement surgery, Heart (British Cardiac Society) Heart, 95, 318-326. | No comparison group |
| Kuwaki,K., Kawaharada,N., Morishita,K. et al (2007) Mitral valve repair versus replacement mitral and aortic valve surgery for rhematic disease, The Society for Thoracic Surgeons, 83, 558-63. | No mention of IE as a long term outcome |
| Legrand,M., Pirracchio,R., Rosa,A. et al (2013) Incidence, risk factors and prediction of post-operative acute kidney injury following cardiac surgery for active infective endocarditis: An observational study, Critical CareCrit.Care, 17 (5) R220. | No data on pre-existing cardiac conditions |
| Lehmann,Sven, Walther,Thomas, Leontjev,Sergey et al. (2007) Mid-term results after Epic xenograft implantation for aortic, mitral, and double valve replacement, The Journal of heart valve diseaseJ Heart Valve Dis, 16, 641-648. | Cardiac procedure |
| Leontyev,Sergey, Borger,Michael A., Davierwala,Piroze et al (2011) Redo aortic valve surgery: early and late outcomes, The Annals of thoracic surgeryAnn Thorac Surg, 91, 1120-1126. | Endocarditis not reported by risk factors of interest |
| Leontyev,Sergey, Borger,Michael A., Modi,Paul et al (2012) Surgical management of aortic root abscess: a 13-year experience in 172 patients with 100% follow-up, The Journal of thoracic and cardiovascular surgeryJ Thorac Cardiovasc Surg, 143, 332-337. | Outcomes not reported by cardiac condition |
| Leontyev,Sergey, Borger,Michael A., Modi,Paul et al (2011) Redo aortic valve surgery: Influence of prosthetic valve endocarditis on outcomes, The Journal of thoracic and cardiovascular surgeryJ Thorac Cardiovasc Surg, 142, 99-105. | Does not answer research question |
| Lesens,O., Hansmann,Y., Storck,D. et al (2003) Risk factors for metastatic infection in patients with Staphylococcus aureus bacteremia with and without endocarditis, European journal of internal medicineEUR.J.INTERN.MED., 14, 227-231. | Does not answer research question |
| Li,W, Somerville,J. (1998) Infective endocarditis in the grown-up congenital heart (GUCH) population, European Heart Journal, 19, 166-73. | No evaluation on odds of IE with congenital heart disease. |
| Lopez,Javier, Revilla,Ana, Vilacosta,Isidre et al (2011) Multiple-valve infective endocarditis: clinical, microbiologic, echocardiographic, and prognostic profile, MedicineMedicine (Baltimore), 90, 231-236. | Does not answer research question |
| Luciani,Giovanni Battista, De Rita,Fabrizio, Lucchese,Gianluca et al (2012) Repair of congenitally dysplastic aortic valve by bicuspidization: midterm results, The Annals of thoracic surgeryAnn Thorac Surg, 94, 1173-1179. | Does not answer research question |
| Luciani,Giovanni Battista, Viscardi,Francesca, Cresce,Giovanni Domenico et al. (2008) Seven-year performance of the Edwards Prima Plus stentless valve with the intact non-coronary sinus technique, Journal of cardiac surgeryJ Card Surg, 23, 221-226. | Does not answer research question |

| Reference | Reason for exclusion |
|---|---|
| Luciani,Giovanni Battista, Viscardi,Francesca, Pilati,Mara et al (2008) Operative risk and outcome of surgery in adults with congenital valve disease, ASAIO journal (American Society for Artificial Internal Organs : 1992)ASAIO J, 54, 458-462. | Cardiac procedure |
| Maciejewski,Marek, Piestrzeniewicz,Katarzyna, Bielecka-Dabrowa, et al. (2011) Redo surgery risk in patients with cardiac prosthetic valve dysfunction, Archives of medical science : AMSArch.Med.Sci., 7, 271-277. | Case series |
| Malekzadeh-Milani,S., Ladouceur,M., Iserin,L. et al (2014) Incidence and outcomes of right-sided endocarditis in patients with congenital heart disease after surgical or transcatheter pulmonary valve implantation, Journal of Thoracic and Cardiovascular SurgeryJ.Thorac.Cardiovasc.Surg. 148(6):2809-10. | Comparing cardiac prodecures |
| Martinez-Quintana,Efren, Rodriguez-Gonzalez,Fayna, Medina-Gil et al (2010) Clinical outcome in Down syndrome patients with congenital heart disease, Cirugia y cirujanosCir Cir, 78, 245-250. | Full article not in English and unclear study design |
| Math,Ravi S., Sharma,Gautam, Kothari,Shyam Sunder et al (2011) Prospective study of infective endocarditis from a developing country, American heart journalAm Heart J, 162, 633-638. | Case series |
| McGonigle,Niall C., Jones,J.Mark, Sidhu,Pushpinder et al (2007) Concomitant mitral valve surgery with aortic valve replacement: a 21-year experience with a single mechanical prosthesis, Journal of cardiothoracic surgeryJ Cardiothorac Surg, 2, 24. | Outcomes not reported by cardiac condition |
| Meszaros,Katharina, Nujic,Sladjan, Sodeck,Gottfried H. et al (2012) Long-term results after operations for active infective endocarditis in native and prosthetic valves, The Annals of thoracic surgeryAnn Thorac Surg, 94, 1204-1210. | No data on comparing pre-existing cardiac conditions and their outcome after IE and treatment |
| Mirabel,M., Sonneville,R., Hajage,D. et al (2014) Long-term outcomes and cardiac surgery in critically ill patients with infective endocarditis, European heart journalEur Heart J, 35, 1195-1204. | No data on pre-existing cardiac before the IE attack |
| Morris,C.D., Reller,M.D., Menashe,V.D. (1998) Thirty-year incidence of infective endocarditis after surgery for congenital heart defect, JAMA, 279, 599-603. | Case series |
| Musci,Michele, Hubler,Michael, Amiri,Aref, et al (2011) Repair for active infective atrioventricular valve endocarditis: 23-year single center experience, Clinical research in cardiology : official journal of the German Cardiac SocietyClin.res.cardiol., 100, 993-1002. | Cardiac procedures |
| Nadji,Georges, Rusinaru,Dan, Remadi,Jean Paul et al (2009) Heart failure in left-sided native valve infective endocarditis: characteristics, prognosis, and results of surgical treatment, European journal of heart failureEur J Heart Fail, 11, 668-675. | IE population but risk factors did not include pre-existing cardiac conditions |
| Nazarov,Vladimir M., Zheleznev,Sergey I., Bogachev-Prokophiev,Alexandr V. et al (2014) CardiaMed mechanical valve: mid-term results of a multicenter clinical trial, Asian cardiovascular & thoracic annalsAsian Cardiovasc Thorac Ann, 22, 9-17. | Focuses on safety of 1 valve used in different valve locations |
| Neragi-Miandoab,S., Skripochnik,E., Michler,R. et al (2014) Risk factors predicting the postoperative outcome in 134 patients with active endocarditis, Heart Surgery ForumHeart Surg.Forum, 17, E35-E41. | No data presented on outcome by risk factor. Cannot back calculate odds ratio |
| Nishida,T., Sonoda,H., Oishi,Y. et al (2013) Mechanical prosthesis is reasonable for mitral valve replacement in patients approximately 65 years of age, Annals of Thoracic SurgeryAnn.Thorac.Surg., 96, 1614-1620. | Does not answer research question |
| Onorati,F., Biancari,F., De,Feo M. et al (2014) Mid-term results of aortic valve surgery in redo scenarios in the current practice: results | Cardiac surgery |

| Reference | Reason for exclusion |
|---|---|
| from the multicentre European RECORD (REdo Cardiac Operation Research Database) initiative, Eur.J.Cardiothorac Surg. 47(2):269-80. | |
| Ota,Takeyoshi, Gleason,Thomas G., Salizzoni,Stefano et al (2011) Midterm surgical outcomes of noncomplicated active native multivalve endocarditis: single-center experience, The Annals of thoracic surgeryAnn Thorac Surg, 91, 1414-1419. | Outcomes not reported by cardiac condition |
| Oz,Bilgehan Savas, Iyem,Hikmet, Akay,Hakki Tankut et al (2006) Risk factors for short- and long-term survival in patients undergoing re-replacement due to prosthetic valve dysfunction, Heart and vesselsHeart Vessels, 21, 339-343. | Cardiac procedure |
| Pfannmueller,Bettina, Eifert,Sandra, Seeburger,Jorg et al (2013) Gender-dependent differences in patients undergoing tricuspid valve surgery, The Thoracic and cardiovascular surgeonThorac Cardiovasc Surg, 61, 37-41. | Gender not on protocol as sub-group of interest |
| Pfannmuller,B., Davierwala,P., Misfeld,M et al (2012) Postoperative outcome of isolated tricuspid valve operation using arrested-heart or beating-heart technique, Annals of ThoracicSurgeryAnn.Thorac.Surg. 94, 1218-1222. | Does not answer research question |
| Preventza,Ourania, Mohamed,Ahmed S., Cooley,Denton A. et al (2014) Homograft use in reoperative aortic root and proximal aortic surgery for endocarditis: A 12-year experience in high-risk patients, The Journal of thoracic and cardiovascular surgeryJ Thorac Cardiovasc Surg, 148, 989-994. | Outcomes not reported by risk factors of interest |
| Rankin,J.Scott, Thourani,Vinod H., Suri,Rakesh M. et al (2013) Associations between valve repair and reduced operative mortality in 21,056 mitral/tricuspid double valve procedures, European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic SurgeryEur J Cardiothorac Surg, 44, 472-477. | Cardiac procedures |
| Remadi,J.P., Nadji,G., Goissen,T. et al (2009) Infective endocarditis in elderly patients: clinical characteristics and outcome, European Journal of Cardio-thoracic SurgeryEur.J.Cardio-thorac.Surg.35,123-129. | Age not a protocol sub-group |
| Remenyi,B., Webb,R., Gentles,T. et al (2013) Improved long-term survival for rheumatic mitral valve repair compared to replacement in the young, World Journal for Pediatric and Congenital Hearth SurgeryWorld J.Pediatr.Congenit.Heart Surg., 4, 155-164. | Cardiac procedure |
| Riess,Friedrich Christian, Bader,Ralf, Cramer,Eva et al (2011) The Mosaic porcine bioprosthesis: role of age on clinical performance in aortic position, The Journal of thoracic and cardiovascular surgeryJ Thorac Cardiovasc Surg, 141, 1440-1448. | Comparison by age of recipient of porcine bioprosthesis in aortic valve replacement |
| Rodrigues,Alfredo Jose, Evora,Paulo Roberto Barbosa, Bassetto,Solange et al (2009) Isolated mitral and aortic valve replacement with the St. Jude Medical valve: a midterm follow-up, Arquivos brasileiros de cardiologiaArq Bras Cardiol, 93, 290-298. | Does not answer research question |
| Roldan,Carlos A., Sibbitt,Wilmer L.J., Qualls,Clifford R. et al (2013) Libman-Sacks endocarditis and embolic cerebrovascular disease, JACC.Cardiovascular imagingJACC Cardiovasc Imaging, 6, 973-983. | Does not answer research question |
| Roumieh,M., Ius,F., Tudorache,I. et al (2014) Comparison between biological and mechanical aortic valve prostheses in middle-aged patients matched through propensity score analysis: long-term results, Eur.J.Cardiothorac Surg. - | Cardiac procedures |
| Samad,Zainab, Kaul,Prashant, Shaw,Linda K. et al (2011) Impact of early surgery on survival of patients with severe mitral regurgitation, Heart (British Cardiac Society)Heart, 97, 221-224, | No mention of IE |
| Sambola,Antonia, Fernandez-Hidalgo,Nuria, Almirante,Benito et al | Gender not a protocol sub- |

| Reference | Reason for exclusion |
|---|---|
| (2010) Sex differences in native-valve infective endocarditis in a single tertiary-care hospital, The American journal of cardiologyAm J Cardiol, 106, 92-98. | group |
| San Martin,Juan, Sarria,Cristina, de las Cuevas,Carmen et al (2010) Relevance of clinical presentation and period of diagnosis in prosthetic valve endocarditis, The Journal of heart valve diseaseJ Heart Valve Dis, 19, 131-138. | Does not answer research question |
| Sawaki,Sadanari, Usui,Akihiko, Abe,Tomonobu et al (2006) Late mortality and morbidity in elderly patients with mechanical heart valves, Asian cardiovascular & thoracic annalsAsian Cardiovasc Thorac Ann, 14, 189-194. | Cannot tease out those who died from IE by pre-existing cardiac conditions |
| Saxena,Anita, Aggarwal,Neeraj, Gupta,Pankaj et al (2011) Predictors of embolic events in pediatric infective endocarditis, Indian heart journalIndian Heart J, 63, 237-240. | Case series |
| Segalote,Rodrigo Coelho, Pomerantzeff,Pablo Maria Alberto, Brandao,Carlos Manuel de Almeida et al (2008) Aortic valve preservation surgery in elderly patients with aortic stenosis, Revista brasileira de cirurgia cardiovascular : orgao oficial da Sociedade Brasileira de Cirurgia CardiovascularRev Bras Cir Cardiovasc, 23, 519-523. | Case series |
| Shang,Eric, Forrest,Graeme N., Chizmar,Timothy et al (2009) Mitral valve infective endocarditis: benefit of early operation and aggressive use of repair, The Annals of thoracic surgeryAnn Thorac Surg, 87, 1728-1734. | Pre-existing cardiac conditions not a risk factor that was evaluated |
| Sheikh,Amir M., Elhenawy,Abdelsalam M., Maganti,Manjula, et al (2009) Outcomes of surgical intervention for isolated active mitral valve endocarditis, The Journal of thoracic and cardiovascular surgeryJ Thorac Cardiovasc Surg, 137, 110-116. | Risk factors focused on surgery type not pre-existing cardiac conditions |
| Shimokawa,Tomoki, Kasegawa,Hitoshi, Matsuyama,Shigefumi et al (2009) Long-term outcome of mitral valve repair for infective endocarditis, The Annals of thoracic surgeryAnn Thorac Surg, 88, 733-739. | Does not answer research question |
| Shinkawa,Takeshi, Anagnostopoulos,Petros V., Johnson,Natalie C. et al (2010) Performance of bovine pericardial valves in the pulmonary position, The Annals of thoracic surgeryAnn Thorac Surg, 90, 1295-1300. | Case series |
| Silberman,Shuli, Oren,Avraham, Dotan,Moshe et al (2008) Aortic valve replacement: choice between mechanical valves and bioprostheses, Journal of cardiac surgeryJ Card Surg, 23, 299-306. | Cardiac surgery |
| Slipczuk,Leandro, Codolosa,J.Nicolas, Davila,Carlos D. et al (2013) Infective endocarditis epidemiology over five decades: a systematic review, PloS one, 8, e82665-, | Does not include pre-existing cardiac conditions. |
| Sohail,Muhammad R., Uslan,Daniel Z., Khan,Akbar H. et al (2007) Risk factor analysis of permanent pacemaker infection, Clinical infectious diseases : an official publication of the Infectious Diseases Society of AmericaClin Infect Dis, 45, 166-173. | PPMI not the same as IE (confirmed with P.Alderson) |
| Tang,G.H.L., Maganti,M., David,T.E. et al (2007) Effect of Prior Valve Type on Mortality in Reoperative Valve Surgery, Annals of Thoracic SurgeryAnn.Thorac.Surg., 83, 938-945. | Can't tease out data by pre-existing cardiac condition |
| Taniguchi,S., Hashizume,K., Ariyoshi,T. et al (2012) Twelve years of experience with the ATS mechanical heart valve prostheses, General thoracic and cardiovascular surgeryGen Thorac Cardiovasc Surg, 60, 561-568. | Endocarditis is not an outcome |
| Taramasso,M., Denti,P., Buzzatti,N. et al (2012) Mitraclip therapy and surgical mitral repair in patients with moderate to severe left ventricular failure causing functional mitral regurgitation: A single- | Does not answer research question |

| Reference | Reason for exclusion |
|---|---|
| centre experience, European Journal of Cardio-thoracic SurgeryEur.J.Cardio-thorac.Surg., 42, 920-926. | |
| Tjang,Yanto Sandy, van Hees,Yvonne, Korfer,Reiner et al (2007) Predictors of mortality after aortic valve replacement, European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic SurgeryEur J Cardiothorac Surg, 32, 469-474. | No comparator/control group. Reviewing predictors of mortality after aortic valve replacement only. |
| Tleyjeh,I.M., Steckelberg,J.M., Georgescu,G. et al (2008) The association between the timing of valve surgery and 6-month mortality in left-sided infective endocarditis, Heart (British Cardiac Society)Heart, 94, 892-896. | Not relevant |
| Tleyjeh,Imad M., Abdel-Latif,Ahmed, Rahbi,Hazim et al (2007) A systematic review of population-based studies of infective endocarditis, Chest, 132, 1025-1035. | Different inclusion criteria to our SR (incl. case series'). Report on change in in proportions of characteristics by decade only. |
| Tleyjeh,Imad M., Ghomrawi,Hassan M.K., Steckelberg,James M. et al (2010) Conclusion about the association between valve surgery and mortality in an infective endocarditis cohort changed after adjusting for survivor bias, Journal of clinical epidemiologyJ Clin Epidemiol, 63, 130-135. | Does not answer research question - about cardiac surgery as treatment of IE |
| Toole,J.Matthew, Stroud,Martha R., Kratz,John M. et al (2010) Twenty-five year experience with the St. Jude medical mechanical valve prosthesis, The Annals of thoracic surgeryAnn Thorac Surg, 89, 1402-1409. | Cardiac procedure |
| Tossios,Paschalis, Reber,Delawer, Oustria,Maria et al (2007) Single-center experience with the On-X prosthetic heart valve between 1996 and 2005, The Journal of heart valve diseaseJ Heart Valve Dis, 16, 551-557. | Cardiac procedures |
| Tribouilloy,C., Rusinaru,D., Sorel,C. et al (2010) Clinical characteristics and outcome of infective endocarditis in adults with bicuspid aortic valves: a multicentre observational study, Heart (British Cardiac Society)Heart, 96, 1723-1729. | No control |
| Tzemos,Nikolaos, Therrien,Judith, Yip,James et al (2008) Outcomes in adults with bicuspid aortic valves, JAMAJ.Am.Med.Assoc., 300, 1317-1325. | IE not reported separately. Data not reported by comparison group |
| Urso,Stefano, Rega,Filip, Meuris,Bart et al (2011) The Contegra conduit in the right ventricular outflow tract is an independent risk factor for graft replacement, European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic SurgeryEur J Cardiothorac Surg, 40, 603-609. | Does not answer research question |
| Uslan,Daniel Z., Dowsley,Taylor F., Sohail,Muhammad R. et al (2010) Cardiovascular implantable electronic device infection in patients with Staphylococcus aureus bacteremia, Pacing and clinical electrophysiology : PACEPacing Clin Electrophysiol, 33, 407-413. | Does not answer research question |
| Verheugt,Carianne L., Uiterwaal,Cuno S.P.M., van der Velde,Enno T. et al (2008) Gender and outcome in adult congenital heart disease, Circulation, 118, 26-32. | Gender not a protocol sub-group |
| Wei,Xufeng, Yi,Wei, Chen,Wensheng et al (2010) Clinical outcomes with the epicholorohydrin-modified porcine aortic heart valve: a 15-year follow-up, The Annals of thoracic surgery Ann Thorac Surg, 89, 1417-1424. | Cardiac procedures |
| Wang,A., Pappas,P., Anstrom,K.J. et al (2005) The use and effect of surgical therapy for prosthetic valve infective endocarditis: a propensity analysis of a multicenter, international cohort, American | No estimations of associations between pre-existing cardiac conditions |

| Reference | Reason for exclusion |
|---|---|
| Heart Journal, 150, 1086-91. | and poorer outcomes from IE |
| Wiese,L., Mejer,N., Schonheyder,H.C. et al (2013) Danish Staphylococcal Bacteraemia Study Group, A nationwide study of comorbidity and risk of reinfection after Staphylococcus aureus bacteraemia, The Journal of infectionJ Infect, 67, 199-205. | Does not answer research question |
| Wilbring,Manuel, Tugtekin,Sems Malte, Alexiou,Konstantin et a (2012) Composite aortic root replacement for complex prosthetic valve endocarditis: initial clinical results and long-term follow-up of high-risk patients, The Annals of thoracic surgeryAnn Thorac Surg, 94, 1967-1974. | Outcomes not reported by cardiac condition |
| Wu,Kuan Sheng, Lee,Susan Shin-Jung, Tsai,Hung Chin et al (2011) Non-nosocomial healthcare-associated infective endocarditis in Taiwan: an underrecognized disease with poor outcome, BMC infectious diseasesBMC Infect Dis, 11, 221. | Does not answer research question |
| Zhao,D., Zhang,B. (2014) Are valve repairs associated with better outcomes than replacements in patients with native active valve endocarditis?, Interact.Cardiovasc.Thorac.Surg.19(6):1036-9. | Does not answer research question (cardiac surgery) |
| Zilberszac,R., Gabriel,H., Schemper,M. et al (2013) Outcome of combined stenotic and regurgitant aortic valve disease, Journal of the American College of CardiologyJ Am Coll Cardiol, 61, 1489-1495. | Study focus was to evaluate need for valve replacement between aortic stenosis and regurgitation. Does not answer research question. |
| Zuzana,H., Katerina,J., Gabriela,D. (2014) Long-term outcome and prosthesis-related complications after valve replacement, Experimental and clinical cardiologyExp.clin.cardiol., 20, 1341-1347. | No report on outcomes by IE status |

## F.31 Review question 3 and 4

| Reference | Reason for exclusion |
|---|---|
| Q3 | |
| Baltimore R (2008) New recommendations for the prevention of infective endocarditis. Current opinion in pediatrics 20: 85-9. | Not primary study |
| Coffey S, Nadarasa K, Pan A et al. (2012) The increasing incidence of Streptococcus bovis endocarditis and bacteraemia: A case series from 1997 to 2010. International journal of cardiology 161: 111-3. | Case series. |
| Durante-Mangoni E, Bradley S, Selton-Suty C et al. (2008) Current features of infective endocarditis in elderly patients: results of the International Collaboration on Endocarditis Prospective Cohort Study. Archives of internal medicine 168: 2095-103. | Not relevant – not about any interventional procedures associated to IE. |
| Duval X, Delahaye F, Alla F et al. (2012) Temporal trends in infective endocarditis in the context of prophylaxis guideline modifications: Three successive population-based surveys. Journal of the American College of Cardiology 59: 1968-76. | Not relevant. |
| Forrest GN, Arnold RS, Gammie JS et al. (2011) Single center experience of a vancomycin resistant enterococcal endocarditis cohort. The Journal of infection 63: 420-8. | Not relevant – about antibiotics resistant. |
| Glenny AM, Oliver R, Roberts GJ et al. (2013) Antibiotics for the prophylaxis of bacterial endocarditis in dentistry. The Cochrane database of systematic reviews 10: CD003813. | Not relevant – about prophylaxis. |
| Gupta A, Gupta A, Kaul U et al. (2013) Infective endocarditis in an Indian setup: Are we entering the 'modern' era? Indian journal of critical care medicine : peer-reviewed, official publication of Indian Society of Critical Care Medicine 17: 140-7. | Cardiac procedures – excluded from the scope. |

| Reference | Reason for exclusion |
|---|---|
| Hsieh J-C, Wang L-Y, Chang H-R et al. (2014) Clinical characteristics and in-hospital prognosis of infective endocarditis in two eastern counties of Taiwan. Acta Cardiologica Sinica 30: 151-6. | Not relevant – only baseline characteristics. |
| Jain V, Yang M-H, Kovacicova-Lezcano G et al. (2008) Infective endocarditis in an urban medical center: Association of individual drugs with valvular involvement. Journal of Infection 57: 132-8. | Not relevant – about substance misusers. |
| Lockhart PB, Brennan MT, Thornhill M et al. (2009) Poor oral hygiene as a risk factor for infective endocarditis-related bacteremia. Journal of the American Dental Association (1939) 140: 1238-44. | Not relevant – not about interventional procedures. |
| Nunes MCP, Gelape CL, Ferrari TCA (2010) Profile of infective endocarditis at a tertiary care center in Brazil during a seven-year period: prognostic factors and in-hospital outcome. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases 14: e394-e398. | About cardiac procedures, which are excluded from the scope. |
| Werdan K, Dietz S, Loffler B et al. (2014) Mechanisms of infective endocarditis: pathogen-host interaction and risk states. Nature reviews.Cardiology 11: 35-50. | Not primary study |
| Q3 – From broad search | |
| Chirouze C, Athan E, Alla F et al. (2013) Enterococcal endocarditis in the beginning of the 21st century: analysis from the International Collaboration on Endocarditis-Prospective Cohort Study. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases 19: 1140-7. | The types of surgical procedures were not clear or defined. |
| Fernandez-Hidalgo N, Almirante B, Tornos P et al. (2008) Contemporary epidemiology and prognosis of health care-associated infective endocarditis. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 47: 1287-97. | Case series. |
| Johnson JA, Boyce TG, Cetta F et al. (2012) Infective endocarditis in the pediatric patient: a 60-year single-institution review. Mayo Clinic proceedings.Mayo Clinic 87: 629-35. | Cardiac procedures – not covered by the scope. |
| Kwang TY, Yin TJ, Naqash N et al. (2013) Infective endocarditis and infected aneurysm of splenic artery post colonoscopy. Annals of Gastroenterology 26: 170-2. | Single case report. |
| Sambola A, Fernandez-Hidalgo N, Almirante B et al. (2010) Sex differences in native-valve infective endocarditis in a single tertiary-care hospital. The American journal of cardiology 106: 92-8. | Not relevant – the procedures were actually the treatment for the IE> |
| Q4 | |
| Abu-Sharar Z, Robinson A, Lavoie PM (2010) Incidence of septicemia immediately after elective gastrointestinal contrast procedures in infants: a cohort study. Journal of pediatric surgery 45: 507-12. | Only post-procedure blood sample, no pre-procedure. |
| Albawardi A, Almarzooqi S, Torab FC (2013) Helicobacter pylori in sleeve gastrectomies: Prevalence and rate of complications. International Journal of Clinical and Experimental Medicine 6: 140-3. | Not relevant |
| Ali MJ, Ayyar A, Motukupally SR et al. (2014) Bacteremia during dacryocystorhinostomy: results of intra-operative blood cultures. Journal of ophthalmic inflammation and infection 4: 27. | Blood sample only taken pre-procedure, no post-procedure blood sample. |
| Alsaywid BS, Smith GHH (2013) Antibiotic prophylaxis for transurethral urological surgeries: Systematic review. Urology annals 5: 61-74. | All studies in the review already included in the original guideline. |
| Bamberger DM (2007) Bacteremia and endocarditis due to methicillin-resistant Staphylococcus aureus: the potential role of daptomycin. Therapeutics and clinical risk management 3: 675-84. | Not primary study. |

| Reference | Reason for exclusion |
|---|---|
| Bang JH, Choe HS, Lee DS et al. (2013) Microbiological characteristics of acute prostatitis after transrectal prostate biopsy. Korean journal of urology 54: 117-22. | Not relevant - case series of prostatitis |
| Barbosa M, Carmona IT, Amaral B et al. (2010) General anesthesia increases the risk of bacteremia following dental extractions. Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics 110: 706-12. | Only post-procedure blood sample, no pre-procedure. |
| Brennan MT, Kent ML, Fox PC et al. (2007) The impact of oral disease and nonsurgical treatment on bacteremia in children. Journal of the American Dental Association (1939) 138: 80-5. | Blood sample only taken pre-procedure, no post-procedure blood sample. |
| Burke RE, Halpern MS, Baron EJ et al. (2009) Pediatric and neonatal Staphylococcus aureus bacteremia: epidemiology, risk factors, and outcome. Infection control and hospital epidemiology : the official journal of the Society of Hospital Epidemiologists of America 30: 636-44. | Not about interventional procedures. |
| Campeggi A, Ouzaid I, Xylinas E et al. (2014) Acute bacterial prostatitis after transrectal ultrasound-guided prostate biopsy: epidemiological, bacteria and treatment patterns from a 4-year prospective study. International journal of urology : official journal of the Japanese Urological Association 21: 152-5. | Not relevant – not about any interventional procedures. |
| Carignan A, Roussy JF, Lapointe V et al. (2012) Increasing risk of infectious complications after transrectal ultrasound-guided prostate biopsies: time to reassess antimicrobial prophylaxis? European urology 62: 453-9. | Not relevant – about other complications caused by infection. |
| Casserly P, Kieran S, Phelan E et al. (2010) Bacteremia during adenoidectomy: a comparison of suction diathermy adenoid ablation and adenoid curettage. The Annals of otology, rhinology, and laryngology 119: 526-9. | Only post-procedure blood sample, no pre-procedure. |
| Chavez-Tapia NC, Barrientos GT, Tellez AF, I et al. (2010) Antibiotic prophylaxis for cirrhotic patients with upper gastrointestinal bleeding. Cochrane Database of Systematic Reviews | Not relevant. |
| Crasta K, Daly CG, Mitchell D et al. (2009) Bacteraemia due to dental flossing. Journal of clinical periodontology 36: 323-32. | About everyday activities. |
| de Smet AM, Kluytmans JAJW, Blok HEM et al. (2011) Selective digestive tract decontamination and selective oropharyngeal decontamination and antibiotic resistance in patients in intensive-care units: an open-label, clustered group-randomised, crossover study. The Lancet infectious diseases 11: 372-80. | Not all study population had blood sample taken. |
| de Smet AM, Bonten MJM, Kluytmans JAJW (2012) For whom should we use selective decontamination of the digestive tract? Current opinion in infectious diseases 25: 211-7. | Not a primary study |
| Duarte H, Santos C, Capelas ML et al. (2012) Peristomal infection after percutaneous endoscopic gastrostomy: a 7-year surveillance of 297 patients. Arquivos de gastroenterologia 49: 255-8. | Wound culture. |
| Dubey R, Jalili VP, Jain S et al. (2012) Transient bacteremia consequent to tooth brushing in orthodontic patients. Progress in orthodontics 13: 237-45. | Not relevant – everyday activities. |
| Eswara JR, Lee H, Dretler SP et al. (2013) The effect of delayed percutaneous nephrolithotomy on the risk of bacteremia and sepsis in patients with neuromuscular disorders. World journal of urology 31: 1611-5. | Not about interventional procedures. |
| Fernandez-Esparrach G, Sendino O, Araujo I et al. (2014) Incidence of bacteremia in cirrhotic patients undergoing upper endoscopic ultrasonography. Gastroenterologia y Hepatologia 37: 327-33. | Cannot tease out the uncontaminated blood sample from the contaminated ones from |

| Reference | Reason for exclusion |
|---|---|
| | the study. |
| Georgiou I, Farber N, Mendes D et al. (2008) The role of antibiotics in rhinoplasty and septoplasty: a literature review. Rhinology 46: 267-70. | Do not meet review protocol – used as cross reference. |
| Grabe M, Botto H, Cek M et al. (2012) Preoperative assessment of the patient and risk factors for infectious complications and tentative classification of surgical field contamination of urological procedures. World journal of urology 30: 39-50. | Not relevant. |
| Guay DR (2012) Antimicrobial prophylaxis in noncardiac prosthetic device recipients. Hospital practice (1995) 40: 44-74. | Not relevant. |
| Hernandez-Roca JJ, Garcia-Vazquez E, Hernandez A et al. (2013) Bacteraemia at a second level hospital: Epidemiological study, analysis of pronostic factors associated to mortality and economic cost estimation. Revista Espanola de Quimioterapia 26: 119-27. | Not in English. |
| Horcajada JP, Busto M, Grau S et al. (2009) High prevalence of extended-spectrum beta-lactamase-producing enterobacteriaceae in bacteremia after transrectal ultrasound-guided prostate biopsy: a need for changing preventive protocol. Urology 74: 1195-9. | Only selected blood samples, not whole study population. |
| Horliana ACRT, Chambrone L, Foz AM et al. (2014) Dissemination of periodontal pathogens in the bloodstream after periodontal procedures: A systematic review. PloS one 9 | Do not match the review protocol – used as cross checking. |
| Ibrahim AIA, Rashid M (2002) Comparison of local povidone-iodine antisepsis with parenteral antibacterial prophylaxis for prevention of infective complications of TURP: A prospective randomized controlled study. European urology 41: 250-6. | Only post-procedure blood sample, no pre-procedure. |
| Jeremiah CJ, Spelman DW, Royce PL et al. (2013) Gentamicin and norfloxacin prophylaxis for transrectal ultrasound-guided prostate biopsy. Healthcare Infection 18: 67-71. | Unclear whther blood sample or urine sample. |
| Jones DJ, Munro CL, Grap MJ et al. (2010) Oral care and bacteremia risk in mechanically ventilated adults. Heart & lung : the journal of critical care 39: S57-S65. | About everyday activities. |
| Jongerden IP, Buiting AG, Leverstein-Van Hall MA et al. (2011) Effect of open and closed endotracheal suctioning on cross-transmission with Gram-negative bacteria: A prospective crossover study. Critical care medicine 39: 1313-21. | No blood sample, only aspirate sample. |
| Juanjuan D, Zhiyong Z, Xiaoju L et al. (2007) Retrospective analysis of bacteremia because of Enterobacter cloacae compared with Escherichia coli bacteremia. International journal of clinical practice 61: 583-8. | Not relevant – not about any interventional procedures. |
| Kamizono K, Sakuraba M, Nagamatsu S et al. (2014) Statistical analysis of surgical site infection after head and neck reconstructive surgery. Annals of Surgical Oncology 21: 1700-5. | Not relevant – about surgical site infection. |
| Kanjanawongdeengam P, Viseshsindh W, Santanirand P et al. (2009) Reduction in bacteremia rates after rectum sterilization before transrectal, ultrasound-guided prostate biopsy: a randomized controlled trial. Journal of the Medical Association of Thailand = Chotmaihet thangphaet 92: 1621-6. | Not relevant – study population had prophylaxis. |
| Kava BR, Kanagarajah P, Ayyathurai R (2011) Contemporary revision penile prosthesis surgery is not associated with a high risk of implant colonization or infection: a single-surgeon series. The journal of sexual medicine 8: 1540-6. | No blood sample. |
| Khatib R, Sharma M (2013) Echocardiography is dispensable in uncomplicated Staphylococcus aureus bacteremia. Medicine 92: 182-8. | Cardiac procedures – excluded from the scope. |
| Klug TE, Henriksen JJ, Rusan M et al. (2012) Bacteremia during | Only post-procedure blood |

| Reference | Reason for exclusion |
|---|---|
| quinsy and elective tonsillectomy: an evaluation of antibiotic prophylaxis recommendations for patients undergoing tonsillectomy. Journal of cardiovascular pharmacology and therapeutics 17: 298-302. | sample, no pre-procedure. |
| Kusachi S, Sumiyama Y, Takahashi Y et al. (2012) Evaluation of the efficacy and safety of intravenous ciprofloxacin versus meropenem in the treatment of postoperative infection. Journal of infection and chemotherapy : official journal of the Japan Society of Chemotherapy 18: 152-9. | Not relevant – about surgical site infection. |
| Lee BS, Hwang J-H, Lee SH et al. (2013) Risk factors of organ failure in patients with bacteremic cholangitis. Digestive diseases and sciences 58: 1091-9. | Not relevant – not about any interventional procedures. |
| Lee MK, Ide M, Coward PY et al. (2008) Effect of ultrasonic debridement using a chlorhexidine irrigant on circulating levels of lipopolysaccharides and interleukin-6. Journal of clinical periodontology 35: 415-9. | No extractable data on blood sample. |
| Lin Y-T, Jeng Y-Y, Lin M-L et al. (2010) Clinical and Microbiological Characteristics of Chryseobacterium indologenes Bacteremia. Journal of Microbiology, Immunology and Infection 43: 498-505. | Not about interventional procedures. |
| Llach J, Bordas JM, Almela M et al. (2006) Prospective assessment of the role of antibiotic prophylaxis in ERCP. Hepato-gastroenterology 53: 540-2. | About prophylaxis. |
| Lodi G, Figini L, Sardella A et al. (2012) Antibiotics to prevent complications following tooth extractions. The Cochrane database of systematic reviews 11: CD003811. | Not relevant – not about bacteraemia. |
| Loffler C, Bohmer F, Hornung A et al. (2014) Dental care resistance prevention and antibiotic prescribing modification-the cluster-randomised controlled DREAM trial. Implementation science : IS 9: 27. | Not relevant |
| Lorente L, Jimenez A, Martin MM et al. (2009) Influence of tracheostomy on the incidence of central venous catheter-related bacteremia. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology 28: 1141-5. | Unclear data on blood samples. |
| Matveychuk A, Guber A, Talker O et al. (2014) Incidence of bacteremia following bronchoscopy with argon plasma coagulation: A prospective study. Lung 192: 615-8. | Only post-procedure blood sample, no pre-procedure. |
| Nishigaki E, Abe T, Yokoyama Y et al. (2014) The detection of intraoperative bacterial translocation in the mesenteric lymph nodes is useful in predicting patients at high risk for postoperative infectious complications after esophagectomy. Annals of surgery 259: 477-84. | Not relevant – study population had prophylaxis. |
| Oliver R, Roberts GJ, Hooper L et al. (2008) Antibiotics for the prophylaxis of bacterial endocarditis in dentistry. The Cochrane database of systematic reviews : CD003813. | About prophylaxis. |
| Rochlen GK, Keenan AV (2014) Value of prophylactic antibiotics for invasive dental procedures unclear. Evidence-based dentistry 15: 12-3. | About prophylaxis. |
| Saha S, Jagannath GV, Sahana S et al. (2012) Relationship between periodontal infections and atherosclerosis - A review. Indian Journal of Public Health Research and Development 3: 111-3. | Not a primary research. |
| Sang JK, Sun IK, Hyun SA et al. (2010) Risk factors for acute prostatitis after transrectal biopsy of the prostate. Korean journal of urology 51: 426-30. | Unclear whether blood sample or urine sample. |
| Schaeffer AJ, Montorsi F, Scattoni V et al. (2007) Comparison of a 3-day with a 1-day regimen of an extended-release formulation of | No blood sample. |

| Reference | Reason for exclusion |
|---|---|
| ciprofloxacin as antimicrobial prophylaxis for patients undergoing transrectal needle biopsy of the prostate. BJU international 100: 51-7. | |
| Segers P, Speekenbrink RGH, Ubbink DT et al. (2006) Prevention of nosocomial infection in cardiac surgery by decontamination of the nasopharynx and oropharynx with chlorhexidine gluconate: A randomized controlled trial. Journal of the American Medical Association 296: 2460-6. | Cardiac procedures – excluded from the scope. |
| Steinfort DP, Johnson DF, Irving LB (2010) Incidence of bacteraemia following endobronchial ultrasound-guided transbronchial needle aspiration. The European respiratory journal 36: 28-32. | Only post-procedure blood sample, no pre-procedure. |
| Templeton A, Schlegel M, Fleisch F et al. (2008) Multilumen central venous catheters increase risk for catheter-related bloodstream infection: prospective surveillance study. Infection 36: 322-7. | Not relevant – not about any interventional procedures. |
| Tomas C, I, Alvarez M, Limeres J et al. (2007) Effect of a chlorhexidine mouthwash on the risk of postextraction bacteremia. Infection Control and Hospital Epidemiology 28: 577-82. | Already in the original guideline. |
| Tomas I, Diz P, Tobias A et al. (2012) Periodontal health status and bacteraemia from daily oral activities: systematic review/meta-analysis. Journal of clinical periodontology 39: 213-28. | Not relevant – about daily activities. |
| Wagenlehner FME, van Oostrum E, Tenke P et al. (2013) Infective complications after prostate biopsy: outcome of the Global Prevalence Study of Infections in Urology (GPIU) 2010 and 2011, a prospective multinational multicentre prostate biopsy study. European urology 63: 521-7. | Not relevant – not about bacteraemia. |
| Yang M, Zhao X, Wu Z et al. (2009) Meta-analysis of antibiotic prophylaxis use in transrectal prostatic biopsy. Zhong nan da xue xue bao.Yi xue ban = Journal of Central South University.Medical sciences 34: 115-23. | Not relevant – about prophylaxis. |

## F.41 Review question 5

| Study | Reason for Exclusion |
|---|---|
| Crasta K, Daly CG., Mitchell D, Curtis B, Stewart D, Heitz-Mayfield L. (2009) Bacteraemia due to dental flossing, Journal of clinical periodontologyJ Clin Periodontol, 36, 323-332. | Study does not assess an everyday activity specified in the protocol but flossing instead |
| Dubey R, Jalili VP, Jain S, Dubey A. (2012) Transient bacteremia consequent to tooth brushing in orthodontic patients, Progress in orthodonticsProg Orthod, 13, 237-245. | No outcomes of interest - study focuses on microbial identity but numbers of each bacteria detected are unclear (poor reporting). Also, unclear whether the different arms of the study did toothbrushing as an isolated procedure before any orthodontic treatment, thus increasing the possibility for confounding bacteraemia from other procedures. |
| Elram T, Livne A, Oren A, Gross I, Shapiro M, Mankuta D. (2008) Labor as a bacteriuric event--assessment and risk factors, The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal ObstetriciansJ Matern Fetal Neonatal Med, 21, 483-486. | Study assesses labour which is not an everyday activity |
| Garcia S, McKenzie J, Patterson T, Rohde R (2012) Snapshot prevalence and characterization of Staphylococcus species, | Study does not assess an everyday activity specified in the protocol but bacteria levels found on various exercise equipment within a |

| | |
|---|---|
| including MRSA, in a student athletic facility: an undergraduate research project, Clinical laboratory science : journal of the American Society for Medical TechnologyClin Lab Sci, 25, 156-164 | student athletic facility |
| Gondhalekar R, Richard,K.M.J., Jayachandra,M.G., Aslam S, Reddy V, Barabde A (2013) Effect of tongue cleaning methods and oral mutans streptococci level, The journal of contemporary dental practiceJ Contemp Dent Pract, 14, 119-122. | Study does not assess an everyday activity specified in the protocol and also does not examine bacteraemia but bacteria in the saliva. |
| Ipe D, Sundac L, Benjamin W, Moore K, Ulett,G (2013) Asymptomatic bacteriuria: prevalence rates of causal microorganisms, etiology of infection in different patient populations, and recent advances in molecular detection, FEMS microbiology lettersFEMS Microbiol Lett, 346, 1-10 | Study requested for reference purposes (does not meet the criteria specified in protocol) |
| Jones DJ, Munro CL (2008) Oral care and the risk of bloodstream infections in mechanically ventilated adults: A review, Intensive & critical care nursing : the official journal of the British Association of Critical Care NursesIntensive Crit Care Nurs, 24, 152-161 | Review requested for reference purposes |
| Lear A, McCord G, Peiffer J, Watkins R, Parikh A, Warrington S (2011) Incidence of Staphylococcus aureus nasal colonization and soft tissue infection among high school football players, Journal of the American Board of Family Medicine : JABFMJ Am Board Fam Med, 24, 429-435 | Study does not assess an everyday activity specified in the protocol and is also of case series design |
| Lockhart P, Brennan M, Thornhill M, Michalowicz B, Noll J, Bahrani-Mougeot F, Sasser H (2009) Poor oral hygiene as a risk factor for infective endocarditis-related bacteremia, Journal of the American Dental Association (1939)J Am Dent Assoc, 140, 1238-1244 | Further results of a previously published study (Lockhart et al., 2008) - no other outcomes of interest were identified in this later publication. |
| Matthews D (2012) Impact of everyday oral activities on the risk of bacteraemia is unclear, Evidence-based dentistryEvid.- based dent., 13, 80 | Commentary of a review article (Tomas et al.,2012) requested for reference purposes |
| Rupesh,S., Winnier,J.J., Nayak,U.A., Rao,Ap, Reddy,V., Peter,J. (2012) The comparative evaluation of the effects of tongue cleaning on salivary levels of mutans streptococci in children, International journal of dental hygieneInt.j.dent.hyg., 10, 107-112 | Study does not assess bacteraemia but bacteria in the saliva instead - therefore this study does not meet the criteria specified in the protocol |
| Schechter-Perkins,EM, Mitchell,PM, Murray K A., Rubin-Smith JE, Weir S, Gupta K (2011) Prevalence and predictors of nasal and extranasal staphylococcal colonization in patients presenting to the emergency department, Annals of emergency medicineAnn Emerg Med, 57, 492-499 | Study looks at contact sports as a risk factor for bacteria colonisation - this is not an everyday activity of interest and bacteraemia is not assessed either. |
| Tomas I, Diz P, Tobias A, Scully C, Donos N (2012) Periodontal health status and bacteraemia from daily oral activities: systematic review/meta-analysis, Journal of clinical | Review for reference purposes: individual studies checked for inclusion |

| | |
|---|---|
| periodontologyJ Clin Periodontol, 39, 213-228 | |
| Zhang W, Daly CG, Mitchell D, Curtis B (2013) Incidence and magnitude of bacteraemia caused by flossing and by scaling and root planing, Journal of clinical periodontologyJ Clin Periodontol, 40, 41-52 | Study does not assess an everyday activity specified in the protocol but flossing compared with scaling and root planning instead |

## F.51 Review question 6a and 7a

| Study | Reason for Exclusion |
|---|---|
| ACOG practice bulletin No. 104 (2009) Antibiotic prophylaxis for gynecologic procedures, Obstetrics and GynecologyObstet.Gynecol., 113, 1180-1189 | Narrative review |
| Aghamir,S.M., Hamidi,M., Salavati,A., Mohammadi,A., Farahmand,H., Meysamie,A.P., Ghorbani,B (2011) Is antibiotic prophylaxis necessary in patients undergoing ureterolithotripsy?, Acta Medica Iranica, 49, 513-516 | Blood cultures only taken in subjects with fever (n=1) therefore bacteraemia not assessed in all subjects |
| Allison,M.C., Sandoe,J.A.T., Tighe,R., Simpson,I.A., Hall,R.J., Elliott,T.S.J. (2009) Antibiotic prophylaxis in gastrointestinal endoscopy, Gut, 58, 869-880 | Summary of various existing guidelines |
| Alsaywid,B.S., Smith,G.H., (2013) Antibiotic prophylaxis for transurethral urological surgeries: Systematic review, Urology annals, 5, 61-74 | Review article: relevant studies included in this review have been checked for inclusion/exclusion |
| Anitua,E., Aguirre,J.J., Gorosabel,A., Barrio,P., Errazquin,J.M., Roman,P., Pla,R., Carrete,J., de,Petro J., Orive,G., (2009) A multicentre placebo-controlled randomised clinical trial of antibiotic prophylaxis for placement of single dental implants, European Journal of Oral Implantology, 2, 283-29 | Study does not assess bacteraemia nor IE |
| Bach,D.S., (2010) Antibiotic prophylaxis for infective endocarditis: ethical care in the era of revised guidelines, Methodist DeBakey cardiovascular journal, 6, 48-52 | Narrative review requested for reference |
| Baecher,L., Grobman,W., (2008) Prenatal antibiotic treatment does not decrease group B streptococcus colonization at delivery, International Journal of Gynaecology & Obstetrics, 101, 125-128 | Study does not assess bacteraemia nor IE |
| Bai,Y., Gao,F., Gao,J., Zou,D.W., Li,Z.S., (2009) Prophylactic antibiotics cannot prevent endoscopic retrograde cholangiopancreatography-induced cholangitis: a meta-analysis, Pancreas, 38, 126-130 | Meta-analysis - no studies of interest |
| Brand,M., Bizos,D., O'Farrell,P.,Jr., (2010) Antibiotic prophylaxis for patients undergoing elective endoscopic retrograde cholangiopancreatography. [Review], Cochrane Database of Systematic Reviews | Review article: relevant studies included in this review have been checked for inclusion/exclusion |
| Brennan,M.T., Kent,M.L., Fox,P.C., Norton,H.J., Lockhart,P.B., (2007) The impact of oral disease and nonsurgical treatment on bacteremia in children, Journal of the American Dental | Secondary analysis of Lockhart 2004 (same data) |

| | |
|---|---|
| Association (1939)J Am Dent Assoc, 138, 80-85 | |
| Brooks,N., (2009) Prophylactic antibiotic treatment to prevent infective endocarditis: New guidance from the national institute for health and clinical excellence, Heart.95 (9) (pp 774-780) | Summary of NICE 2008 guidance |
| CADTH (2013) Antibiotic prophylaxis for patients with cardiac or orthopedic implants undergoing dental procedures: a review of the clinical effectiveness and guidelines (Structured abstract), Health Technology Assessment Database | Review article: relevant studies included in this review have been checked for inclusion/exclusion |
| Dinsbach,N.A., (2008) Antibiotics in dentistry: Bacteremia, antibiotic prophylaxis, and antibiotic misuse. [Review], General Dentistry, 60, 200-207 | Review article requested for reference |
| Diz,P., Alvarez,J., Limeres,J., Feijoo,J.F., Castro,M., Vazquez,E., (2013) A new antimicrobial prophylactic regimen to prevent bacteraemia following dental procedures [abstract], European heart journal, Conference: European Society of Cardiology, ESC Congress 2013 Amsterdam Netherlands. Conference Start: 20130831 Conference End: 20130904. Conference Publication:, 861-862 | Conference abstract |
| Ellervall,E., Vinge,E., Rohlin,M., Knutsson,K., (2010) Antibiotic prophylaxis in oral healthcare - the agreement between Swedish recommendations and evidence. [Review] [32 refs], British Dental Journal, 208, E5-E5 | Review article: relevant studies included in this review have been checked for inclusion/exclusion |
| Esposito,M., Cannizzaro,G., Bozzoli,P., Consolo,U., Felice,P., Ferri,V., Landriani,S., Leone,M., Magliano,A., Pellitteri,G., Todisco,M., Torchio,C., (2008) Efficacy of prophylactic antibiotics for dental implants: a multicentre placebo-controlled randomised clinical trial, European Journal of Oral Implantology, 1, 23-31 | Study does not assess bacteraemia nor IE |
| Esposito,M., Grusovin,M.G., Coulthard,P., Oliver,R., Worthington,H.V., (2008) The efficacy of antibiotic prophylaxis at placement of dental implants: a Cochrane systematic review of randomised controlled clinical trials. [Review] [18 refs], European Journal of Oral Implantology, 1, 95-103 | Review article - studies included do not assess bacteraemia nor IE |
| Farbod,F., Kanaan,H., Farbod,J., (2009) Infective endocarditis and antibiotic prophylaxis prior to dental/oral procedures: latest revision to the guidelines by the American Heart Association published April 2007, International Journal of Oral and Maxillofacial SurgeryInt.J.Oral Maxillofac.Surg., 38, 626-631 | Review of existing guidelines |
| Glenny,Anne Marie, Oliver,Richard, Roberts,Graham J., Hooper,Lee, Worthington,Helen,V, (2013) Antibiotics for the prophylaxis of bacterial endocarditis in dentistry, Cochrane Database of Systematic ReviewsCochrane Database Syst.Rev., | No relevant studies |
| Gopalakrishnan,P.P., Shukla,S.K., Tak,T., | Narrative review: comparison of existing |

| | |
|---|---|
| (2009) Infective endocarditis: Rationale for revised guidelines for antibiotic prophylaxis, Clinical Medicine and Research, 7, 63-6 | guidelines |
| Gregoriou,O., Bakas,P., Grigoriadis,C., Creatsa,M., Sofoudis,C., Creatsas,G., (2012) Antibiotic prophylaxis in diagnostic hysteroscopy: is it necessary or not?, European Journal of Obstetrics, Gynecology, & Reproductive Biology, 163, 190-192 | Study does not assess bacteraemia nor IE |
| Gregoriou,O., Vlahos,N., Bakas,P., Grigoriadis,C., Gregoriou,V., Liapis,A., Creatsas,G., (2012) The role of antibiotic prophylaxis in operative hysteroscopy, Gynecological surgery, 9, S99- | Abstract only (also does not assess bacteraemia) |
| Harrison,J.L., Hoen,B., Prendergast,B.D., (2008) Antibiotic prophylaxis for infective endocarditis, Lancet, 371, 1317-1319 | Commentary |
| Juthani-Mehta,M., (2013) Should antibiotic prophylaxis after urinary catheter removal be standard practice?, BMJ (Online).346 (7914) | Narrative review, no data of interest to this review question |
| Kanazawa,H., (2007) Efficacy of azithromycin administration in prevention of respiratory tract infection after bronchoscopic biopsy: a randomized, controlled trial, Respirology (Carlton, Vic.), 12, 70-75 | Study does not assess bacteraemia nor IE |
| Legout,L., Beltrand,E., Migaud,H., Senneville,E., (2012) Antibiotic prophylaxis to reduce the risk of joint implant contamination during dental surgery seems unnecessary. [Review], Orthopaedics & traumatology, surgery & research, 98, 910-914 | Literature review for reference |
| Llach,J., Bordas,J.M., Almela,M., Pellise,M., Mata,A., Soria,M., Fernandez-Esparrach,G., Gines,A., Elizalde,J.I., Feu,F., Pique,J.M., (2006) Prospective assessment of the role of antibiotic prophylaxis in ERCP, Hepato-gastroenterologyHepatogastroenterology, 53, 540-542 | Comparator not as specified in protocol |
| Lodi,G., Figini,L., Sardella,A., Carrassi,A., Del,Fabbro M., Furness,S., (2012) Antibiotics to prevent complications following tooth extractions. [Review], Cochrane Database of Systematic Reviews, 11, CD003811- | Review article: relevant studies included in this review have been checked for inclusion/exclusion |
| Niederau C, Pohlmann U, Lubke H et al. (1994) Prophylactic antibiotic treatment in therapeutic or complicated diagnostic ERCP: results of a randomized controlled clinical study.[see comment]. Gastrointestinal Endoscopy 40: 533-7 | This study is included in the Harris 1999 meta-analysis |
| Oliver,R., Roberts,G.J., Hooper,L., Worthington,H.V., (2008) Antibiotics for the prophylaxis of bacterial endocarditis in dentistry, Cochrane Database of Systematic Reviews | Review article: relevant studies included in this review have been checked for inclusion/exclusion |
| Pitak-Arnnop,P., Pausch,N.C., Dhanuthai,K., Neff,A., (2013) Oral amoxicillin as antibiotic prophylaxis before dental surgery - "faux pas" or "dernier cri"?, Revue de Stomatologie, de Chirurgie Maxillo-faciale et de Chirurgie Orale, | Narrative review |

| | |
|---|---|
| 114, 338-340 | |
| Rochlen,G.K., Keenan,A.V., (2014). Value of prophylactic antibiotics for invasive dental procedures unclear, Evidence-Based Dentistry, 15, 12-13 | Commentary |
| Schaeffer,A.J., Montorsi,F., Scattoni,V., Perroncel,R., Song,J., Haverstock,D.C., Pertel,P.E., (2007) Comparison of a 3-day with a 1-day regimen of an extended-release formulation of ciprofloxacin as antimicrobial prophylaxis for patients undergoing transrectal needle biopsy of the prostate, BJU internationalBJU Int, 100, 51-57 | Comparator not as specified in protocol. Also, study does not assess bacteraemia nor IE. |
| Sauter G, Grabein B, Huber G et al. (1990) Antibiotic prophylaxis of infectious complications with endoscopic retrograde cholangiopancreatography. A randomized controlled study. Endoscopy 22: 164-7. | This study is included in the Harris 1999 meta-analysis. |
| Smaill,F.M., Gyte,G.M., (2010) Antibiotic prophylaxis versus no prophylaxis for preventing infection after cesarean section. [Review] [177 refs], Cochrane Database of Systematic Reviews, CD007482 | Review article: relevant studies included in this review have been checked for inclusion/exclusion |
| Smaill,Fiona M., Grivell,Rosalie M., (2014) Antibiotic prophylaxis versus no prophylaxis for preventing infection after cesarean section, Cochrane Database of Systematic Reviews | Review - studies included in this review do not assess bacteraemia nor incidence of IE as an outcome |
| Strom BL AEBJeal (1998) Dental and cardiac risk factors for infective endocarditis: a population- based case-control study. Ann Int Med 1998 | It is not clear whether those with and without antibiotics were those with underlying cardiac conditions; therefore population not met. |
| Tempelhof,M.W., Reeves,G., (2012) Infective endocarditis and antibiotic prophylaxis: A systematic review of efficacy and safety of the AHA guidelines, Research Journal of Medical SciencesRes.J.Med.Sci., 6, 193-202 | Review of AHA guidelines |
| Tomas,Carmona,I, Diz,Dios P., Scully,C., (2007) Efficacy of antibiotic prophylactic regimens for the prevention of bacterial endocarditis of oral origin. [Review] [175 refs], Journal of Dental Research, 86, 1142-1159 | Review requested for reference |
| Wagenlehner,F.M.E., Wagenlehner,C., Schinzel,S., Naber,K.G., Bach,D., Basting,R., Bruns,T., Friesen,A., Hofstetter,A.G., Keller,H.J., Peters,H.J., Rothenberger,K.H., Schmitz,H.J., Seiter,H.-J., Sinagowitz,E., Tauber,R., Wittenberger,R., (2005) Prospective, randomized, multicentric, open, comparative study on the efficacy of a prophylactic single dose of 500 mg levofloxacin versus 1920 mg trimethoprim/sulfamethoxazole versus a control group in patients undergoing TUR of the prostate, European urologyEur Urol, 47, 549-556 | Study does not assess bacteraemia but bacteruria |
| Xu,H.W., Wang,J.H., Tsai,M.S., Wu,K.L., Chiou,S.S., Changchien,C.S., Hu,T.H., Lu,S.N., Chuah,S.K., (2011) The effects of cefazolin on cirrhotic patients with acute variceal hemorrhage | Study design not as specified in protocol. This was a cross sectional retrospective chart review. |

| | |
|---|---|
| after endoscopic interventions, Surgical Endoscopy, 25, 2911-2918 | |
| Yang,M., Zhao,X., Wu,Z., Xiao,N., Lu,C., 2009, Meta-analysis of antibiotic prophylaxis use in transrectal prostatic biopsy, Zhong Nan da Xue Xue Bao, Yi, 115-123 | Meta-analysis: no new (post 2008) relevant studies |
| Zani,E.L., Clark,O.A., Rodrigues,Netto N.,Jr., (2011) Antibiotic prophylaxis for transrectal prostate biopsy. [Review], Cochrane Database of Systematic Reviews, CD006576- | Review article: relevant studies included in this review have been checked for inclusion/exclusion |
| Hall, G., Nord, CE., Heimdahl, A. (1996) Elimination of bacteraemia after dental extraction: comparison of erythromycin and clindamycin for prophylaxis of infective endocarditis. Journal of Antimicrobial Chemotherapy, 37, 783-795, [included in CG64] | Comparator not as specified in protocol |
| Roberts, G., Holzel, H.(2002) Intravenous antibiotic regimens and prophylaxis of odontogenic bacteremia. British Dental Journal, 193, 525-527 [included in CG64] | Comparator not as specified in protocol |
| Brewster, SF., Macgowan, AP., Gingell, JC. (1995) Antimicrobial prophylaxis for transrectal prostatic biopsy: a prospective randomised trial of cefuroxime versus piperacillin/tazobactam, 76, 351-354 [included in CG64] | Comparator not as specified in protocol |
| Duvall, X., Alla, F et al (2006) Estimated risk of endocarditis in adults with predisposing cardiac conditions undergoing dental procedures with or without antibiotic prophylaxis. Clinical infectious diseases, 42 [included in CG64] | Cross sectional study |
| Van der Meer, JTM. et al (1992) Epidemiology of bacterial endocarditis in the Netherlands. Arch Intern Med. 152, 1869-1873 [included in CG64] | Case series study design |
| Glenny, AM., Oliver, R., Roberts, GJ., Hooper, L., Worthington, HV (2004) Antibiotics for the prophylaxis of bacterial endocarditis in dentistry [Review], Cochrane Database of Systematic Reviews, CD003813-[included in CG64] | Study included in this Cochrane review has been reviewed separately |

## F.61 Review question 6b and 7b

| Study | Reason for Exclusion |
|---|---|
| Attin,R., Yetkiner,E., Aykut-Yetkiner,A., Knosel,M., Attin,T., (2013) Effect of chlorhexidine varnish application on streptoococcus mutans colonisation in adolescents with fixed orthodontic appliances, Australian Orthodontic Journal, 29, 52-57 | Study does not assess bacteraemia nor IE |
| Bebek,B., Bago,I., Skaljac,G., Plecko,V., Miletic,I., Anic,I., (2009) Antimicrobial effect of 0.2% chlorhexidine in infected root canals, Collegium Antropologicum, 33, 1159-1163 | Study does not assess bacteraemia nor IE |
| Beus,C., Safavi,K., Stratton,J., Kaufman,B., (2012) Comparison of the effect of two endodontic irrigation protocols on the elimination of bacteria from root canal system: a prospective, randomized clinical trial, Journal of Endodontics, 38, 1479-1483 | Study does not assess bacteraemia nor IE |

| | |
|---|---|
| Cabov,T., Macan,D., Husedzinovic,I., Skrlin-Subic,J., Bosnjak,D., Sestan-Crnek,S., Peric,B., Kovac,Z., Golubovic,V., (2010) The impact of oral health and 0.2% chlorhexidine oral gel on the prevalence of nosocomial infections in surgical intensive-care patients: a randomized placebo-controlled study, Wiener Klinische Wochenschrift, 122, 397-404 | Study does not assess bacteraemia nor did the subjects undergo an interventional procedure |
| Cosyn,J., Sabzevar,M.M., (2007) Subgingival chlorhexidine varnish administration as an adjunct to same-day full-mouth root planing. II. Microbiological observations, Journal of periodontologyJ Periodontol, 78, 438-445 | Study does not assess bacteraemia nor IE |
| Devker,N.R., Mohitey,J., Vibhute,A., Chouhan,V.S., Chavan,P., Malagi,S., Joseph,R., (2012), A study to evaluate and compare the efficacy of preprocedural mouthrinsing and high volume evacuator attachment alone and in combination in reducing the amount of viable aerosols produced during ultrasonic scaling procedure, Journal of Contemporary Dental Practice [Electronic Resource], 13, 681-689 | Study does not assess bacteraemia nor IE |
| Diz,P., Tomas,I., Barbosa,M., Amaral,B., Cerqueira,C., Limeres,J., Alvarez,M., A (2007) chlorhexidine mouthwash reduces the risk of bacteraemia following dental extractions performed unter either general or local anaesthesia, Clinical research in cardiology, 96, 443 | Abstract only |
| Duss,C., Lang,N.P., Cosyn,J., Persson,G.R., (2010) A randomized, controlled clinical trial on the clinical, microbiological, and staining effects of a novel 0.05% chlorhexidine/herbal extract and a 0.1% chlorhexidine mouthrinse adjunct to periodontal surgery, Journal of Clinical Periodontology, 37, 988-997 | Comparator not as specified in protocol. Also, study does not assess bacteraemia. |
| Fedorowicz,Zbys, Nasser,Mona, Sequeira,Byron Patrick, de-Souza,Raphael Freitas, Carter,Ben, Heft,Marc, Irrigants for non-surgical root canal treatment in mature permanent teeth, Cochrane Database of Systematic Reviews, -, 2012 | No relevant studies |
| Feres,M., Figueiredo,L.C., Faveri,M., Stewart,B., de,Vizio W., (2010) The effectiveness of a preprocedural mouthrinse containing cetylpyridinium chloride in reducing bacteria in the dental office, Journal of the American Dental Association, 141, 415-422 | Study does not assess bacteraemia nor IE |
| Guarnelli,M.E., Franceschetti,G., Manfrini,R., Trombelli,L., (2008) Adjunctive effect of chlorhexidine in ultrasonic instrumentation of aggressive periodontitis patients: a pilot study, Journal of Clinical Periodontology, 35, 333-341 | Study does not assess bacteraemia nor IE |
| Jolly,M., Singh,N., Rathore,M., Tandon,S., Banerjee,M., (2013) Propolis and commonly used intracanal irrigants: comparative evaluation of antimicrobial potential, Journal of Clinical Pediatric Dentistry, 37, 243-249 | Study does not assess bacteraemia nor IE |
| Kusahara,D.M., Friedlander,L.T., Peterlini,M.A., | Study does not assess bacteraemia nor did the |

| | |
|---|---|
| Pedreira,M.L., (2012). Oral care and oropharyngeal and tracheal colonization by Gram-negative pathogens in children, Nursing in Critical Care, 17, 115-122 | subjects undergo an interventional procedure |
| Lee,M.K., Ide,M., Coward,P.Y., Wilson,R.F., (2008) Effect of ultrasonic debridement using a chlorhexidine irrigant on circulating levels of lipopolysaccharides and interleukin-6, Journal of Clinical Periodontology, 35, 415-419 | Study does not assess bacteraemia specifically but a surrogate outcome (lipopolysaccharide levels) |
| Matesanz,P., Herrera,D., Echeverria,A., O'Connor,A., Gonzalez,I., Sanz,M., (2013) A randomized clinical trial on the clinical and microbiological efficacy of a xanthan gel with chlorhexidine for subgingival use, Clinical Oral Investigations, 17, 55-66 | Study does not assess bacteraemia nor IE |
| Paiva,S.S., Siqueira,J.F.,Jr., Rocas,I.N., Carmo,F.L., Ferreira,D.C., Curvelo,J.A., Soares,R.M., Rosado,A.S., (2012) Supplementing the antimicrobial effects of chemomechanical debridement with either passive ultrasonic irrigation or a final rinse with chlorhexidine: a clinical study, Journal of Endodontics, 38, 1202-1206 | Study does not assess bacteraemia nor IE |
| Paolantonio,M., Perinetti,G., D'Ercole,S., Graziani,F., Catamo,G., Sammartino,G., Piccolomini,R., (2008) Internal decontamination of dental implants: an in vivo randomized microbiologic 6-month trial on the effects of a chlorhexidine gel, Journal of Periodontology, 79, 1419-1425 | Study does not assess bacteraemia nor IE |
| Swierkot,K., Nonnenmacher,C.I., Mutters,R., Flores-de-Jacoby,L., Mengel,R,. (2009) One-stage full-mouth disinfection versus quadrant and full-mouth root planing, Journal of Clinical Periodontology, 36, 240-249 | Study does not assess bacteraemia nor IE |

1

# 1 Appendix G: Evidence tables

## G.1 2 Review question 1a and 1b

3 **Table 33: THIS STUDY IS ALSO INCLUDED FOR Q2.**

| | |
|---|---|
| **Bibliographic reference** | **Alagna, L et al. (2014) Repeat endocarditis: analysis of risk factors based on the International collaboration of Endocarditis – Prospective Cohort Study. Clinical Microbiology and Infection. 20: 566-575.** |
| **Study type** | Prospective cohort study |
| **Aim** | Describe clinical characteristics, identify risk factors and examine 1 year mortality of patients with repeat IE. |
| **Patient characteristics** | Patients enrolled in International Collaboration on Endocarditis – Prospective Cohort Study (ICE-PCS) with definite diagnosis of native (NVE) or prosthetic valve IE (PVE) (Duke Criteria) and 1 year follow-up data.<br>New IE cases occurring within 10 weeks from initial episode were included (arbitrary threshold).<br>***Relapse*** defined as new episode caused by same bacterial species, within 6 months of the first episode.<br>***Presumed new infection*** was defined as new IE caused by a different bacterial species OR by the same bacterial species >6 months from the initial episode.<br><br>**Exclusion Criteria**<br>Missing data at one year (2521/5594), intra-cardiac lead IE (N=270) as repeat IE could be related to a retained device, missing information on IE type (n=49), bacterial culture negative for the suspected second episode as it was impossible to differentiate between relapse and new infection (n=8). |
| **Number of patients** | 1874 patients had a complete data set.<br>Of these 174 patients had repeat IE, minus exclusions, 91 patients (4.8%) with repeat IE were included.<br>Presumed relapse (n=17), presumed new infection (n=74). |
| **Outcomes** | Single episodes of IE and<br>Recurrent IE |
| **Predictors/risk factors and effect estimates** | **Bivariate and multivariate analysis comparing patients with single episode IE with repeat IE patients** |

| Bibliographic reference | Alagna, L et al. (2014) Repeat endocarditis: analysis of risk factors based on the International collaboration of Endocarditis – Prospective Cohort Study. Clinical Microbiology and Infection. 20: 566-575. |
|---|---|

| | Single episode IE | Repeat IE (Recurrence or relapse) | P-value | Multivariate model odds ratio (95%CI) |
|---|---|---|---|---|
| Sample | 1783 (95) | 91 (4.8) | | Not reported |
| Male sex | 1213 (68) | 63 (69) | 0.90 | Not reported |
| Age median (25-75$^{th}$ percentiles), yr. | 58.7 (45-71) | 50.9 (38-66) | 0.001 | Not reported |
| *Type of valve IE* | | | | |
| Native valve IE | 1352 (76) | 75 (82) | 0.17 | Not reported |
| Prosthetic valve IE 447/1874 | 431 (24) | 16 (18) | | |
| History of previous endocarditis | 135 (7.4) | 17 (19) | 0.001 | 2.8 (1.5-5.1) |
| History of congenital heart disease 173/1874 | 165 (9.2) | 8 (8.7) | 1.00 | Not reported |

**FOR QUESTION 2**

**Clinical characteristics of patients with repeat endocarditis: bivariate analysis comparing presumed relapse vs. presumed new infection.**

| | Repeat IE Total | Presumed new infection | Presumed relapse | p-value |
|---|---|---|---|---|
| Sample [n (%)] | 91 (4.8) | 74 (4) | 17 (0.8) | Not reported |
| Age [median (25-75$^{th}$ percentiles)] | 51 (37-66) | 51 (37-66) | 49 (33-66) | 0.48 |
| Type of Valve IE [n (%)] | | | | |
| Native valve | 75 (82) | 58 (78) | 17 (100) | **0.03** |
| Prosthetic Valve | 16 (18) | 16 (22) | 0 | |
| History of previous | 17 (19) | 17 (23) | 0 | **0.03** |

| | |
|---|---|
| **Bibliographic reference** | **Alagna, L et al. (2014) Repeat endocarditis: analysis of risk factors based on the International collaboration of Endocarditis – Prospective Cohort Study. Clinical Microbiology and Infection. 20: 566-575.** |
| | endocarditis \| \| \| \| \|<br>History of congenital heart disease \| 8 (8.7) \| 7 (9) \| 1 (6) \| 1<br><br>Statistically significant increase in recurrence with history of IE on native valve vs prosthetic valve. |
| **Analysis used** | Bivariate analysis using Fisher's exact test.<br>Multiple logistic regression used to determine factors associated with repeat IE as well as for mortality.<br>Variables in final adjusted regression models were selected according to statistical significance and clinical judgement. |
| **Length of follow-up** | 1 year |
| **Location** | Data from 64 sites in 28 countries worldwide |
| **Source of funding** | The work was supported in part by grants from the American Heart Association and various non-commercial Spanish research organisations. |
| **Comments** | **Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))**<br>Study Participation – Y<br>Study attrition – N Authors cite a limitation in the amount of missing data.<br>Prognostic factor measurement – Y.<br>Outcome measurement – Y although follow-up status beyond 1 year was not collected – long enough?<br>Confounding measurement and account – N No data on medical treatment (e.g. antibiotic type/duration) by study arm is provided which could be an important influencer of outcome.<br>Analysis – N Reviewer had to back calculate unadjusted ORs. No sample size calculation.<br>3/6 met = HIGH RISK OF BIAS |

1 **Table 34**

| | |
|---|---|
| **Bibliographic reference** | **Ammar, W et al. (2013) Case-Control study of potential culprit procedures for infective endocarditis in an Egyptian tertiary care centre. The Egyptian Heart Journal. 65, 153-157** |
| **Study type** | Retrospective case-control study |
| **Aim** | To test the hypothesis that underlying medical conditions, not culprit procedures, are the most important risk factor for development of IE. |

| | |
|---|---|
| **Bibliographic reference** | **Ammar, W et al. (2013) Case-Control study of potential culprit procedures for infective endocarditis in an Egyptian tertiary care centre. The Egyptian Heart Journal. 65, 153-157** |
| **Patient characteristics** | 175 patients with definite IE (Duke Criteria) from the IE database of the Cardiology Department, Cairo University Hospital (between March 2005 and June 2008) were matched with 175 control cases without IE, matched for age, sex, and underlying heart disease (including prosthetic valves and intra cardiac devices). |
| **Number of patients** | 350. |
| **Outcomes** | IE |
| **Predictors/risk factors and effect estimates** | **Clinical characteristics and underlying heart disease between cases and controls** |

| Variable | IE Case N (%) | Control N (%) | P-value |
|---|---|---|---|
| Number of patients | 175 | 175 | n/a |
| Age (Mean ±SD) | 32.13 ±13.76 | 32.90 ±12.12 | NS |
| Male | 102 (58.3) | 103 (58.9) | NS |
| Female | 73 (41.7) | 72 (41.1) | NS |
| Known structural heart disease | 117 (66.9) | 111 (63.4) | NS |
| Valvular heart disease | 53 (30.3) | 54 (30.9) | NS |
| Prosthetic valve | 49 (28.0) | 45 (25.7) | NS |
| Congenital heart disease | 15 (8.6) | 12 (6.9) | NS |
| No structural heart disease | 58 (33.1) | 64 (36.6) | NS |

**Medical co-morbidities associated with increased risk of IE.**

| Host related risk factors | IE cases N (%) | Controls N (%) | P value | Odds Ratio (95%CI) |
|---|---|---|---|---|
| Prior endocarditis | 9 (5.1) | 2 (1.1) | 0.032 | 4.69 (0.998-22.027) |

**Significant Predictors of IE (adjusted for age and sex)**

| Predictors for IE | P value | Odds ratio (95%CI) |
|---|---|---|
| Prior IE | 0.029 | **5.841 (1.201-28.411)** |

| | |
|---|---|
| **Bibliographic reference** | **Ammar, W et al. (2013) Case-Control study of potential culprit procedures for infective endocarditis in an Egyptian tertiary care centre. The Egyptian Heart Journal. 65, 153-157** |
| **Analysis used** | Comparisons - continuous variables (normally distributed) - t-tests; categorical variables Pearson's Chi-square test<br>Correlations measured using Pearson's correlation coefficient. No correction for multiple testing. |
| **Length of follow-up** | Study duration 2 years 9 months |
| **Location** | Cairo |
| **Source of funding** | Not specified. |
| **Comments** | **Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))**<br>Study Participation – U Retrospective design.<br>Study attrition – Y<br>Prognostic factor measurement – N Clinical data was collected by telephone r/v and this was patient reported for controls. No mention of verification of this data.<br>Outcome measurement – Y<br>Confounding measurement and account – Y<br>Analysis – N Reviewer had to back calculate ORs. No sample size calculation regarding number of controls required.<br>3/6 met = HIGH RISK OF BIAS |

1 **Table 35**

| | |
|---|---|
| **Bibliographic reference** | **[from CG64]**<br>**Clemens JD, Horwitz RI, Jaffe CC, et al. (1982) A controlled evaluation of the risk of bacterial endocarditis in persons with mitral-valve prolapse. N Engl J Med 307: 776–81.** |
| **Study type** | Case-control |
| **Aim** | To evaluate whether mitral valve prolapse is an important risk factor for bacterial endocarditis |
| **Patient characteristics** | Cases – n=51. people with bacterial endocarditis and<br>Controls –n=153 people without bacterial endocarditis selected from a group of 4335 adult inpatients.<br><br>hospital in-patients who had undergone echocardiography and who lacked any known cardiovascular risk factors for endocarditis apart from mitral valve prolapse and isolated mitral-regurgitant murmurs; age ≥15 yrs. at the time of hospital admission [a]<br><br>**Inclusion:** |

| Bibliographic reference | [from CG64]<br>**Clemens JD, Horwitz RI, Jaffe CC, et al. (1982) A controlled evaluation of the risk of bacterial endocarditis in persons with mitral-valve prolapse. N Engl J Med 307: 776–81.** |
|---|---|
| | cases: data extracted from medical records, who fulfilled the diagnostic and/or pathological criteria for bacterial endocarditis<br>controls: selected from those who had undergone echocardiography during the period covered by the study; matched with age, sex and nearest date of echocardiography (excluded those with antecedent heart disease) using first 3 eligible candidates.<br>**Exclusion:**<br>cases: antecedent heart disease acting as a risk factor for endocarditis; discharge diagnosis referable only to episodes occurring in previous admissions; inadequate diagnostic evidence of BE; no echocardiogram<br>controls: antecedent heart disease acting as a risk factor for endocarditis; medical records not located<br><br>MVP was defined by either auscultatory or echocardiographic data<br><br>The cases and controls were similar in age and sex, the cases groups had higher proportions of those with a history of parenteral drug use, recommendations for prophylaxis before instrumentation and high-risk cardiovascular lesions that were unsuspected before echocardiography, adjustment was made for these inequalities [b]<br><br>**Mitral valve prolapse**<br>n = 13 (25%) of the cases and n = 10 (7%) of the controls had mitral valve prolapse.<br>**Bacterial endocarditis diagnosis** was based on pathological documentation and clinical criteria (existence of a heart murmur and at least two blood cultures obtained at separate time indicating the same organism). |
| **Number of patients** | n = 204 (cases 51, controls 153) |
| **Predictors** | Mitral valve prolapse |
| **Outcomes** | Bacterial endocarditis |
| **Analysis used** | Calculation of Odds ratios from matched analyses. |
| **Length of follow-up** | 4yrs of cases Between 1 Nov 1976 and 1 Nov 1980 |
| **Location** | USA |
| **Effect estimates** | In 16 matched sets, the cases and controls were discordant for the presence or absence of mitral-valve prolapse; the matched OR for the association was 8.2 (2.4 to 28.4, CI 95%), p<0.001 |

| | |
|---|---|
| **Bibliographic reference** | **[from CG64]**<br>**Clemens JD, Horwitz RI, Jaffe CC, et al. (1982) A controlled evaluation of the risk of bacterial endocarditis in persons with mitral-valve prolapse. N Engl J Med 307: 776–81.** |
| | Indicating a substantially higher risk of endocarditis for people with MVP than those without it.<br><br>Analysis was completed using only the echocardiographic criteria for MVP (the association was unaffected – OR 7.2 (2.1-25.5).<br>and also to adjust for risk factors for endocarditis that were unequally distributed between the cases and the controls - the association remained substantial for both addicts and non addicts.<br>No drug users (per protocol population) Matched **OR 4.7 (1.1-19.5).**<br>(the authors consider that these results demonstrate a substantial association between MVP and BE) |
| **Source of funding** | Not stated |
| **Comments** | **Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))**<br>Study Participation – N Retrospective. Cases selected from people having had echocardiography during study period, without endocarditis. Unclear other criteria for selection of cases. No sample size calculation although 3 cases were selected for each case.<br>Study attrition – Y<br>Prognostic factor measurement – Y<br>Outcome measurement – Y although study conducted before Duke Criteria developed diagnosis was confirmed with echo.<br>Confounding measurement and account – Y<br>Analysis – N although IVDUs were included, adjustment was made for this. Adjusted ORs were not calculated. No sample size calculation.<br>4/6 criteria met = LOW RISK OF BIAS |

*(a)The one exception was the inclusion of those with antecedent findings of isolated mitral regurgitation, since mitral valve prolapse is commonly accompanied by auscultatory findings of mitral regurgitation*

*(b)The eligibility of patients was determined by a 'blinded' researcher, without knowledge of the echocardiograph findings*

**Table 36**

| | |
|---|---|
| **Bibliographic reference** | **[from CG64]**<br>**Hickey AJ, MacMahon SW, Wilcken DE, et al. (1985) Mitral valve prolapse and bacterial endocarditis: when is antibiotic prophylaxis necessary? American Heart Journal 109: 431–35.** |
| **Study type** | Case-control |
| **Aim** | To investigate the association between mitral valve prolapse (MVP) and bacterial endocarditis. |

| | |
|---|---|
| **Bibliographic reference** | **[from CG64]**<br>**Hickey AJ, MacMahon SW, Wilcken DE, et al. (1985) Mitral valve prolapse and bacterial endocarditis: when is antibiotic prophylaxis necessary? American Heart Journal 109: 431–35.** |
| **Patient characteristics** | **Cases**<br>n = 56 cases [c]<br>(n = 66 met the criteria, n = 10 excluded due to antecedent lesions)<br>Inclusion: cases ≥15yrs admitted to hospital, all who had echocardiography, met the criteria set for diagnosis for endocarditis<br>**Controls**<br>n = 168 controls matched for age, sex and date of echocardiography<br>(n = 4620 met the criteria)<br>Inclusion: inpatients who did not have bacterial endocarditis and underwent echocardiography during the period of the study, 3 controls were chosen for each case<br><br>Exclusion: for both cases and controls, known to have had antecedent cardiovascular lesions warranting antibiotic prophylaxis<br><br>Prevalence of mitral valve prolapse<br>MVP was identified in n = 11/56(20%) of cases and in n = 7/168 (4%) of controls<br>11 sets had BE and MVP were present, in one of these MVP was also present in a control<br>39 sets had BE without MVP, in 6 of these MVP was present in a control [a] |
| **Number of patients** | n = 224 |
| **Predictors** | MVP |
| **Outcomes** | Endocarditis |
| **Analysis used** | Odds ratios for matched sets together with Chi squared values and 95% CIs |
| **Length of follow-up** | Between Jan 1976 to Jan 1984 |
| **Location** | Australia |
| **Effect estimates** | OR for the association of MVP and BE was 5.3 (2.0 to 14.4, 95% CI)<br>Systolic murmur<br>In n = 9/11 of those with MVP and BE, there were pre-existing systolic murmurs<br>OR for the association between BE and MVP with pre-existing systolic murmurs was **6.8 (2.1 to 22.0, 95%CI)** |

| | |
|---|---|
| **Bibliographic reference** | **[from CG64]**<br>**Hickey AJ, MacMahon SW, Wilcken DE, et al. (1985) Mitral valve prolapse and bacterial endocarditis: when is antibiotic prophylaxis necessary? American Heart Journal 109: 431–35.** |
| | Probability of developing endocarditis<br>(the incidence of BE in the adult population of New South Wales in 1980 was 145 out of 3,852,638 [b] , also assuming that 15% of patients with BE had known high-risk lesions other than MVP and mitral regurgitation, as was the case in this study)<br>The probability of BE occurring in a person with MVP in a 1-year period is 0.00014, this is x4.7 greater than in the general population<br>Results suggest that 14 out of every 100,000 adult patients with MVP will develop BE over a 1-year period, compared with 3 people in every 100,000 in the general population |
| **Source of funding** | Not stated |
| **Comments** | **Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))**<br>Study Participation – N haemodialysis patients and IVDUs were included in the cases (not protocol). Retrospective design.<br>Study attrition – Y<br>Prognostic factor measurement – Y<br>Outcome measurement – Y (pre-Duke criteria)<br>Confounding measurement and account – N no reporting on other pre-existing cardiac conditions between the cases and controls.<br>Analysis – N - no adjusted ORs. No sample size calculation.<br>3/6 criteria met = HIGH RISK OF BIAS |

*(a) In no set was MVP present in more than one of the 3 controls*
*(b) Taken from the New South Wales State hospital morbidity and mortality statistics for 1980*
*(c) 7 of the cases were on chronic haemodialysis and 6 were parenteral drug users*

**Table 37**

| | |
|---|---|
| **Bibliographic reference** | **Richet, H. et al (2008). Development and assessment of a new early scoring system using non-specific clinical signs and biological results to identify children and adult patients with a high probability of infective endocarditis on admission. Journal of Antimicrobial Chemotherapy; 62:1434-1440.** |
| **Study type** | Prospective cohort study (the collection of data was prospective but the study itself was retrospective). |
| **Aim** | To assess whether non-specific clinical signs or biological results can identify patients with a high probability of infective endocarditis (IE) to improve outcomes. |
| **Patient characteristics** | All patients consulting or hospitalised with suspected IE were screened. |

<table>
<tr><td>Bibliographic reference</td><td>Richet, H. et al (2008). Development and assessment of a new early scoring system using non-specific clinical signs and biological results to identify children and adult patients with a high probability of infective endocarditis on admission. Journal of Antimicrobial Chemotherapy; 62:1434-1440.</td></tr>
<tr><td></td><td>Definite IE diagnosed in 409 of 2039 participants (Modified Duke Criteria).<br>Patients with rejected IE served as controls.<br>All definite or suspected IE patients underwent blood cultures and other blood tests. Suspected IE patients also were assessed according to presence of one major Duke Criterion or trans-oesophageal echocardiographic abnormalities.<br>A standardized questionnaire was used to prospectively collect data on all patients with suspected IE.<br>1870 patients subjected to 2039 diagnostic episodes/assessments.<br><br>Of this initial population, mean age 61, 60% were male and 1206 (59.4%) had prior valvular damage (PVD) 11% had a bio-prosthesis, 12.3% had a mechanical prosthesis and 13% had a pacemaker. Most frequently damaged valve was the mitral valve 595 (37.3%) followed by the aortic valve 544 (34%) and the tricuspid valve 64 (4.3%).<br><br>Adults and children were included in the study of 402 patients. Mean age was 63±17 (range not provided by definite IE).<br><br>After exclusion of 66 patients with possible endocarditis, 1152 of the remaining patients had PVD. (This included patients with prosthetic heart valves, pacemaker or congenital heart disease), 288 (69.7% were male) and mean age was 63±17, median 67 (range 4-95)</td></tr>
<tr><td>Number of patients</td><td>402</td></tr>
<tr><td>Outcomes</td><td>IE</td></tr>
<tr><td>Predictors/risk factors and effect estimates</td><td>Multivariate analysis for risk factors of IE
<table>
<tr><th>Variable</th><th>Odds ratio (95%) CI</th><th>P-value</th></tr>
<tr><td>Prior valve damage 1152/1939</td><td>8.2 (5-13.3)</td><td><0.00001</td></tr>
</table></td></tr>
<tr><td>Analysis used</td><td>Univariate and multivariate analysis were performed.</td></tr>
<tr><td>Length of follow-up</td><td>1 October 1999 to 31 January 2006.</td></tr>
<tr><td>Location</td><td>Marseille, France.</td></tr>
<tr><td>Source of funding</td><td>No funding was sought or obtained for this study.</td></tr>
<tr><td>Comments</td><td>Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))<br>Study Participation – N. Although the collection of data was prospective the study itself was retrospective. Adults</td></tr>
</table>

| Bibliographic reference | **Richet, H. et al (2008). Development and assessment of a new early scoring system using non-specific clinical signs and biological results to identify children and adult patients with a high probability of infective endocarditis on admission. Journal of Antimicrobial Chemotherapy; 62:1434-1440.** |
|---|---|
| | and children mixed population.<br>Study attrition – Y<br>Prognostic factor measurement – Y<br>Outcome measurement – Y<br>Confounding measurement and account – Y<br>Analysis – N While multivariate analysis was carried out, there is limited detail of the description of the methods and no adjusted odds ratios are reported.<br>4/6 met = LOW RISK OF BIAS |

1 **Table 38**

| Bibliographic reference | **Rushani, D. et al. (2013) Infective Endocarditis in Children with congenital heart disease. Cumulative incidence and predictors. Circulation. 128:1412-1419.** |
|---|---|
| **Study type** | Population based cohort including nested case-control design to analyse predictors of IE |
| **Aim** | Identify cumulative incidence and predictors for the development of IE in children with CHD. |
| **Patient characteristics** | Children (0-18 years) between 1988 and 2010 in the Quebec CHD database.<br>Matched each on calendar time with 20 controls.<br><br>IE diagnosis during observation period.<br><br>**Distribution of CHD Lesions in Children Followed Since Birth, 1988 to 2010** |

| CHD Lesions | No. of Children (%) | Person-Years of Follow-Up |
|---|---|---|
| Cyanotic CHD | 2196 (6) | 21 757 |
| Endocardial cushion defects | 975 (3) | 10 389 |
| Left-sided lesions | 2811 (8) | 31 974 |
| Right-sided lesions | 2201 (6) | 20 574 |
| Patent ductus arteriosus | 2170 (6) | 17 329 |
| Ventricular septal defect | 8646 (25) | 84 386 |
| Atrial septal defect | 12 343 (36) | 111 989 |
| Other CHD | 2937 (9) | 29 787 |

| | |
|---|---|
| **Bibliographic reference** | **Rushani, D. et al. (2013) Infective Endocarditis in Children with congenital heart disease. Cumulative incidence and predictors. Circulation. 128:1412-1419.** |

| | | |
|---|---|---|
| Total | 34 279 (100) | 328 185 |

Numbers may not add up because of rounding. The absolute numbers in this table do not reflect the birth prevalence of CHD lesions. Some defects may be asymptotic early in life and only captured after an extended observation period. CHD indicates congenital heart disease.

**Number of patients**

All CHD children during above time frame n=47,518

Predictors of IE evaluated in 47,518 children with CHD – IE cases 185, controls n=3,700.

Incidence - Total children followed from birth N=34,279. IE cases 136.

**Outcomes**

IE

**Predictors/risk factors and effect estimates**

**Incidence**

**Lesion Group-Specific Cumulative Incidence and Incidence Rate of IE in Children with CHD**

| **Cumulative Incidence (95% CI) per 1000 Children** | | | | |
|---|---|---|---|---|
| **CHD Lesions** | **0–6 y** | **0–12 y** | **0–18 y** | **Incidence Rate (95% CI) per 10 000 Person-Years** |
| Cyanotic CHD | 16.8 (11.9–23.8) | 23.3 (17.0–31.8) | 31.0 (22.5–42.7) | 20.7 (15.4–27.7) |
| Endocardial cushion defects | 5.5 (2.3–13.1) | 8.7 (4.1–18.6) | 11.1 (5.4–22.9) | 7.7 (3.9–15.4) |
| Left-sided lesions | 2.7 (1.3–5.7) | 4.8 (2.6–8.7) | 7.9 (4.4–14.0) | 4.4 (2.6–7.4) |
| Right-sided lesions | 2.3 (1.0–5.5) | 2.3 (1.0–5.5) | 4.2 (1.5–11.5) | 2.9 (1.3–6.5) |
| Patent ductus arteriosus* | 3.2 (1.4–7.1) | 3.2 (1.4–7.1) | 3.2 (1.4–7.1) | 3.5 (1.6–7.7) |
| Ventricular septal defect | 2.0 (1.2–3.2) | 2.4 (1.5–3.8) | 3.2 (1.9–5.3) | 2.4 (1.5–3.7) |
| Atrial septal defect | 1.9 (1.3–2.9) | 2.2 (1.5–3.4) | 3.0 (1.9–4.8) | 2.3 (1.6–3.4) |
| Other CHD | 2.9 (1.4–5.8) | 3.7 (1.8–7.3) | 5.5 (2.9–10.6) | 3.7 (2.0–6.7) |
| Overall | 3.2 (2.6–3.9) | 4.2 (3.5–5.1) | 6.1 (5.0–7.5) | 4.1 (3.5–4.9) |

*No IE events were observed in children with PDA past 4 years of age.

| Bibliographic reference | Rushani, D. et al. (2013) Infective Endocarditis in Children with congenital heart disease. Cumulative incidence and predictors. Circulation. 128:1412-1419. |
|---|---|

**Predictors**

**Characteristics of Children (0–18 Years of Age) With IE and Their Calendar Time–Matched Controls (from the full population of children with CHD)**

| Characteristic | IE cases (n=185), n (%) | Controls (n=3700), n (%) | Unadjusted Rate Ratio (95% CI) | Adjusted rate ratio (95% CI) |
|---|---|---|---|---|
| Cardiac surgery 6 mo before* | 17 (9) | 25 (1) | 15.52 (8.08–29.80) | **5.34 (2.49-11.43)** |
| Valve surgery 6 mo before | 3 (2) | 8 (0) | 7.50 (1.28–31.25)†‡ | Not reported |
| Shunt surgery 6 mo before | 13 (7) | 13 (0) | 21.06 (9.59–46.25)† | Not reported |
| Other cardiac surgery 6 mo before | 13 (7) | 25 (1) | 11.67 (5.76–23.63)† | Not reported |
| CHD type | | | | |
| Cyanotic CHD | 62 (34) | 348 (9) | 6.38 (4.02–10.13) | **6.44 (3.95-10.50)** |
| Endocardial cushion defects | 18 (10) | 154 (4) | 4.37 (2.35–8.15) | **5.47 (2.89-10.36)** |
| Left-sided lesions | 18 (10) | 414 (11) | 1.57 (0.86–2.88) | **1.88 (1.01-3.49)** |
| Right-sided lesions | 7 (4) | 216 (6) | 1.12 (0.49–2.59) | 1.22 (0.52-2.86) |
| Patent ductus arteriosus | 6 (3) | 161 (4) | 1.33 (0.54–3.27) | 1.25 (0.50-3.13) |
| Ventricular septal defect | 27 (15) | 988 (27) | 0.95 (0.56–1.62) | 0.97 (0.56-1.66) |
| Atrial septal defect | 29 (16) | 1004 (27) | Reference** | Not reported |
| Other CHD | 18 (10) | 415 (11) | 1.54 (0.84–2.81) | **1.86 (1.01-3.42)** |
| Age, y | | | | |
| Median (IQR) | 3.5 (0.6–10.2) | 7.6 (3.6–12.2) | | |
| 0–3 | 89 (48) | 788 (21) | 3.30 (2.40–4.53) | |
| 3–6 | 20 (11) | 698 (19) | 0.84 (0.51–1.39) | |
| 6–18 | 76 (41) | 2214 (60) | Reference | |
| Male sex | 97 (52) | 1761 (48) | 1.22 (0.90–1.64) | |

Cardiac surgery subcategories do not add up to the total because the procedures performed in 1 operation may

| Bibliographic reference | Rushani, D. et al. (2013) Infective Endocarditis in Children with congenital heart disease. Cumulative incidence and predictors. Circulation. 128:1412-1419. |
|---|---|

fall under >1 category. Percentages do not add to 100% because of rounding. CHD indicates congenital heart disease; CI, confidence interval; IE, infective endocarditis; and IQR, interquartile range.

* 6 mo before is with respect to the index date for cases and the time of matching for controls.

** This figure was not reported but was used as a reference category (see below). Reviewer calculated **OR 0.449 (0.33-0.75).**

† These are combined into a single variable in the multivariate model.

‡ Estimated with exact logistic regression owing to sparse data.

Results are reported comparing the above characteristics to atrial septal defect as reference category as this defect was the most common CHD (36%). Relative to ASD, the following lesions were most strongly associated with an elevated risk of IE: Cyanotic CHD (adjusted RR, 6.44; 95%CI, 3.95, 10.50), endocardial cushion defects (aRR, 5.47; 2.89,10.36) and left-sided lesions (aRR, 1.88; 1.01, 3.49).

Young age was a strong predictor of IE: in comparison with those aged 6 to 18, children <3 years of age were at higher risk of IE (aRR 3.53, 2.53-4.96) but not those 3 to 6 years (aRR 0.91; 0.54-1.51).

Male sex and IE (aRR 1.09, 0.80-1.50)

**CHD Lesions at Elevated Risk of IE Stratified by History of Cardiac Surgery**

| CHD Lesions | IE Cases, n (%) | Controls, n (%) | Adjusted Rate Ratio (95% CI) |
|---|---|---|---|
| Cyanotic CHD | 45 | 178 | |
| Unoperated | 27 (60) | 100 (56) | 7.56 (4.03–14.18) |
| Operated | 18 (40) | 78 (44) | 9.22 (4.39–19.34) |
| Endocardial cushion defects | 8 | 84 | |
| Unoperated | 5 (63) | 51 (61) | 3.00 (1.06–8.51) |
| Operated | 3 (37) | 33 (39) | –* |
| Left-sided lesions | 14 | 253 | |
| Unoperated | 13 (93) | 233 (92) | 2.35 (1.16–4.73) |
| Operated | 1 (7) | 20 (8) | –* |

Analysis was performed in the subset of children followed since birth. History of cardiac surgery was measured

| Bibliographic reference | **Rushani, D. et al. (2013) Infective Endocarditis in Children with congenital heart disease. Cumulative incidence and predictors. Circulation. 128:1412-1419.** |
|---|---|
| | from birth to 6 months before time of matching and did not include catheterization procedures. Adjustment was for age, sex, and cardiac surgery in the previous 6 months. CHD categories not stratified by history of cardiac surgery (right-sided lesions, VSD, PDA, and other CHD) are not shown. The reference CHD category is atrial septal defects (26 IE cases, 928 controls). CHD indicates congenital heart disease; CI, confidence interval; IE, infective endocarditis; PDA, patent ductus arteriosus; and VSD, ventricular septal defect.<br>* Covariate adjustment is impossible because of sparse data. |
| **Analysis used** | IE estimated using Kaplan-Meier estimator.<br>Incidence rate = cumulative incidence (first cases of IE) divided by the total person-time at risk with CIs computed using Poisson distribution.<br>Predictors analysed using conditional and exact logistic regression.<br>Wald test used to evaluate differences in risk of IE between different CHD lesions. |
| **Length of follow-up** | 1 January 1988 – 31 March 2010 (22years) |
| **Location** | Quebec, Canada. |
| **Source of funding** | Dr Kaufman is funded by the Canada Research Chairs program. Drs Marelli, Ionescu-Ittu, and Pilote are funded by the Fonds de la recherche en santé du Québec. Drs Marelli and Mackie are funded by the Heart and Stroke Foundation of Canada and the Canadian Institutes of Health Research. Dr Pilote holds a James McGill Chair at McGill University. |
| **Comments** | **Potential bias (Hayden)**<br>Study Participation – Y<br>Study attrition – Y<br>Prognostic factor measurement – Y<br>Outcome measurement – Y<br>Confounding measurement and account – Y<br>Analysis - U. No sample size calculation and N for each variable <20.<br>5/6 met - Low risk of bias |

1 **Table 39**

| Bibliographic reference | **[from CG64]**<br>**Strom BL, Abrutyn E, Berlin J et al (1998) Dental and cardiac risk factors for infective endocarditis: a population-based case-control study. Ann Int Med; 129:761-9.** |
|---|---|

| | |
|---|---|
| **Bibliographic reference** | **[from CG64]**<br>**Strom BL, Abrutyn E, Berlin J et al (1998) Dental and cardiac risk factors for infective endocarditis: a population-based case-control study. Ann Int Med; 129:761-9.** |
| **Study type** | Population based Case-control. Retrospective interviews/data collection |
| **Aim** | To quantify the risk of endocarditis from dental treatment and cardiac abnormalities. |
| **Patient characteristics** | Surveillance completed for IE in 54 hospitals.<br>**Cases**; Community acquired IE not associated with IVDU - defined from self-reporting structured telephone interviews, dental visit (information was obtained from dental records)<br>**Controls:** Controls were community residents.<br><br>Case-patients were matched for age, sex and neighbourhood of residence.<br>One control from the community selected for each case-patient (using a modification of the Waksberg random-digit dialling method)<br><br>Information was obtained from case-patients by a structured telephone interview, medical and dental records were subsequently requested. Case records were examined and classified by experts in IE.<br><br>Host characteristics were collected and the following conditions were classified as a variable called “any valvular heart abnormality”<br>mitral valve prolapse, congenital heart disease, rheumatic fever with heart involvement, cardiac valvular surgery, previous episode of endocarditis and other valvular heart disease, those reporting >1 of these factors were only reported once<br><br>Case-patients and controls were similar for age (range 18-98yrs, mean 59.1±17.1 and 59.1±17.0, respectively), sex, ethnicity, education, occupation, and dental insurance status.<br><br>Excluded: <18yrs, IV drug users, those who developed endocarditis in the hospital<br><br>Interviewers and medical records abstractors were not blinded but were extensively trained in good interviewing and abstracting techniques. |
| **Number of patients** | 416 enrolled potential case-patients. 287 community acquired IE not associated with IV drug use. Of these 287 included patients, 273 patients completed the interview. |
| **Predictors** | Pre-existing cardiac condition / Valvular abnormality |
| **Outcomes** | Endocarditis |

<table>
<tr><td>Bibliographic reference</td><td>[from CG64]<br>Strom BL, Abrutyn E, Berlin J et al (1998) Dental and cardiac risk factors for infective endocarditis: a population-based case-control study. Ann Int Med; 129:761-9.</td></tr>
<tr><td>Analysis used</td><td>Conditional logistical regression. Variables were included in multiple regression models if they were significant (P<0.2) in unadjusted (matched) analyses if there inclusion had a substantial effect (>15 change) on coefficients for variables in the model or if they were strongly suspected confounders. Adjusted ORs and 95% CIs were provided.</td></tr>
<tr><td>Length of follow-up</td><td>From August 1988 – November 1990</td></tr>
<tr><td>Location</td><td>Philadelphia, USA</td></tr>
<tr><td>Effect estimates</td><td>Cardiac risk factors<br>Patient-reported history of any cardiac valvular abnormality was highly associated with IE (adjusted odds ratio 16.7, CI 7.4 to 37.4) (Adjusted for socioeconomic status variables (ethnic group, education, occupation, health insurance status, and dental insurance status))<br><br>
<table>
<tr><th>Risk factor</th><th>Cases (n = 273)</th><th>Controls (n = 273)</th><th>Adjusted OR[1] (CI 95%)</th></tr>
<tr><td>Mitral valve prolapse</td><td>52(19.0%)</td><td>6(2.2%)</td><td>19.4 (6.4 to 58.4)</td></tr>
<tr><td>Congenital heart disease</td><td>26(9.5%)</td><td>7(2.6%)</td><td>6.7 (2.3 to 19.4)</td></tr>
<tr><td>Rheumatic fever</td><td>32(11.7%)</td><td>10(3.7%)</td><td>13.4 (4.5 to 39.5)</td></tr>
<tr><td>Cardiac valvular surgery</td><td>37(13.6%)</td><td>2(0.7%)</td><td>74.6 (12.5 to 447)</td></tr>
<tr><td>Other valvular heart disease *</td><td>12(4.4%)</td><td>1(0.4%)</td><td>131 (6.9 to 2489)</td></tr>
<tr><td>Heart murmur</td><td>37(13.6%)</td><td>14(5.1%)</td><td>4.2 (2.0 to 8.9)</td></tr>
<tr><td>Any cardiac valvular abnormality **</td><td>104 (38.1%)</td><td>17(6.2%)</td><td>16.7 (7.4 to 37.4)</td></tr>
<tr><td>(previous episode of endocarditis)</td><td>17(6.2%)</td><td>1(0.4%)</td><td>37.2 (4.4 to 317)</td></tr>
</table>
*defined as patient reported “other valvular disease”<br>
**includes any of; mitral valve prolapse, congenital heart disease, rheumatic fever with heart involvement, cardiac valvular surgery, previous episode of endocarditis and other valvular heart disease, those reporting >1 of these factors were only reported once<br><br>
[1] Adjusted for socioeconomic status variables (ethnic group, education, occupation, health insurance status, and dental insurance status), diabetes mellitus and severe kidney disease)</td></tr>
</table>

| | |
|---|---|
| **Bibliographic reference** | **[from CG64]**<br>**Strom BL, Abrutyn E, Berlin J et al (1998) Dental and cardiac risk factors for infective endocarditis: a population-based case-control study. Ann Int Med; 129:761-9.** |
| | Case patients were substantially more likely than controls to report previous known mitral valve prolapse; history of CHD; rheumatic fever; cardiac valvular surgery; previous endocarditis; other valvular heart disease; heart murmur without other known cardiac abnormalities |
| **Source of funding** | National Heart, Lung and Blood Institute |
| **Comments** | **Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))**<br>Study Participation – N Data Were collected retrospectively and case selection insufficiently describe to limit potential bias.<br>Study attrition – Y although only 58% of recruited controls completed questionnaire<br>Prognostic factor measurement – Y Includes cardiac conditions that were patient reported but made efforts to validate reports and indicated 90% agreement.<br>Outcome measurement – Y<br>Confounding measurement and account – Y<br>Analysis – Y adjusted rate ratios provided<br>5/6 = LOW RISK OF BIAS |

# G.2 Review question 2

**Table 40**

<table>
<tr><td>Bibliographic reference</td><td>Aksoy, O. et al (2007). Early surgery in patients with infective endocarditis: A propensity score analysis. Clinical Infectious diseases; 44:364-72.</td></tr>
<tr><td>Study type</td><td>Longitudinal cohort study</td></tr>
<tr><td>Aim</td><td>Prospective evaluation of predictors of long term mortality after IE</td></tr>
<tr><td>Patient characteristics</td><td>Data was obtained from Duke University Prosthetic Cohort Study on endocarditis.<br>426 adult patients with infective endocarditis (modified Duke criteria for definite or possible endocarditis)<br>Initial analysis L or R-sided involvement. Patients with >1 occurrence only the 1st was included in analysis as well as IE of native or prosthetic valve. Cardiac device related IE was also included.<br>Matched cohort - LSA IE did not undergo surgery (n=255), underwent surgery (n=78)<br><br>Patient characteristic/risk factors of interest as per outcome tables.</td></tr>
<tr><td>Number of patients</td><td>426</td></tr>
<tr><td>Outcomes</td><td>Surgery<br>All-cause mortality at 5 years after discharge.</td></tr>
<tr><td>Predictors/risk factors and effect estimates</td><td>Characteristics of IE cohort according to whether SURGERY was performed.
<table>
<tr><th rowspan="2">Characteristic</th><th rowspan="2">Total cohort (n=426)</th><th rowspan="2">Total Patients with LSA* IE (n=333)</th><th colspan="2">Matched Cohort</th><th rowspan="2">P-value</th></tr>
<tr><th>LSA IE no surgery (n=255)</th><th>LSA IE surgery (n=78)</th></tr>
<tr><td>Age (y) mean SD</td><td>58.3±26,2</td><td>56.6±25.3</td><td>58.4±26.8</td><td>54.2±20.6</td><td>0.089</td></tr>
<tr><td>Male</td><td>242 (56.8)</td><td>186 (55.9)</td><td>134 (52.6)</td><td>52 (66.7)</td><td>0.028</td></tr>
<tr><td>Female</td><td>184 (43.2)</td><td>147 (44.1)</td><td>121 (47.5)</td><td>26 (33.3)</td><td>0.028</td></tr>
<tr><td>Type of IE</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Native valve</td><td>295 (69.3)</td><td>248 (74.5)</td><td>192 (75.3)</td><td>56 (71.8)</td><td>0.535</td></tr>
<tr><td>Prosthetic valve</td><td>81 (19.0)</td><td>57 (17.1)</td><td>38 (14.9)</td><td>19 (24.4)</td><td>0.052</td></tr>
<tr><td>Other</td><td>50 (11.7)</td><td>28 (8.4)</td><td>25 (9.8)</td><td>3 (3.9)</td><td>0.097</td></tr>
<tr><td>Previous episode</td><td>20 (4.7)</td><td>12 (3.6)</td><td>11 (4.3)</td><td>1 (1.3)</td><td>0.209</td></tr>
</table></td></tr>
</table>

| Bibliographic reference | **Aksoy, O. et al (2007). Early surgery in patients with infective endocarditis: A propensity score analysis. Clinical Infectious diseases; 44:364-72.** |
|---|---|

| | | | | | |
|---|---|---|---|---|---|
| of IE | | | | | |
| Congenital heart disease | 45 (10.6) | 36 (10.8) | 26 (10.2) | 10 (12.8) | 0.514 |

P-value analysis based on comparison of the non-surgical cohort with the surgical cohort.
*LSA = left sided association without concomitant intra-cardiac devices.

With the exception of gender, there were no significant differences between those having surgery vs no surgery (medical therapy only) in the above characteristics/risk factors.

**5year mortality of patients with L-sided IE by characteristic**

| **Characteristic (Total n=333)** | **Patients who survived (total n=171) (%)** | **Patients who died (total n=162) (48.6%)** | **P-value** |
|---|---|---|---|
| Age, mean years± SD | 53.2 ±26.1 | 62.6 ±24.8 | **<0.001** |
| Male | 102 (59.7) | 784 (51.9) | 0.152 |
| Aortic Valve IE | 0 | 5 (3.1) | **0.003** |
| Congenital heart disease | 26 (15.2) | 10 (6.2) | **0.008** |

Older patients as well as those with history of congenital heart disease and those with aortic valve IE were significantly more likely to be dead at 5 years post event.

| | |
|---|---|
| **Analysis used** | Chi-square test for categorical variables. Wilcoxon rank-sum test for continuous variables.<br>Patients were matched to patients who did not undergo surgery using individual propensity scores (using minimum absolute distance) between propensities for surgery. Matching tolerance was a score difference of 0.075. |
| **Length of follow-up** | 5 year follow up period. duration 1 April 1996 - 31 December 2002 |
| **Location** | North Carolina, USA |
| **Source of funding** | Financial support: National Institutes of Health grant. |
| **Comments** | **Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))**<br>Study Participation – Y<br>Study attrition – Y Based on numbers reported on 5 year follow-up this appears that follow-up was 100%.<br>Prognostic factor measurement – Y<br>Outcome measurement – Y |

| Bibliographic reference | **Aksoy, O. et al (2007). Early surgery in patients with infective endocarditis: A propensity score analysis. Clinical Infectious diseases; 44:364-72.** |
|---|---|
| | Confounding measurement and account – N some concern as although the propensity score matching reduces the effect of treatment bias it does not completely control for confounding. ? potential for confounding by referral bias.<br>Analysis – N Odds ratios needed to be back calculated by reviewer.<br>4/6 met = LOW RISK OF BIAS |

1 **Table 41:**

| Bibliographic reference | **Alonso-valle, H. et al. (2010). Clinical course and predictors of death in prosthetic valve endocarditis over a 20-year period. The Journal of Thoracic and Cardiovascular Surgery. 139:4887-893** |
|---|---|
| **Study type** | Retrospective observational study. |
| **Aim** | To compare early and late outcome of patients with prosthetic valve endocarditis (PVE) over 20 year period. |
| **Patient characteristics** | 133 episodes (in 122 adult patients). 112 patients had 1 episode, 9 patients had 2 episodes and 1 patient had 3 episodes).<br>PVE defined by Duke criteria.<br>Early PVE = within 60 days of implantation. Late onset 2 or more months from replacement.<br>In hospital death was recorded according to various parameters.<br>Data were collected using retrospective review of patient records.<br><br>There were 24 cases of early and 109 cases of late PVE (total 133).<br>64/133 cases had a mechanical prosthesis.<br>Mechanical PVE was more frequent in early onset group (78% vs. 22%).<br>Bioprosthetic PVE was more frequent in late onset group (58% vs. 42%).<br><br>Men n=87, women n=34, mean age 59y (95%CI 56-62). |
| **Number of patients** | 133 episodes (in 122 patients). |
| **Outcomes** | (e.g. mortality, 10-year survival, event rate of interest e.g. number of heart attack, no. of sudden infant death, etc.)<br><br>Mortality<br>39 patients died (in-hospital mortality rate of 29.3%).<br>Of the 94 patients who were discharged alive, 26 (27%) died during mean follow-up period of 31 months. |

<table>
<tr><td>Bibliographic reference</td><td>Alonso-valle, H. et al. (2010). Clinical course and predictors of death in prosthetic valve endocarditis over a 20-year period. The Journal of Thoracic and Cardiovascular Surgery. 139:4887-893</td></tr>
<tr><td></td><td>Recurrence<br>Recurrent PVE was observed in 12 cases (9%). (Recurrent episode n=10, relapse 2).<br>50% of patients with recurrence were carriers of mechanical valve prosthesis.</td></tr>
<tr><td>Predictors/risk factors and effect estimates</td><td>Actual data (numbers/percentages) with outcome were not provided by risk factor.<br><br>Univariate analyses: risk factors for in-hospital death in 133 episodes of PVE
<table>
<tr><th rowspan="2">Variable</th><th colspan="3">Crude Mortality (in-hospital death)</th></tr>
<tr><th>RR</th><th>95%CI</th><th>P Value</th></tr>
<tr><td>Age >75 y</td><td>1.6</td><td>0.6-4.3</td><td>NS</td></tr>
<tr><td>Female gender</td><td>1.2</td><td>0.4-1.9</td><td>NS</td></tr>
<tr><td>Previous IE</td><td>1.7</td><td>0.7-4.4</td><td>NS</td></tr>
<tr><td>Previous valve replacement</td><td>0.9</td><td>0.4-2.1</td><td>NS</td></tr>
<tr><td>Mechanical Prosthesis implantation</td><td>1.1</td><td>0.5-2.4</td><td>NS</td></tr>
</table>
<br>Multivariate analyses was conducted but the variables of interest were clearly not in the model. (Adjusted for age, sex, year of PVE onset, referral hospital, nosocomial infection after original valve replacement).<br><br>Recurrence was observed in a total of 12 patients (9%). These data were not provided by outcome/risk factor.<br><br>Long-term mortality was not reported by risk factor.</td></tr>
<tr><td>Analysis used</td><td>Logistic regression model was used to identify prognostic factors of in-hospital mortality.<br>Mortality rates were derived evaluated by plotting survival distribution derived from Kaplan-Meier estimates and differences evaluated using log-rank test.<br>Cox regression analysis was used to assess the effect of different variables on risk of death.</td></tr>
<tr><td>Length of follow-up</td><td>Duration January 1986 – December 2005. Mean follow up was 32.2 months (SD 46.8, range 0-212 months).</td></tr>
<tr><td>Location</td><td>Santander, Spain. (single centre)</td></tr>
<tr><td>Source of funding</td><td>No external funding was received.</td></tr>
</table>

| Bibliographic reference | **Alonso-valle, H. et al. (2010). Clinical course and predictors of death in prosthetic valve endocarditis over a 20-year period. The Journal of Thoracic and Cardiovascular Surgery. 139:4887-893** |
|---|---|
| **Comments** | **Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))**<br>Study Participation – N Retrospective design. Selection bias could also occur regarding treatment options (medical vs. medical & surgical) and this could bias the outcomes.<br>Study attrition – U No final numbers were reported.<br>Prognostic factor measurement – Y Surgery rates were higher than usual in this study due to referral from other hospitals of patients with complicated clinical course, although in-hospital mortality was lower in surgical group (NS). Survival after 12 months was markedly different in favour of surgically treated patients (71% vs. 42%) but Multivariate analysis included referral bias as a covariate to reduce the likelihood of referral bias.<br>Outcome measurement – Y<br>Confounding measurement and account – Y.<br>Analysis – N No adjusted odds ratios/risk ratios were provided by predictor despite them being calculated. No sample size calculation.<br>3/6 = HIGH RISK OF BIAS |

1 **Table 42**

| Bibliographic reference | **Bannay, A et al. (2011) The impact of valve surgery on short- and long-term mortality in left-sided infective endocarditis: do differences in methodological approaches explain previous conflicting results? European Heart Journal; 32, 2003-2015..** |
|---|---|
| **Study type** | Long term prospective follow up study |
| **Aim** | Evaluate the effect of valve surgery (VS) in infective endocarditis on 5 year mortality |
| **Patient characteristics** | Adult patients with IE were selected from a prospective, population based study.<br>Original study - Cases were collected during a cross-sectional prospective population-based survey between 1 December 1998 and 31 March 2000. 559 patients with definite IE (Duke Criteria). Of these 449 with left sided IE were included in the current study.<br>Inclusion criteria included IVDUs.<br>See results tables for baseline characteristics of interest. |
| **Number of patients** | 449 with L-sided IE |
| **Outcomes** | Surgery<br>Mortality |
| **Predictors/risk factors and effect estimates** | Previous cardiac conditions were not found to be independent predictors of valve surgery after IE. |

| Bibliographic reference | **Bannay, A et al. (2011) The impact of valve surgery on short- and long-term mortality in left-sided infective endocarditis: do differences in methodological approaches explain previous conflicting results? European Heart Journal; 32, 2003-2015..** |
|---|---|

**Characteristics (pre-existing cardiac conditions) of 449 patients by those undergoing valve SURGERY**

| | **Total sample N (%)** | **Valve surgery (n=240)** | **No valve surgery (n=209)** | **P-value** |
|---|---|---|---|---|
| Age y (mean, SD) | 60.8 (14.0) | 57.6 (13.5) | 64.4 (15.6) | **<0.0001** |
| Male | 344 (74.4) | 188 (78.3) | 146 (69.9) | 0.051 |
| History of Predisposing cardiac diseases (Valvular diseases with/without prosthesis) | 257 (57.2) | 142 (59.2) | 115 (55.0) | 0.446 |
| History of Valvular disease (both native and prosthetic valves) | 233 (51.9) | Not reported | Not reported | N/A |
| Valvular prosthesis | 71 (15.8) | 37 (15.4) | 34 (16.3) | 0.897 |
| Native valve disease (no prosthesis) | 162 (36.1) | 105 (43.8) | 81 (38.8) | 0.292 |
| Intracardiac device | 15 (3.3) | 5 (2.1) | 10 (4.8) | 0.123 |
| History of previous IE | 38 (8.5) | 24 (10.0) | 14 (6.7) | 0.237 |

**Mortality**

In hospital mortality reported as overall percentage only – 19%. Not reported separately by risk factor.

160 patients died in total (including in-hospital deaths) resulting in a 41% 5-year mortality rate. (61 (25.4%) in surgical group vs 99 (47.4%) in non-surgical group).

5-year survival rates were thus 69.6% and 48.0% respectively (crude P<0.0001) (log rank).

**Independent prognostic factors of 5 year death rate (449 patients with a definitely left sided IE, adjusted Cox model n=449)**

| **Characteristic** | **HR (95% CI)** | **P-value** |
|---|---|---|
| Age (years) | 1.04 (1.02-1.05) | **<0.0001** |
| Number of serious comorbid diseases* | 1.40 (1.23-1.58) | **<0.0001** |
| *History of valvular disease* | | |
| No previously known valvular disease | 1.00 | |
| Native valve disease | 0.67 (0.46-0.97) | **0.032** |

| | |
|---|---|
| **Bibliographic reference** | **Bannay, A et al. (2011) The impact of valve surgery on short- and long-term mortality in left-sided infective endocarditis: do differences in methodological approaches explain previous conflicting results? European Heart Journal; 32, 2003-2015..** |
| | Valvular prosthesis \| 1.09 (0.72-1.67) \| 0.677<br>*Serious comorbid diseases: ischaemic cardiomyopathy, heart failure, peripheral vascular disease, previous stroke, chronic pulmonary disease, renal insufficiency, connective tissue disease, immunodeficiency, liver disease and malignant disease.<br>(All covariates fulfilled proportional hazard assumption).<br><br>Length of stay was reported as mean of total sample only (42 days) and not by risk factor. |
| **Analysis used** | Categorical variables – Fisher's exact test<br>Continuous variables – unpaired t-test or median test.<br>Bivariable and multivariable ascending stepwise Cox proportional hazard model was used to determine independent predictors of valve surgery and independent 5-year survival predictors. Unclear which variables adjusted for. ? ask Toni to check. |
| **Length of follow-up** | 5 years. Median follow up was 5.0 years (loss to follow-up rate was 12.5% at 5 years. |
| **Location** | 7 centres in France |
| **Source of funding** | Funded by the Programme Hospitalier de Recherche Clinique. |
| **Comments** | **Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))**<br>Study Participation – Y<br>Study attrition – U reported loss to follow-up of 12.5% could be a potential source of bias<br>Prognostic factor measurement – Y<br>Outcome measurement – Y<br>Confounding measurement and account – Y IVDUs were included (non- protocol criteria)but not grouped with those with pre-existing cardiac conditions<br>Analysis – N Odds ratios were not provided and needed to be back calculated by reviewer. No sample size calculation.<br>4/6 = LOW RISK OF BIAS |

1 **Table 43**

| | |
|---|---|
| **Bibliographic reference** | **Da COSTA, M.A.C. et al. (2007) Risk index for death by infective endocarditis: a multivariate logistic model. Brazilian Journal of Cardiovascular Surgery. 22(2):192-200.** |

<table>
<tr><td>Bibliographic reference</td><td>Da COSTA, M.A.C. et al. (2007) Risk index for death by infective endocarditis: a multivariate logistic model. Brazilian Journal of Cardiovascular Surgery. 22(2):192-200.</td></tr>
<tr><td>Study type</td><td>Retrospective observational study</td></tr>
<tr><td>Aim</td><td>To identify predictive variables for in-hospital mortality after IE and create a risk index for death.</td></tr>
<tr><td>Patient characteristics</td><td>186 consecutive episodes of IE confirmed using Duke criteria in 179 patients.<br>Adults and children included. Mean age 7 – 70 years (mean 33.9 years, no SD.</td></tr>
<tr><td>Number of patients</td><td>186 episodes (179 patients)</td></tr>
<tr><td>Outcomes</td><td>Mortality after IE</td></tr>
<tr><td>Predictors/risk factors and effect estimates</td><td>Post IE Mortality in univariate analysis of quantitative variables
<table>
<tr><th>Characteristic</th><th>Total (N=186)</th><th>Death (n=49 = 26.3%) (n)</th><th>Mortality (%)</th><th>P-value</th><th>Odds ratio (95% CI)</th></tr>
<tr><td><40 Years old</td><td>133</td><td>23</td><td>9.1</td><td><0.0001</td><td>4.61 (2.28, 9.29)</td></tr>
<tr><td>40 or over</td><td>53</td><td>26</td><td>49.1</td><td></td><td></td></tr>
<tr><td>Male</td><td>12</td><td>29</td><td>25.9</td><td>0.867</td><td>Not reported</td></tr>
<tr><td>Prosthesis</td><td>56</td><td>20</td><td>35.7</td><td>0.3965</td><td>Not reported</td></tr>
<tr><td>Prosthesis (from Echo)</td><td>55</td><td>20</td><td>36.4</td><td>0.0008</td><td>4.57 (1.89, 11.07)</td></tr>
<tr><td>Rheumatic<br>(fever in table, disease in text)</td><td>45</td><td>9</td><td>20.0</td><td>0.3652</td><td>Not reported</td></tr>
</table>
After multivariate analysis, complicated valve or valve prosthesis were significantly associated with mortality - OR 4.77 (1.44, 15.76), p<0.01.<br><br>ROC Curve for probability of death – area under the curve 0.872.</td></tr>
<tr><td>Analysis used</td><td>Univariate inference analysis using Chi-square test, Fisher’s exact test, logistic regression and Mann-Whitney U test. Multivariate inference analysis using logistic regression with the stepwise procedure by the forward method. (independent variables had to be significant at p<0.20 to be included. To remain in the model p needed to be <0.05).<br>A formula was developed to calculate the risk of death and a Receiver Operating Characteristic (ROC) curve was developed.</td></tr>
<tr><td>Length of follow-up</td><td>January 1988-december 1998. Patients followed-up until discharge.</td></tr>
</table>

| | |
|---|---|
| **Bibliographic reference** | **Da COSTA, M.A.C. et al. (2007) Risk index for death by infective endocarditis: a multivariate logistic model. Brazilian Journal of Cardiovascular Surgery. 22(2):192-200.** |
| **Location** | Curitiba, Brazil. |
| **Source of funding** | Not mentioned |
| **Comments** | **Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))**<br>Study Participation – N Retrospective design. Adults and children grouped together. Mean but no SD for age reported.<br>Study attrition – Y.<br>Prognostic factor measurement – N Age is separated with 40 years as the threshold. Those <40 include children but it is not reported how many and what ages. Lack of clarity about rheumatic fever/rheumatic heart disease – inconsistently reported.<br>Outcome measurement – Y<br>Confounding measurement and account – Y<br>Analysis – Y No sample size calculation but n= min 20 for some variables.<br>4/6 met = LOW RISK OF BIAS |

1 **Table 44**

| | |
|---|---|
| **Bibliographic reference** | **Delahaye, F. et al. (2007) In-hospital mortality of infective endocarditis: Prognostic factors and evaluation over an 8-year period. Scandinavian Journal of Infectious Diseases. 39:849-857.** |
| **Study type** | Prospective population based survey |
| **Aim** | To report on in-hospital mortality from IE |
| **Patient characteristics** | Age >15 years living in one of the study regions. Physician lead patient selection (faxed notification form to study centre for each IE patient treated) and the physician and microbiologist were asked to complete a questionnaire.<br>653 cases of IE (Duke Criteria) were entered into database.<br>Exclusions – no evidence of diagnosis according to Duke Criteria (n=94).<br>559 cases included.<br><br>(390 were retained for case description and 1 yr. incidence calculation in the original manuscript (published previously) based on 1999 data only). Data was also collected in 1991 to enable comparison of mortality rates between 1991 and 1999.<br><br>The current study included all 559 cases.<br>Mean Age 59±16.8 y. 72% male. |

| Bibliographic reference | **Delahaye, F. et al. (2007) In-hospital mortality of infective endocarditis: Prognostic factors and evaluation over an 8-year period. Scandinavian Journal of Infectious Diseases. 39:849-857.** |
|---|---|

| Variable | Percentage |
|---|---|
| Underlying heart disease | |
| Native valve disease | 34 |
| Prosthetic valve | 15 |
| Congenital heart disease | 1 |
| No previously known underlying disease | 46 |

| | |
|---|---|
| **Number of patients** | 559 |
| **Outcomes** | Mortality |
| **Predictors/risk factors and effect estimates** | In-hospital mortality rate in this study period was 17% (95/559). |

**Univariate analysis in-hospital mortality after IE by patient characteristics**

| Variable | | % deaths | p-value |
|---|---|---|---|
| Age (y) | <60 | 11.2 | |
| | 60-70 | 18.0 | |
| | 70-80 | 25.2 | |
| | >80 | 21.6 | **0.004** |
| Gender | Not | | |
| History of prosthetic valve | No | 15.6 | |
| | Yes | 24.7 | **0.04** |
| Rheumatological manifestations | No | 8.9 | |
| | Yes | 14.1 | **0.01** |

Multiple regression (stepwise logisitic) was carried out for baseline variables but the above variables of interest were not reported as they were not retained in the model.

| | |
|---|---|
| **Analysis used** | Prognostic influence of variables on in-hospital mortality tested first in univariate analysis ( Pearson's $X^2$ test) then multivariate analysis (stepwise logistic regression, variables with $p<0.10$ in univariate analysis). |

| | |
|---|---|
| **Bibliographic reference** | **Delahaye, F. et al. (2007) In-hospital mortality of infective endocarditis: Prognostic factors and evaluation over an 8-year period. Scandinavian Journal of Infectious Diseases. 39:849-857.** |
| **Length of follow-up** | Launched 1 December 1998 and stopped 31 March 2000. (Plus cross-sectional incidence carried out 1999). |
| **Location** | France |
| **Source of funding** | Funded by a Programme Hospitalier de Recherche Clinicque grant, the Federation Francaise de Cardiologie and the Aventis and GlaxoSmithKline laboratories, France. |
| **Comments** | **Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))**<br>Study Participation - N Inclusion was based on physician referrals of patients with IE which could introduce a source of bias<br>Study attrition – U study reports outcomes for 100% of participants but the data on percentages with mortality does not add up to 100%.<br>Prognostic factor measurement – Y<br>Outcome measurement – Y<br>Confounding measurement and account – Y<br>Analysis – N Odds ratios inconsistently reported and insufficient data provided to enable back calculation by reviewer. No sample size calculation.<br>3/6 met = HIGH RISK OF BIAS |

1 **Table 45**

| | |
|---|---|
| **Bibliographic reference** | **Erbay, A.R. et al. (2010). Risk Factors for In-Hospital Mortality in Infective Endocarditis: Five years' Experience at a Tertiary Care Hospital in Turkey. Journal Heart Valve Disease; 19:2:216-224.** |
| **Study type** | Retrospective cohort design |
| **Aim** | To determine the clinical, laboratory and echocardiographic features of IE and evaluate the risk factors for in-hospital mortality. |
| **Patient characteristics** | All adult patients (≥18y) admitted to hospital with IE – Modified Duke criteria for definitive IE.<br>>1 episode of IE only the first episode was included.<br>People with pacemakers were excluded.<br>TEE was carried out for all patients with suspected IE and PVE<br>Data obtained from medical records and computerised database.<br>(79 male, 28 female, mean age 45±16 years) |
| **Number of patients** | 107 |
| **Outcomes** | In-hospital mortality |

**Bibliographic reference**

**Erbay, A.R. et al. (2010). Risk Factors for In-Hospital Mortality in Infective Endocarditis: Five years' Experience at a Tertiary Care Hospital in Turkey. Journal Heart Valve Disease; 19:2:216-224.**

**Predictors/risk factors and effect estimates**

**Risk factors associated with in-hospital mortality after infective endocarditis, based on univariate analysis**

| Risk Factor | Total (n=107) | Survived (n=78) | Died (n=29) (27%) | p-value |
|---|---|---|---|---|
| Age (y) | 45± 16 | 45±16 | 44±17 | 0.736 |
| Male gender | 79 (74) | 55(71) | 24(83) | 0.200 |
| Previous IE history | 10 (9) | 4(5) | 6(21) | **0.023** |
| Predisposing heart disease | 87 (81) | 62(80) | 25(86) | 0.312 |
| Prosthetic valve | 47 (44) | 37(47) | 10(35) | 0.230 |
| Native Valves | | | | |
| Degenerative valve disease | 15(14) | 11(14) | 4(14) | 0.608 |
| Rheumatic heart disease | 11(10) | 6(8) | 5(17) | 0.148 |
| Congenital heart disease | 7(7) | 5(6) | 2(7) | 0.613 |
| Bicuspid aortic valve | 3(3) | 1(1) | 2(7) | 0.178 |
| Other | 4(4) | 2(3) | 2(7) | 0.296 |

**Estimated Standard Error (SE), p-value and hazard ratio (HR) as a function of the risks of the variables for IE according to Cox proportional hazards model.**

| Risk Factor | SE | p-value | HR | 95%CI |
|---|---|---|---|---|
| Previous IE history | 2.1 | 0.026 | 3.5 | 1.2-11.0 |

**Analysis used**

Categorical variables/proportions - Chi-square or Fisher's exact test

Continuous variables – independent Student's t-test or Wilcoxon rank sum test.

A cox regression was used to model in-hospital mortality.

For multivariate analysis, only variables with a p-value of <0.05 were entered into the model. Stepwise selection procedure applied.

HRs were computed from estimated parameters of the final regression model.

**Length of follow-up**

January 2004 - December 2008.

| | |
|---|---|
| **Bibliographic reference** | **Erbay, A.R. et al. (2010). Risk Factors for In-Hospital Mortality in Infective Endocarditis: Five years' Experience at a Tertiary Care Hospital in Turkey. Journal Heart Valve Disease; 19:2:216-224.** |
| **Location** | Ankara, Turkey |
| **Source of funding** | Not mentioned |
| **Comments** | **Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))**<br>Study Participation – N Retrospective design. Relatively small numbers. May have been subjected to referral bias (data collected at a referral and tertiary-care hospital) as the patients referred to specialized units tend to be more complex and severe.<br>Study attrition – Y<br>Prognostic factor measurement – Y<br>Outcome measurement – Y<br>Confounding measurement and account – Y<br>Analysis – N no odds ratios were reported and needed to be back calculated by the reviewer. No sample size calculation.<br>4/6 met = LOW RISK OF BIAS |

1 **Table 46**

| | |
|---|---|
| **Bibliographic reference** | **Fernandez Guerrero, M.L. et al. (2007). Enterococcal endocarditis on native and prosthetic valves. A review of clinical and prognostic factors with emphasis on hospital-acquired infections as a major determinant of outcome. Medicine. 86:6:363-377** |
| **Study type** | Retrospective observational study |
| **Aim** | To determine the risk factors for mortality in patients with enterococcal endocarditis on native vs prosthetic valves |
| **Patient characteristics** | Data collected from patient records from a database.<br>Diagnosis was based on strict case definitions using modified Duke criteria.<br>Methods for blood cultures changed over the years but at least 3 sets of cultures were taken from each patient with suspected endocarditis.<br>IVDUs were included.<br><br>Median age 58 years (noted by authors to be younger than other published studies)<br><br>Predisposing heart conditions were observed in 38/47 (86.3%) patients.<br>17 had prosthetic valve (of which 13 were metallic valves and 4 bioprosthetic) endocarditis.<br>10 had degenerative valvular disease |

<table>
<tr><td>Bibliographic reference</td><td>Fernandez Guerrero, M.L. et al. (2007). Enterococcal endocarditis on native and prosthetic valves. A review of clinical and prognostic factors with emphasis on hospital-acquired infections as a major determinant of outcome. Medicine. 86:6:363-377</td></tr>
<tr><td></td><td>4 had rheumatic valve disease<br>3 had congenital cardiac disease (1 ductus arteriosus and 2 bicuspid aortic valves).<br>3 had previous endocarditis and<br>1 had mitral valve prolapse.<br><br>Only the first episode of endocarditis was considered in the analysis of the risk factors for mortality.<br>Mortality related to either in-hospital mortality or within 30 days of discharge. Patients were also followed up in outpatient clinics with visits at 1, 3, 6 and 12 months after discharge. (Unclear if mortality figure includes deaths after 30 days of discharge).</td></tr>
<tr><td>Number of patients</td><td>47 episodes in 44 patients</td></tr>
<tr><td>Outcomes</td><td>Mortality - occurred in 8 cases (18.1%).<br>Brain emboli (9 cases)<br>Surgery (Valve replacement due to cardiac failure) (18 cases)</td></tr>
<tr><td>Predictors/risk factors and effect estimates</td><td>Clinical findings of 44 patients with Enterococcal Endocarditis
<table>
<tr><th>Variable</th><th>Native Valve endocarditis (N=27 patients) N (%)</th><th>Prosthetic Valve endocarditis (N=17) N (%)</th><th>P value</th></tr>
<tr><td>Mortality</td><td>6 (22.2)</td><td>2 (11.7)</td><td>NS</td></tr>
<tr><td>Brain emboli</td><td>5 (18.5)</td><td>4(23.5)</td><td>NS</td></tr>
<tr><td>Valve replacement (due to cardiac failure)</td><td>12 (44.4)</td><td>6 (35.2)</td><td>NS</td></tr>
</table></td></tr>
<tr><td>Analysis used</td><td>Continuous variables – Student t test or nonparametric test<br>Categorical variables – Chi-square or Fisher’s exact test.<br>Stepwise logistic regression was applied to variables the yielded significant results in the univariate analysis to identify risk factors for mortality.</td></tr>
<tr><td>Length of follow-up</td><td>January 1988 to December 2005</td></tr>
<tr><td>Location</td><td>Single centre, Madrid, Spain.</td></tr>
</table>

| | |
|---|---|
| **Bibliographic reference** | **Fernandez Guerrero, M.L. et al. (2007). Enterococcal endocarditis on native and prosthetic valves. A review of clinical and prognostic factors with emphasis on hospital-acquired infections as a major determinant of outcome. Medicine. 86:6:363-377** |
| **Source of funding** | Not mentioned. |
| **Comments** | **Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))**<br>Study Participation – N Retrospective design. Enterococcal endocarditis only. Small number over long study period – ?changing practices in that time. No sample size calculation<br>Study attrition – Y<br>Prognostic factor measurement – Y<br>Outcome measurement – U follow up periods were not explicit for mortality and complications (brain emboli)<br>Confounding measurement and account – Y<br>Analysis – N did not report odds ratios for mortality or complications as listed in results. Back calculation by reviewer was necessary. No sample size calculation.<br>3/6 met = HIGH RISK OF BIAS |

1 **Table 47**

| | |
|---|---|
| **Bibliographic reference** | **Fernandez Guerrero, M.L. et al (2010) Left-sided Endocarditis caused by staphylococcus aureus. A comparison of clinical and prognostic factors of patients with native and prosthetic valve endocarditis. Infectious Diseases in Clinical Practice; 18:308-312.** |
| **Study type** | Retrospective observational study |
| **Aim** | To compare the epidemiology, manifestations and outcome of patients with NVE and PVE due to S. aureus and to assess the risk factors associated with mortality. |
| **Patient characteristics** | Review of records of all patients with a definite diagnosis of endocarditis (modified Duke's criteria).<br>533 cases of IE. 151 were definite S. aureus endocarditis.<br>Exclusion : R-sided endocarditis (n=67).<br>84 patients with definite L-Sided endocarditis caused by S. aureas were included.<br>Incidence ranged from 2 to 4 cases per 10,000 admissions per year.<br>54 patients (64%) had a pre-determined valve condition (not specified by type of endocarditis nor by protocol outcomes).<br>Mean age was 57 in those with NVE and 61 in those with PVE. No SD Reported. |
| **Number of patients** | **84** |
| **Outcomes** | Mortality<br>Surgery (Valve-replacement) |

<table>
<tr><td>Bibliographic reference</td><td>Fernandez Guerrero, M.L. et al (2010) Left-sided Endocarditis caused by staphylococcus aureus. A comparison of clinical and prognostic factors of patients with native and prosthetic valve endocarditis. Infectious Diseases in Clinical Practice; 18:308-312.</td></tr>
<tr><td></td><td>Stroke (CNS complications including brain bleeding)</td></tr>
<tr><td>Predictors/risk factors and effect estimates</td><td>Overall mortality n=28<br><br>Mortality by IE valve type in Patients with L-Sided endocarditis caused by S. aureus.
<table>
<tr><th>All n=84</th><th>Mortality</th><th>OR (95% CI)</th><th>P-value</th></tr>
<tr><td>NVE (Total n=56)</td><td>16 (28)</td><td rowspan="2">0.53 [0.21-1.37]</td><td rowspan="2">Not reported</td></tr>
<tr><td>PVE Total n=28)</td><td>12 (43)</td></tr>
</table>
Subsequent Surgery (valve replacement) by IE valve type in Patients with L-Sided endocarditis caused by S. aureus
<table>
<tr><th>All n=84</th><th>Surgery (Valve Replacement)</th><th>OR (95% CI)</th><th>P-value</th></tr>
<tr><td>NVE (Total n=56)</td><td>21 (37)</td><td rowspan="2">0.24 [0.09-0.64]</td><td rowspan="2">Not reported</td></tr>
<tr><td>PVE Total n=28)</td><td>20 (71)</td></tr>
</table>
Stroke (CNS complications including brain bleeding) by IE valve type in Patients with L-Sided endocarditis caused by S. aureus
<table>
<tr><th>All n=84</th><th>Stroke</th><th>OR (95% CI)</th><th>P-value</th></tr>
<tr><td>NVE (Total n=56)</td><td>16 (28)</td><td rowspan="2">0.72 [0.27-1.89]</td><td rowspan="2">Not reported</td></tr>
<tr><td>PVE Total n=28)</td><td>10 (36)</td></tr>
</table>
(percentage only reported)</td></tr>
<tr><td>Analysis used</td><td>Association of continuous variables – Fisher’s exact test.<br>Strength of association – odds ratio (OR) or Haldane’s estimator for small sample 2 x 2 tables.</td></tr>
<tr><td>Length of follow-up</td><td>1987-2009</td></tr>
<tr><td>Location</td><td>Madrid, Spain</td></tr>
<tr><td>Source of funding</td><td>Not mentioned</td></tr>
</table>

| | |
|---|---|
| **Bibliographic reference** | **Fernandez Guerrero, M.L. et al (2010) Left-sided Endocarditis caused by staphylococcus aureus. A comparison of clinical and prognostic factors of patients with native and prosthetic valve endocarditis. Infectious Diseases in Clinical Practice; 18:308-312.** |
| **Comments** | **Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))**<br>Study Participation – N Retrospective design. ? age of population/adults only? – mean age but no SD reported. S aureus population only.<br>Study attrition – Y.<br>Prognostic factor measurement – U The author's state that a limitation could be the length of time over which the data were collected in that substantial medical improvements in medical practice occurred.<br>Outcome measurement – P the authors could not control for selection of surgical versus medical therapy.<br>Confounding measurement and account – Y<br>Analysis – N multivariate regression analysis has been carried out but aOR not reported. No sample size calculation<br>2/6 met = HIGH RISK OF BIAS |

1 **Table 48**

| | |
|---|---|
| **Bibliographic reference** | **Galvez-Acebal, J. et al (2010). Prognostic factors in left-sided endocarditis: results from the Andalusian multicentre cohort. BMC Infectious diseases. 10:17.** |
| **Study type** | Observational multi-centre study |
| **Aim** | To identify predictors of in-hospital mortality |
| **Patient characteristics** | Left sided IE (Duke criteria) for definite and possible IE. 624 (88%) were definite IE and 81 (12%) possible cases.<br>46 (7%) were IVDUs.<br>Consecutively registered to a database during study period. (5 tertiary referral hospitals, 2 community hospitals).<br>Patients registered before 1994 where retrospectively assigned diagnostic criteria.<br>For relapses, only the first episode was included.<br>Excluded : patients with insufficient follow-up data (not longer than 1 month).<br><br>5patients were ≤15 years old.<br>486 (69%) patients were male. |
| **Number of patients** | 705 |
| **Outcomes** | In-hospital mortality |
| **Predictors/risk factors and effect estimates** | Overall In-hospital mortality n=208, 29.5% |

<table>
<tr><td>Bibliographic reference</td><td>Galvez-Acebal, J. et al (2010). Prognostic factors in left-sided endocarditis: results from the Andalusian multicentre cohort. BMC Infectious diseases. 10:17.</td></tr>
<tr><td></td><td>Univariate analysis of in-hospital mortality: patient characteristics and etiology.
<table>
<tr><th colspan="2">Variable</th><th>Alive (n=497)<br>N (%)</th><th>Deaths (n=208)<br>N (%)</th><th>RR (95%CI)</th><th>P-value</th></tr>
<tr><td>Age (y)</td><td>Mean±SD</td><td>51.6 ±17</td><td>28.8 ±16</td><td>-</td><td><0.001</td></tr>
<tr><td>Gender</td><td>Male</td><td>345 (71)</td><td>141 (29)</td><td rowspan="2">1.07 (0.76-1.52)</td><td rowspan="2">0.367</td></tr>
<tr><td></td><td>Female</td><td>152 (69.4)</td><td>67 (30.6)</td></tr>
<tr><td rowspan="2">Valve type</td><td>Prosthetic</td><td>104 (60.8)</td><td>67 (39.2)</td><td rowspan="2">1.48 (1.17-1.87)</td><td rowspan="2">0.001</td></tr>
<tr><td>Native</td><td>393 (73.6)</td><td>141 (26.4)</td></tr>
</table>
Multivariate analysis<br>Prosthetic endocarditis, β 0.688, OR 1.99 (1.26-3.14), p=0.003<br><br>Recurrence and relapse was reported as overall percentages only and not according to variables of interest.</td></tr>
<tr><td>Analysis used</td><td>Categorical variables – Chi-Square or Fisher’s exact test<br>Continuous variables – Student’s T test or Mann-Whitney U test.<br>Univariate analysis (RR) for mortality was performed followed by multivariate analyses using logistic regression. (model built including all variables with a significant association in univariate analysis and those considered potentially clinically relevant. Modification between variables were also studied and selection of variables was performed using stepwise backward procedure.</td></tr>
<tr><td>Length of follow-up</td><td>January 1984 – December 2006</td></tr>
<tr><td>Location</td><td>Andalusia, Spain. (7 hospitals)</td></tr>
<tr><td>Source of funding</td><td>Supported by Spanish Network for the Research in infectious diseases.</td></tr>
<tr><td>Comments</td><td>Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))<br>Study Participation – N Retrospective analysis. Age – 5 patients children, grouped with adults.<br>Study attrition – Y<br>Prognostic factor measurement – Y<br>Outcome measurement – Y<br>Confounding measurement and account – N Included all patients with definite and possible IE.<br>Analysis – Y<br>4/6 met = LOW RISK OF BIAS</td></tr>
</table>

1 **Table 49**

<table>
<tr><td>Bibliographic reference</td><td>Lin, Y-T. et al (2013) Infective endocarditis in children without underlying heart disease. Journal of Microbiology, Immunology and Infection. 46, 121-128.</td></tr>
<tr><td>Study type</td><td>Retrospective analysis</td></tr>
<tr><td>Aim</td><td>To review the clinical and laboratory characteristics of paediatric IE patients with and without underlying heart disease</td></tr>
<tr><td>Patient characteristics</td><td>January 1991 – April 2011.<br>All consecutive paediatric patients (age≤18years) with a diagnosis of definite or possible IE (Modified Duke criteria) were enrolled. Data collected from medical records.<br>Mean age was 9.2 years (range 3 days to 18.7 years)</td></tr>
<tr><td>Number of patients</td><td>47 (with 48 episodes of IE). Of these 31 (64.6%) had CHD, 6 (12.5%) had non CHD chronic disease and 11 (22.9%) were previously healthy adolescents.</td></tr>
<tr><td>Outcomes</td><td>IE, Need for surgery (incl. valve surgery), in-hospital death, microbial pathogens (not reported here as non-protocol outcome)</td></tr>
<tr><td>Predictors/risk factors and effect estimates</td><td>IE in children with and without CHD
<table>
<tr><td rowspan="2"></td><td rowspan="2">CHD (n=31)</td><td colspan="2">NON CHD (n=17)</td><td rowspan="2">P-value (CHD vs non CHD)</td><td rowspan="2">P-value (CHD vs healthy)</td></tr>
<tr><td>Chronic disease (n=6)</td><td>Previously healthy (n=11)</td></tr>
<tr><td>Definite/Possible IE</td><td>19 / 12</td><td>4 / 2</td><td>11 / 0</td><td>0.095</td><td>0.018</td></tr>
</table>
(Protocol) Outcomes in Children with IE by health status (For Q2)
<table>
<tr><td rowspan="2"></td><td rowspan="2">CHD (n=31) (%)</td><td colspan="2">NON CHD (n=17)</td><td rowspan="2">P-VALUE</td></tr>
<tr><td>Chronic disease (n=6)</td><td>Previously healthy (n=11)</td></tr>
<tr><td>Need for cardiac surgery (total = 17)</td><td>9/31 (29)</td><td>0 (0)</td><td>8/11 (72.7)</td><td>Not calculated</td></tr>
<tr><td>Valve replacement surgery specifically (total = 11/17)</td><td>3 / 9 (33.3%)</td><td>0</td><td>8 / 8 (100)</td><td>Not calculated</td></tr>
<tr><td>In-hospital mortality (total deaths =7)</td><td>6 / 7</td><td>0</td><td>1 / 7</td><td>Not calculated</td></tr>
</table>
No odds ratios reported.</td></tr>
</table>

| Bibliographic reference | Lin, Y-T. et al (2013) Infective endocarditis in children without underlying heart disease. Journal of Microbiology, Immunology and Infection. 46, 121-128. |
|---|---|
| | |
| **Analysis used** | Categorical variables were compared using Pearson Chi-square test or Fisher's exact test in univariate analysis. |
| **Length of follow-up** | 20 years 3 months study duration |
| **Location** | Kaohsiung Hospital, Taiwan |
| **Source of funding** | This work was supported by a grant from the Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan |
| **Comments** | **Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))**<br>Study Participation – U retrospective design (but consecutive enrolment)<br>Study attrition – Y<br>Prognostic factor measurement – Y<br>Outcome measurement – N Diagnosis of IE included possible and definite.<br>Confounding measurement and account – Y<br>Analysis – N No odds ratios. Reviewer needed to back calculate. No sample size calculations.<br>3/6 met = HIGH RISK OF BIAS |

1 **Table 50**

| Bibliographic reference | Murakami, T. et al (2012) Factors associated with surgery for active endocarditis in congenital heart disease. International Journal of Cardiology 157; 59-62. |
|---|---|
| **Study type** | Retrospective observational cohort (multi-centre) |
| **Aim** | To determine the surgical indications for active infective endocarditis in congenital heart diseases. |
| **Patient characteristics** | N=239 paediatric and adult patients with IE surveyed. (Children n=170)<br>216 had congenital heart diseases, 23 were not diagnosed. Of these 147 had CHD and 23 without apparent CHD)<br>61 underwent surgical therapy for active IE.<br>Age<br>Children 7.4 years±5.7 years (range 14 days to17 years).<br>Adults 32.5±14.1 years (range 18-69years)<br><br>Diagnoses of underlying congenital diseases given as single number/percentage of total. |
| **Number of patients** | 239 |
| **Outcomes** | Surgery |

<table>
<tr><td>Bibliographic reference</td><td>Murakami, T. et al (2012) Factors associated with surgery for active endocarditis in congenital heart disease. International Journal of Cardiology 157; 59-62.</td></tr>
<tr><td>Predictors/risk factors and effect estimates</td><td>7 deaths (11%).<br><br>Number of patients that underwent surgery with active endocarditis with or without each risk factor, odds ratio and p values by univariate regression analysis.
<table>
<tr><th>Risk Factor</th><th>Surgery</th><th>No surgery</th><th>Odds Ratio (95% CI)</th><th>P value</th></tr>
<tr><td>Male</td><td>42/143 (29)</td><td>19/96 (20)</td><td>1.69 (0.91-3.13)</td><td>0.13</td></tr>
<tr><td>Diagnosis of underlying heart disease before IE</td><td>49/216 (23)</td><td>12/23 (52)</td><td>0.27 (0.11-0.65)</td><td>0.0044</td></tr>
<tr><td>Previous surgery for CHD</td><td>26/119 (22)</td><td>35/120 (29)</td><td>0.68 (0.38-1.22)</td><td>0.24</td></tr>
<tr><td>History of IE</td><td>4/21 (19)</td><td>57/218 (26)</td><td>0.67 (0.22-2.06)</td><td>0.61</td></tr>
</table>
Data are expressed as number of operated patients during active infective endocarditis period of the group of the presence or absence of the risk factors and the ratio of operated patients in parenthesis.<br><br>Lack of diagnosis of CHD before onset of IE was significantly associated with need for surgical intervention.</td></tr>
<tr><td>Analysis used</td><td>Univariate logistic regression analysis to evaluate risk factors associated with need for surgical intervention for IE<br>Multivariate analysis (stepwise approach) was conducted.</td></tr>
<tr><td>Length of follow-up</td><td>Duration : January 1997 to December 2001</td></tr>
<tr><td>Location</td><td>Japan (66 separate institutions)</td></tr>
<tr><td>Source of funding</td><td>Not reported</td></tr>
<tr><td>Comments</td><td>Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))<br>Study Participation – N retrospective design<br>Study attrition – Y<br>Prognostic factor measurement – Y<br>Outcome measurement – Y<br>Confounding measurement and account – Y<br>Analysis – N unadjusted OR reported only. Multivariate analysis conducted but results not provided for each predictor evaluated.</td></tr>
</table>

| | |
|---|---|
| **Bibliographic reference** | **Murakami, T. et al (2012) Factors associated with surgery for active endocarditis in congenital heart disease. International Journal of Cardiology 157; 59-62.** |
| | 4/6 met = LOW RISK OF BIAS |

1 **Table 51**

| | |
|---|---|
| **Bibliographic reference** | **Murdoch, D.R. et al. (2009). Clinical presentation, etiology, and outcome of Infective endocarditis in the 21st century. Archives of Internal Medicine; 169:5:463-473** |
| **Study type** | Prospective Cohort Study |
| **Aim** | To provide a picture of the presentation, etiology and outcome of infective endocarditis (IE) in a large cohort from multiple locations worldwide. |
| **Patient characteristics** | Adult patients with definite IE (Modified Duke Criteria)<br>Median age 57.9 (IQR 43.2-71.8)y.<br>72.1% had native valve IE.<br><br>Site of enrolment minimum criteria – 12 cases per year, access to cardiac surgery, consecutive enrolment and to minimise ascertainment bias, high quality data and institutional review board approval.<br>Data submitted to main co-ordinating centre – Duke University. |
| **Number of patients** | 2781 (with definite IE out of a total of 3284 who were screened). |
| **Outcomes** | IE<br>Complications from IE including mortality |
| **Predictors/risk factors and effect estimates** | **Predisposing conditions of people with definite IE** / **Total cohort**<br>Prosthetic valve IE: 563/2636 (21)<br>Previous IE: 222/2780 (8)<br>Congenital heart disease: 311/2656 (12)<br>There was no reporting of associations between risk factors of interest and IE.<br><br>In hospital mortality was 17.7%<br><br>**Results of multivariable regression modelling of associations with in-hospital death in 2781 patients**<br>**Variable** / **OR (95% CI)** / **P-value**<br>Prosthetic valve endocarditis / 1.47 (1.13-1.90) / **0.004** |

| | |
|---|---|
| **Bibliographic reference** | **Murdoch, D.R. et al. (2009). Clinical presentation, etiology, and outcome of Infective endocarditis in the 21st century. Archives of Internal Medicine; 169:5:463-473** |
| | Congenital heart disease \| 1.22 (0.74-2.02) \| 0.44 |
| **Analysis used** | Univariable comparisons made using Chi-square or Kruskal-Wallis test. Those with P<0.10 were entered into final explanatory model. |
| **Length of follow-up** | Duration June 1, 2000 – September 1, 2005. |
| **Location** | 58 hospitals in 25 countries |
| **Source of funding** | Supported in part by grants from NIH, American Heart Association and Ministerio de Sanidad y Consumo, Madrid, Spain and two other Spanish research centres. |
| **Comments** | **Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))**<br>Study Participation – Y<br>Study attrition – U Unclear why numbers of total sample (denominator) changes during reporting of pre-existing cardiac condition.<br>Prognostic factor measurement – Y<br>Outcome measurement – Y<br>Confounding measurement and account –U All participating centres were referral centres which may mean the results to do not fully reflect those of the general population as referral centres tend to see more complex cases. The weighting of geographical distribution is towards wealthier countries in Europe, North America and Australasia.<br>Analysis – Y<br>4/6 met = LOW RISK OF BIAS. |

1 **Table 52**

| | |
|---|---|
| **Bibliographic reference** | **San Roman, J A. et al. (2007) Prognostic Stratification of patients with left sided endocarditis determined at admission. The American Journal of Medicine; 120, 369.e1-369.e7.** |
| **Study type** | Prospective study |
| **Aim** | To identify high risk patients with first few days after admission with IE. |
| **Patient characteristics** | 441 Patients who met Duke criteria (406 with definite and 35 with possible IE) were included. Consecutive enrolment during study period.<br>N=333 had L-sided IE.<br>Exclusions : (n= 16) patients with septic shock at admission due to it being an absolute indication for urgent surgery. |

<table>
<tr><td>Bibliographic reference</td><td>San Roman, J A. et al. (2007) Prognostic Stratification of patients with left sided endocarditis determined at admission. The American Journal of Medicine; 120, 369.e1-369.e7.</td></tr>
<tr><td></td><td>In patients with more than one event, only the first was considered.<br>Not specified if adults only.</td></tr>
<tr><td>Number of patients</td><td>N=317</td></tr>
<tr><td>Outcomes</td><td>Events – (death or active phase surgery)</td></tr>
<tr><td>Predictors/risk factors and effect estimates</td><td>Of the 130 who had events, 65 died and 65 underwent operation in the active phase.<br><br>There were no significant differences in death or operation in those with left sided IE according to previous cardiopathy or previous endocarditis.<br><br>Univariate analysis of clinical characteristics by event (death or active phase surgery)
<table>
<tr><th>Clinical characteristics</th><th>Total (n=317) N (%)</th><th>No Events* (n=187) N (%)</th><th>Events* (n=130) N (%)</th><th>P value</th></tr>
<tr><td>Age (y)</td><td>57 ±16</td><td>57 ±16</td><td>58 ±16</td><td>0.82</td></tr>
<tr><td>Male gender</td><td>209 (66)</td><td>128 (68)</td><td>81 (62)</td><td>0.26</td></tr>
<tr><td>Previous cardiopathy</td><td>202 (65)</td><td>121 (66)</td><td>81 (64)</td><td>0.26</td></tr>
<tr><td>Degenerative</td><td>29 (9)</td><td>16 (9)</td><td>13 (10)</td><td>0.65</td></tr>
<tr><td>Prosthesis</td><td>124 (40)</td><td>72 (39)</td><td>52 (41)</td><td>0.76</td></tr>
<tr><td>Rheumatic</td><td>32 (10)</td><td>17 (9)</td><td>15 (12)</td><td>0.47</td></tr>
<tr><td>Previous endocarditis</td><td>28 (9)</td><td>16 (9)</td><td>12 (9)</td><td>0.80</td></tr>
<tr><td colspan="5">Echocardiographic Characteristics (relating to pre-existing cardiac conditions)</td></tr>
<tr><td>Prosthetic</td><td>114 (36)</td><td>63 (34)</td><td>51 (39)</td><td>0.31</td></tr>
<tr><td>Aortic mechanical prosthesis</td><td>36 (11)</td><td>17 (9)</td><td>19 (15)</td><td>0.13</td></tr>
<tr><td>Mitral mechanical prosthesis</td><td>55 (17)</td><td>35 (19)</td><td>20 (15)</td><td>0.44</td></tr>
<tr><td>Mitral bioprosthesis</td><td>16 (5)</td><td>30 (18)</td><td>25 (17)</td><td>0.80</td></tr>
<tr><td>Aortic bioprosthesis</td><td>10 (3)</td><td>7 (4)</td><td>9(7)</td><td>0.31</td></tr>
</table>
*Death and surgery in the active phase were regarded as events. Elective surgery (after antibiotic regimen was completed) were not classed as events.</td></tr>
</table>

| Bibliographic reference | San Roman, J A. et al. (2007) Prognostic Stratification of patients with left sided endocarditis determined at admission. The American Journal of Medicine; 120, 369.e1-369.e7. |
|---|---|
| | Results provided for statistically significant variables only (after multivariate analysis) associated with an event (death or surgery). None of the protocol characteristics of interested remained significant. |
| **Analysis used** | 2 group analysis using 2 tailed Student t-tests or Wilcoxon rank-sum tests and Chi-square or Fisher's exact tests where appropriate.<br>Univariate and multivariate analysis (logistic regression model) including a backward stepwise method were performed with events as the dependent variable. In consecutive steps variables that were statistically significant in the univariate analysis were analysed further. Max 1 variable per 10 outcomes was entered into models. Hosmer-Lemeshow test and model was used to examine goodness of fit of the final model. |
| **Length of follow-up** | Duration : 1996 and 2003 |
| **Location** | 5 tertiary care centres Spain |
| **Source of funding** | Financed in part by the red de centros cardiovasculares which is supported by the Instituo de Salud Carlos III |
| **Comments** | **Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))**<br>Study Participation – Y.<br>Study attrition – Y<br>Prognostic factor measurement – Y<br>Outcome measurement – N classification of the outcome as event vs no event, and defining event as death OR surgery (and counting only the first event if there were more than one) introduces potential bias. If surgery was performed and then patients died this could affect the significance of the identified predictors.<br>Confounding measurement and account – Y.<br>Analysis – N aOR were not reported. Reviewer needed to back calculate odds ratios. No sample size calculation.<br>4/6 met = LOW RISK OF BIAS |

1 **Table 53**

| Bibliographic reference | Smith MJ, So RR, Engel AM. (2007) Clinical predictors of mortality from infective endocarditis. International journal of Surgery. 5, 31-34. |
|---|---|
| **Study type** | Prospective cohort |
| **Aim** | To determine which risk factors and outcome variables are statistically significant predictors of mortality from IE. |
| **Patient characteristics** | Original cohort of prospective hospitalisation n=11,230.<br>This study included patients from this original cohort who had IE diagnosed between October 1993 and Feb 2004, |

<table>
<tr><td>Bibliographic reference</td><td>Smith MJ, So RR, Engel AM. (2007) Clinical predictors of mortality from infective endocarditis. International journal of Surgery. 5, 31-34.</td></tr>
<tr><td></td><td>adults, (≥18y). N=87.<br>No exclusion criteria given</td></tr>
<tr><td>Number of patients</td><td>87</td></tr>
<tr><td>Outcomes</td><td>Mortality</td></tr>
<tr><td>Predictors/risk factors and effect estimates</td><td>Univariate analysis of risk factors for death
<table>
<tr><th></th><th>Deceased N (%)<br>(Total n =10 (11.5%)</th><th>Alive N (%)<br>(n=77)</th><th>P-value</th></tr>
<tr><td>Age (y)</td><td>65.1±15.5</td><td>53.9±14.2</td><td>0.023</td></tr>
<tr><td>Male</td><td>7 (13)</td><td>45 (86)</td><td>0.734</td></tr>
<tr><td>Previous cardiac surgery</td><td>3 (12)</td><td>21 (88)</td><td>1.00</td></tr>
<tr><td>Type of prosthesis (mechanical)</td><td>2 (9)</td><td>20 (91)</td><td>0.665</td></tr>
</table>
(unclear if type of prosthesis relates to inserted post IE or if was present prior to diagnosis)<br><br>Multivariate regression was used to generate the adjusted risk for the significant risk factors. There was no significant difference in mortality for endocarditis patients for any of the risk factors of interest.</td></tr>
<tr><td>Analysis used</td><td>Risk Factors – (unadjusted) chi squire or Fisher’s exact tests where appropriate and t-tests comparing survival and non-survival. Multivariate regression was used to generate the adjusted risk for the significant risk factors.<br>Outcome variables – survival vs non survival comparisons were conducted using chi-square or Fisher’s exact test and t-tests.</td></tr>
<tr><td>Length of follow-up</td><td>Not specified. Mortality is defined as in-house.</td></tr>
<tr><td>Location</td><td>Cincinnati, USA</td></tr>
<tr><td>Source of funding</td><td>No specified</td></tr>
<tr><td>Comments</td><td>Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))<br>Study Participation – U Exclusion criteria not specified (? Reported elsewhere)<br>Study attrition – Y sample population accounted for the study period (sub population)<br>Prognostic factor measurement – Y<br>Outcome measurement – Y<br>Confounding measurement and account – Y<br>Analysis – N no odds ratios or adjusted ORs were reported. The former were back calculated by the reviewer.</td></tr>
</table>

| Bibliographic reference | **Smith MJ, So RR, Engel AM. (2007) Clinical predictors of mortality from infective endocarditis. International journal of Surgery. 5, 31-34.** |
|---|---|
| | No sample size calculation.<br>4/6 met = LOW RISK OF BIAS |

1 **Table 54**

| Bibliographic reference | **Ternhag A et al. (2013) A nationwide cohort study of mortality risk and long-term prognosis in infective endocarditis in Sweden. 8, 7, e67519.** |
|---|---|
| **Study type** | Retrospective cohort study |
| **Aim** | To investigate the incidence of IE as well as associated short and long term mortality rates |
| **Patient characteristics** | IE patients (hospitalised and treated) identified from Swedish National inpatient register and linked to population register to identify deaths. Not specified if adults only.<br>Crude mortality rates were obtained at different time intervals. These were standardized using age and sex matched controls in the general population.<br>IVDUs were included (5%) |
| **Number of patients** | 7063 with 7817 episodes of IE during study period. |
| **Outcomes** | Mortality (all cause attributable IE Mortality by the end of the follow-up period).<br>Surgery (cardiac, i.e. valve surgery) |
| **Predictors/risk factors and effect estimates** | Average annual incidence 7.7 cases of IE per 100000<br>Of these 12% had prosthetic valve IE (80% had native valve, remainder were IVDUs).<br>All cause 30 day crude mortality rate was 10.4% |

| | **No of patients (% men)** | **Age, mean (IQR)** | **Crude 30 day mortality (%)** |
|---|---|---|---|
| Total | 7609 (59.2) | 65.7 (55-79) | 788 (10.4) |
| Native Valve | 6138 (57.6) | 66.8 (57-80) | 642 (10.5) |
| Prosthetic Valve | 890 (62.7) | 70.4 (65-79) | 100 (11.2) |
| Native valve surgery | 778 (72.1) | 55.8 (47-67.8) | 42 (5.4) |
| Native Valve non surgery | 5360 (55.5) | 68.4 (60-81) | 600 (11.2) |
| Prosthetic Valve surgery | 104 (74) | 61.3 (56.8-72) | 16 (15.4) |
| Prosthetic Valve non Surgery | 786 (61.2) | 71.6 (67-80) | 84 (10.7) |

<table>
<tr><td>Bibliographic reference</td><td>Ternhag A et al. (2013) A nationwide cohort study of mortality risk and long-term prognosis in infective endocarditis in Sweden. 8, 7, e67519.</td></tr>
<tr><td></td><td>No significant differences in absolute or relative mortality risks were found between patients with native valve and prosthetic valve IE during 1 year follow up but those with prosthetic valve IE had a lower 5 year survival.<br><br>Long term mortality in the infective endocarditis cohort compared to the age and sex matched Swedish General Population (n=7603).
<table>
<tr><th></th><th colspan="2">Time 1-5 years</th><th>SMR</th><th>95%CI</th></tr>
<tr><th></th><th>Obs No. of deaths (%)</th><th>Expected number of deaths</th><th></th><th></th></tr>
<tr><td>Total</td><td>1117 (14.7)</td><td>518.6</td><td>2.2</td><td>2.0-2.3</td></tr>
<tr><td>Native valve</td><td>894 (14.6)</td><td>441.9</td><td>2.0</td><td>1.9-2.2</td></tr>
<tr><td>Prosthetic valve</td><td>154 (17.3)</td><td>67.9</td><td>2.3</td><td>1.9-2.7</td></tr>
<tr><td>Age≤65 years</td><td>228 (7.4)</td><td>36.3</td><td>6.3</td><td>5.4-7.2</td></tr>
<tr><td>Age >65</td><td>889 (19.6)</td><td>482.3</td><td>1.8</td><td>1.7-2.0</td></tr>
<tr><td>Men</td><td>623 (13.9)</td><td>296.1</td><td>2.1</td><td>1.9-2.3</td></tr>
<tr><td>Women</td><td>494 (15.9)</td><td>222.5</td><td>2.2</td><td>2.0-2.5</td></tr>
</table></td></tr>
<tr><td>Analysis used</td><td>Comparisons of mortality for each category were stratified using and sex Mantel-Haenszel estimates of the OR. Time trend for incidence and mortality rate of IE was evaluated using linear regression model using quasi-poisson distribution and t-test for significance.</td></tr>
<tr><td>Length of follow-up</td><td>Duration 1997-1007.</td></tr>
<tr><td>Location</td><td>Sweden</td></tr>
<tr><td>Source of funding</td><td>Not specified</td></tr>
<tr><td>Comments</td><td>Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))<br>Study Participation – N Retrospective design. IVDUs were included (analysed separately). The authors cite a possible selection bias that explains the divergent results concerning mortality after surgery among different types of IE (native or prosthetic valve). Also the younger and those with fewer morbidities were probably more likely to have surgery than the oldest and most vulnerable individuals.<br>Study attrition – Y All patients were accounted for in analysis.<br>Prognostic factor measurement – Y<br>Outcome measurement – Y<br>Confounding measurement and account – Y</td></tr>
</table>

| Bibliographic reference | **Ternhag A et al. (2013) A nationwide cohort study of mortality risk and long-term prognosis in infective endocarditis in Sweden. 8, 7, e67519.** |
|---|---|
| | Analysis – Y<br>4/6 met = LOW RISK OF BIAS |

1 **Table 55**

| Bibliographic reference | **Thuny, F et al. (2012) Excess mortality and morbidity in patients surviving infective endocarditis. Valvular and congenital heart disease. 164:94-101.** |
|---|---|
| **Study type** | Observational cohort study (majority of data collected retrospectively). |
| **Aim** | To evaluate survival in people with IE who survive the acute phase and had treatment completed. |
| **Patient characteristics** | Consecutive patients admitted with a first definite diagnosis of IE (Duke Criteria) were eligible for participation.<br>Those who survived the inpatient episode were retrospectively included. Not specified if adults only.<br>Exclusion criteria : absence of data after hospitalisation and an isolated pacemaker or defibrillator leads IE.<br>Early surgery was defined as valve surgery performed during the course of antibiotic therapy. |
| **Number of patients** | 328 (followed up for 731 person-years, median 2.2 years, range, 6 days to 7 years). |
| **Outcomes** | All-cause mortality (after completion of treatment for acute IE)<br>Recurrence of IE (includes relapses and reinfections defined by the European guidelines for Cardiology).<br>Need for late surgery (surgery indicated as consequence of the initial or recurrent IE episode. |
| **Predictors/risk factors and effect estimates** | **Characteristics of the 328 patients surviving the acute phase of IE** |

| Characteristic | Overall (n=328) | Alive (n-273) | Died (n=55) | p-value |
|---|---|---|---|---|
| Age (y) mean ±SD | 61 ±16 | 60±16 | 68±13 | 0.0003 |
| Sex ratio male/female | 233/95 | 199/74 | 34/21 | 0.10 |
| Underlying heart disease | 206(63) | 176 (64) | 30 (55) | 0.16 |
| Prosthetic valve | 93 (28) | 80 (29) | 13 (24) | 0.39 |

Recurrence and late surgery are reported but not included here as they are not reported by characteristic (i.e. underlying cardiac condition).

**Predictors of IE excess mortality in the univariate excess hazard mortality analysis adjusted for age and sex.**

| | |
|---|---|
| **Bibliographic reference** | **Thuny, F et al. (2012) Excess mortality and morbidity in patients surviving infective endocarditis. Valvular and congenital heart disease. 164:94-101.** |
| | <table><tr><th>Predictor</th><th>Age and sex adjusted EHR</th><th>95% CI</th><th>P value</th></tr><tr><td>Underlying heart disease</td><td>NOT REPORTED</td><td></td><td></td></tr><tr><td>Prosthetic valve</td><td>0.72</td><td>0.35-1.50</td><td>0.39</td></tr></table><br>No significant differences in death directly attributable to IE by characteristics of interest. |
| **Analysis used** | Statistical test not specified for baseline characteristics although univariate and multivariate analysis (adjusted for age and sex) using excess mortality hazard regression model. (Although results not reported here for the latter).<br>Expected survival was calculated acco0rding to Hakulinen method by applying age, sex and calendar year specific mortality hazard rates of the Bouche-du-Rhone French district population (2002-2006) to the number of person years of follow-up in the study cohort.<br>Excess mortality hazard model for individual data was used with a generalized linear model and Poisson error structure. This enabled calculation of specific IE mortality hazard in the absence of other causes of death. |
| **Length of follow-up** | Duration January 2002 to December 2008. Follow up period was restricted to 7 years. |
| **Location** | Marseille, France |
| **Source of funding** | No extramural funding was used. |
| **Comments** | **Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))**<br>Study Participation – N Retrospective design (although consecutive). ? Referral bias as was performed in referral centres.<br>Study attrition – Y<br>Prognostic factor measurement – Y<br>Outcome measurement – Y<br>Confounding measurement and account – Y<br>Analysis – N Reviewer had to back calculate ORs as none were reported. No sample size calculation.<br>4/6 = LOW RISK OF BIAS |

1 **Table 56**

| | |
|---|---|
| **Bibliographic reference** | **Thuny F, et al (2007) Impact of cerebrovascular complications on mortality and neurologic outcome during infective endocarditis: a prospective multicentre study. 28, 1155-1161.** |
| **Study type** | Prospective Study |

<table>
<tr><td>Bibliographic reference</td><td>Thuny F, et al (2007) Impact of cerebrovascular complications on mortality and neurologic outcome during infective endocarditis: a prospective multicentre study. 28, 1155-1161.</td></tr>
<tr><td>Aim</td><td>To analyse the risk of death according to the type of cerebrovascular complication during infective endocarditis and to analyse the determinants of outcome.</td></tr>
<tr><td>Patient characteristics</td><td>496 patients with definite IE (Duke criteria)<br>Consecutive patients admitted with IE were eligible for entry (n=545). 49 patients were excluded due to pacemaker IE.<br>Diagnosis of CVC was based on clinical and CT scan data or both. 453 patients had a CT scan. CVC included stroke, TIA and silent cerebral embolism.</td></tr>
<tr><td>Number of patients</td><td>496</td></tr>
<tr><td>Outcomes</td><td>CVC (cerebro-vascular complications)</td></tr>
<tr><td>Predictors/risk factors and effect estimates</td><td>CVC (n=109) complications were<br>Silent cerebral embolism n=17, ischaemic stroke n=50, TIA n=30, Primary intracerebral haemorrhage n=12.<br><br>
<table>
<tr><th></th><th>All patients (n=496)</th><th>CVC* (n=109)</th><th>Without CVC (n=387)</th><th>p-value</th></tr>
<tr><td>Age (mean ±SD, y)</td><td>58±16</td><td>59±16</td><td>58±16</td><td>0.61</td></tr>
<tr><td>Male</td><td>364(73)</td><td>81(74)</td><td>283(73)</td><td>0.80</td></tr>
<tr><td>Prosthetic Valve</td><td>110 (22)</td><td>24(22)</td><td>86(22)</td><td>0.96</td></tr>
<tr><td>Underlying heart disease[b]</td><td>275 (55)</td><td>59(54)</td><td>216(56)</td><td>0.75</td></tr>
</table>
*222 patients (45%) had ≥1 embolic event.<br>[b]Including Rheumatic valve disease, non-rheumatic valve disease, congenital heart disease and degenerative cardiac disease.</td></tr>
<tr><td>Analysis used</td><td>Categorical variables – Chi-Square test, Fisher’s exact test (two-tailed), Student’s t-test or Mann Whitney U test.</td></tr>
<tr><td>Length of follow-up</td><td>January 1990-March 2005. Median follow up was 2.9yrs (IQR 1.4-5.8 yrs.).</td></tr>
<tr><td>Location</td><td>Two referral centres, Marseille, France</td></tr>
<tr><td>Source of funding</td><td>Not mentioned.</td></tr>
<tr><td>Comments</td><td>Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))<br>Study Participation – Y<br>Study attrition – Y<br>Prognostic factor measurement – Y</td></tr>
</table>

| Bibliographic reference | **Thuny F, et al (2007) Impact of cerebrovascular complications on mortality and neurologic outcome during infective endocarditis: a prospective multicentre study. 28, 1155-1161.** |
|---|---|
| | Outcome measurement – U authors cite that the predictive value of a mechanical valve PVE on risk of neurological death in patients with CVC could be explained by the potential effect of anticoagulant therapy in these patients. The potential of referral bias was also cited by the authors as these two centres have an early surgery policy. This could have reduced the incidence of CVC. Definition of CVC is broad and large proportion TIA.<br>Confounding measurement and account –Y<br>Analysis – N No odds ratios reported. Back calculated by reviewer. No sample size calculation.<br>4/6 met = LOW RISK OF BIAS |

1 **Table 57**

| Bibliographic reference | **Tleyjeh, IM et al (2007) The impact of valve surgery on 6 month mortality in left-sided infective endocarditis. Circulation. 115:1721-1728.** |
|---|---|
| **Study type** | Cohort (retrospective/prospective) |
| **Aim** | To evaluate the role of valve surgery and all cause 6 month mortality among patients with L-sided IE |
| **Patient characteristics** | Consecutive patients 18yrs+ diagnosed and treated for Left-sided IE (modified Duke Criteria).<br>546 patients were included. (Of these 512 (93.8%) met the definite IE criteria).<br>Exclusion criteria : pt refusal to consent to medical record review or if left hospital before a complete diagnosis/treatment plan. |
| **Number of patients** | 546 |
| **Outcomes** | Surgery<br>All cause 6 month mortality after date of IE diagnosis. |
| **Predictors/risk factors and effect estimates** | **Characteristics by surgery or no surgery after IE.** |

| Characteristic | Total Cohort (N=546) | Non-surgical (n=417) | Surgical (n=129) | p-value |
|---|---|---|---|---|
| Age (y, mean (SD) | 62.3 (16.31) | 64.03 (15.58) | 26.72 (17.4) | <0.0001 |
| Male sex n(%) | 359 (65.75) | 273 (65.47) | 86 (66.67) | 0.80 |
| Previous IE | 59 (10.81) | 43(10.31) | 16(12.40) | 0.50 |
| Prosthetic valve ≤2 months after IE | 23(4.21) | 18(4.32) | 5(3.88) | 0.07 |
| Prosthetic valve >2months after IE | 167(30.59) | 117(28.06) | 50(38.76) | - |

| | |
|---|---|
| **Bibliographic reference** | **Tleyjeh, IM et al (2007) The impact of valve surgery on 6 month mortality in left-sided infective endocarditis. Circulation. 115:1721-1728.** |
| | No multivariate regression was carried out for predictors of surgery. |
| **Analysis used** | Surgical and non-surgical patients were compared with 2 sample t-tests (continuous variables) and either Chi-square or Fisher exact tests for nominal variables. Ordinal variables were compared with Wilcoxon rank-sum test.<br>Adjustment for treatment selection and survivor biases with propensity score and time-dependent covariate analyses was carried out.<br>Subgroup analyses was carried out using Cox proportional hazards regression models for mortality after surgery (not reported here). |
| **Length of follow-up** | 1980-1998 |
| **Location** | Minnesota, USA |
| **Source of funding** | Supported by grants from the Infectious Diseases Division Small Grants Program and the ENHANCE Award from the Department of Medicine, Mayo Clinic. |
| **Comments** | **Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))**<br>Study Participation – N authors cite referral bias as a potential limitation (to limit the applicability of findings).<br>Study attrition – Y<br>Prognostic factor measurement – Y<br>Outcome measurement – Y<br>Confounding measurement and account – U authors cite potential for unmeasured confounders despite the statistical adjustments applied.<br>Analysis – N No Calculation of odds ratios or multivariate analysis. Reviewer back calculated ORs. No sample size calculation.<br>3/6 met = HIGH RISK OF BIAS |

1 **Table 58**

| | |
|---|---|
| **Bibliographic reference** | **[CG64]**<br>**Wang A, Athan E, Pappas PA et al. (2007) Contemporary clinical profile and outcome of prosthetic valve endocarditis 2926. JAMA: Journal of the American Medical Association 297: 1354-61** |
| **Study type** | Observational cohort |
| **Aim** | To describe the clinical characteristics and outcome of prosthetic valve endocarditis (PVE) and to determine prognostic factors associated with in-hospital mortality. |

| Bibliographic reference | **[CG64]**<br>**Wang A, Athan E, Pappas PA et al. (2007) Contemporary clinical profile and outcome of prosthetic valve endocarditis 2926. JAMA: Journal of the American Medical Association 297: 1354-61** |
|---|---|
| **Patient characteristics** | Inclusion: patients with definite IE PVE defined by Duke criteria enrolled in the International Collaboration on Endocarditis-Prospective Cohort Study (61 medical centres in 28 countries)<br>Data from the International Collaboration on endocarditis (ICE) were used for this study.<br>n = 2670 with definite IE, n = 556 (20.1%) with PVE.<br><br>Compared with NVE (n = 1895) those with PVE were significantly older; 65.0 (49.9 to 74.3) vs. 56.3 (41.1 to 69.9), p<0.001, less likely to use injection drugs; 10 (1.8) vs. 235 (12.4%), p<0.001, and more likely to have health care associated infection; 203 (36.5%) vs. 587 (31.0%), p=0.01 and previous IE; 112 (20.1%) vs. 91 (4.8%), p<0.001 |
| **Number of patients** | n = 556 |
| **Predictors** | Prior infective endocarditis and PVIE |
| **Outcomes** | In-hospital mortality |
| **Analysis used** | Univariate comparisons of clinical characteristics were made with the Wilcoxon rank-sum test or the $X^2$ test as appropriate. Multivariate analysis was carried out (adjusting for 15 variables). |
| **Length of follow-up** | Study from June 2000 to August 2005 |
| **Location** | Duke University – co-ordination. Participating sites USA (10), S.America (7), Northern/Central Europe (14), Southern Europe/Middle East/S.Africa (11 sites) and Australia/New Zealand/Asia (11). |
| **Effect estimates** | 203 patients had a history of prior infective endocarditis.<br>Of these, 112 had a subsequent diagnosis of PVIE vs. 91 who had a diagnosis of native valve IE.<br>Of these 112 PVE patients, 21 patients died in hospital (18.8%) giving an unadjusted OR of **0.74 (0.49-1.12).**<br><br>There was no significant difference in mortality after PV IE vs NVE in those with prior history of IE. |
| **Source of funding** | American Heart Association Grant-in-Aid |
| **Comments** | **Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))**<br>Study Participation – Y<br>Study attrition – Y no patients appeared to be lost to follow-up.<br>Prognostic factor measurement - Y<br>Outcome measurement – Y<br>Confounding measurement and account – U Authors cite that mortality rates were high in the study.<br>Analysis – N odds ratio provided was unadjusted. |

| | |
|---|---|
| **Bibliographic reference** | **[CG64]**<br>**Wang A, Athan E, Pappas PA et al. (2007) Contemporary clinical profile and outcome of prosthetic valve endocarditis 2926. JAMA: Journal of the American Medical Association 297: 1354-61** |
| | 4/6 met = LOW RISK OF BIAS |

1 **Table 59**

| | |
|---|---|
| **Bibliographic reference** | **Wong, CW. Et al (2009). Outcome and prognostic factors on 57 cases of infective endocarditis in a single centre. Journal of the New Zealand Medical Association. 122:1304:54-62.** |
| **Study type** | Retrospective review |
| **Aim** | Evaluate the clinical characteristics and outcome of infective endocarditis and the prognostic significance of recurrent endocarditis. |
| **Patient characteristics** | 57 episodes of IE in 47 patients.<br>41 (70%) were definite IE (modified Duke Criteria 2000) and 16 were possible.<br>41 cases of native valve IE and 15 cases of bioprosthetic/mechanical valve IE and 1 permanent pacemaker lead endocarditis.<br><br>Demographic characteristics of patients were provided as numbers/percentages.<br>Mean age 66 (range 16-93), male 36 (77%). |
| **Number of patients** | 47 (57 episodes IE) |
| **Outcomes** | Recurrence of IE |
| **Predictors/risk factors and effect estimates** | Time to recurrence was from 3 weeks to 41 months (mean 8.9 months)<br>4 patients had a remote history of IE outside the study period.<br>17% of patients with underlying heart conditions had a recurrence.<br><br>**Risk factors of recurrent endocarditis** |

| **Parameters** | **Total** **N=**47 | **Recurrence** N=8 | **No recurrence** N=39 | **P-value** |
|---|---|---|---|---|
| Underlying heart conditions | | | | |
| Prosthetic valve | 13 | 1 | 12 | 0.41 |
| Rheumatic heart disease | 9 | 1 | 8 | 1.0 |
| Mitral valve prolapse | 8 | 1 | 7 | 1.0 |

| | |
|---|---|
| **Bibliographic reference** | **Wong, CW. Et al (2009). Outcome and prognostic factors on 57 cases of infective endocarditis in a single centre. Journal of the New Zealand Medical Association. 122:1304:54-62.** |
| | Aortic stenosis \| 4 \| 2 \| 2 \| 0.12 |
| **Analysis used** | Unpaired t-test on continuous data.<br>Categorical risk factors were assessed using Fisher's exact test. |
| **Length of follow-up** | June 2002-June2007. |
| **Location** | Tauranga, New Zealand (Single centre) |
| **Source of funding** | Not mentioned |
| **Comments** | **Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))**<br>Study Participation – N Retrospective from single centre.<br>Study attrition – Y<br>Prognostic factor measurement - Y<br>Outcome measurement – P Results were not separated between definite and possible diagnoses.<br>Confounding measurement and account – Y<br>Analysis – N No odds ratios for univariate analysis for risk factors of interest. No multivariate analysis was carried out. Reviewer back calculated odds ratios. No Sample size calculation.<br>3/6 met = LOW RISK OF BIAS |

1 **Table 60**

| | |
|---|---|
| **Bibliographic reference** | **Yoshinaga, M et al. (2008) Risk factors for in-hospital mortality during infective endocarditis in patients with congenital heart disease. American Journal of Cardiology. 101:114-118.** |
| **Study type** | Retrospective observational cohort study. |
| **Aim** | To determine the risk factors for mortality in paediatric and adults with congenital heart disease (CHD). |
| **Patient characteristics** | Of 239 data sets of patients with CHD reviewed, 216 data sets of patients were complete.<br>Of these 137 patients with IE (modified Duke's criteria) were included.<br>Adults and Children - Age 1 month – 62 years (median 12 years). |
| **Number of patients** | 137 |
| **Outcomes** | In hospital mortality was 10% (14/137 patients). |
| **Predictors/risk factors and effect estimates** | **Number of deceased patients with or without each risk factor, odds ratio and p-values by univariate regression analysis** |

| Risk Factor | Present | Absent | Odds ratio (95% CI) | p-value |
|---|---|---|---|---|

| Bibliographic reference | **Yoshinaga, M et al. (2008) Risk factors for in-hospital mortality during infective endocarditis in patients with congenital heart disease. American Journal of Cardiology. 101:114-118.** |
|---|---|

| | | | | |
|---|---|---|---|---|
| Male | 8/75(11) | 6/62(10) | 1.11(0.365-3.40) | 0.85 |
| Age <18 | 11/98 (11) | 3/39 (8) | 1.52 (0.400-5.76) | 0.54 |
| Age<1 year | 5/9 | 9/128(7) | 16.5(3.77-72.5) | <0.001 |
| Cyanotic CHD | 9/40(23) | 5/97(5) | 5.34(1.66-17.2) | **0.005** |
| Previous surgery for CHD | 11/65(17) | 3/72(4) | 4.69(1.25-17.6) | **0.02** |
| Previous IE | 3/12(25) | 11/125(9) | 3.46(0.814-14.7) | 0.09 |
| Prosthetic heart valve | 0/4 | 14/133(11) | 0 | 0.99 |

Data expressed as number of deceased patients/total number of the group of the presence or absence of the risk factor and the (ratio of deceased patients).

After stepwise logistic regression analysis, previous cardiac conditions were not significantly associated with in hospital death. (Actual values not reported).

Age <1 year was an independent risk factor for in hospital mortality. Estimate 2.972, Estimate/SE 2.408, p-value 0.02, OR 19.5 (1.74-219)

| | |
|---|---|
| **Analysis used** | Fisher's exact probability test was used for prevalence in children and adults.<br>Univariate logistic regression was used to evaluate the association between each risk factor and in hospital death.<br>Stepwise logistic regression analysis was further performed to account for confounders and included variables that were significant (p<0.1) after univariate analysis. |
| **Length of follow-up** | January 1997 – December 2001 |
| **Location** | Japan |
| **Source of funding** | Not specified. |
| **Comments** | **Potential bias (Hayden) (6 Criteria met? Y/N/Unclear (U))**<br>Study Participation – N Retrospective design. Adults and children. Included those with complete data sets only.<br>Study attrition – Y<br>Prognostic factor measurement – Y<br>Outcome measurement – U Authors cite that mortality was low (10%) which might be affected by the study population/geographical region.<br>Confounding measurement and account – P authors cite potential for unmeasured confounders despite the |

| Bibliographic reference | Yoshinaga, M et al. (2008) Risk factors for in-hospital mortality during infective endocarditis in patients with congenital heart disease. American Journal of Cardiology. 101:114-118. |
|---|---|
| | statistical adjustments applied.<br>Analysis – N adjusted ORs were not reported. No Sample size calculation.<br>2/6 met = HIGH RISK OF BIAS |

1

# G.3 Review question 3

## Dental procedures

**Table 61**

| | |
|---|---|
| **Bibliographic reference** | **Mohee (2014): A case-control study: are urological procedures risk factors for the development of infective endocarditis?**<br>**ID:** |
| **Study type** | Case-control study |
| **Aim** | To evaluate the association between urological procedures and the development of infective endocarditis (IE). |
| **Patient characteristics** | • *Inclusion criteria:*<br>Adult patients treated for IE between 1 January 2001 and 31 December 2010, at the Leeds Teaching Hospitals NHS Trust, using the Leeds endocarditis audit database.<br>• IE was diagnosed according to the Duke criteria.<br>Identified cases were split into 4 groups based on organisms:<br>• (group 1) enterococci IE<br>• (group 2) CoNS IE<br>• (group 3) Streptococcus bovis-group IE<br>• (group 4) oral streptococci IE<br><br>*CoNS = coagulase-negative staphylococcal* |
| **Number of patients** | Total = 384<br><br>*Enterococci IE group*<br>N = 111; Age >60 years = 79/111 (71.1%), male = 80/111 (72.1%)<br>Lower GI procedures = 5/111 (4.5%); upper GI procedures = 5/111 (4.5%); urological procedures = 24/111 (21.6%)<br><br>*CoNS IE group*<br>N = 86; Age >60 years = 56/86 (65.1%), male = 56/86 (65.1%)<br>Lower GI procedures = 3/86 (3.5%); upper GI procedures = 6/86 (7.0%); urological procedures = 4/86 (4.7%)<br><br>*Streptococcus bovis-group IE group*<br>N = 36; Age >60 years = 29/36 (80.6%), male = 21/36 (58.3%)<br>Lower GI procedures = 1/36 (2.8%); upper GI procedures = 2/36 (5.6%); urological procedures = 2/36 (5.6%)<br><br>*Oral streptococci IE group*<br>N = 151; Age >60 years = 59/151 (39.1%), male = 122/151 (81.3%)<br>Lower GI procedures = 5/151 (3.3%); upper GI procedures = 4/151 (2.6%); urological procedures = 4/151 (2.6%) |

| Bibliographic reference | **Mohee (2014): A case-control study: are urological procedures risk factors for the development of infective endocarditis?**<br>**ID:** |
|---|---|
| | |
| **Procedures** | Upper and lower GI procedures, urological procedures (including transurethral endoscopic procedure, cystoscopy, endoscopic resection of the prostate and bladder tumour and ureterorenoscopy) |
| **Outcomes and effect estimates** | *Univariate ananlysis in patients with IE:*<br>Enterococcal IE group (n=111)<br>Upper GI procedures: OR = 0.95 (95%CI: 0.33 to 2.72)<br>Lower GI procedures: OR = 1.25 (95%CI: 0.41 to 3.73)<br>Urological procedures: OR = 7.28 (95%CI: 3.35 to 15.8)<br><br>CoNS IE group (n=86)<br>Upper GI procedures: OR = 1.19 (95%CI: 0.65 to 4.93)<br>Lower GI procedures: OR = 0.86 (95%CI: 0.24 to 3.14)<br>Urological procedures: OR = 0.44 (95%CI: 0.15 to 1.28)<br><br>Streptococcus bovis group (n=36)<br>Upper GI procedures: OR = 1.22 (95%CI: 0.27 to 5.55)<br>Lower GI procedures: OR = 0.68 (95%CI: 0.09 to 5.36)<br>Urological procedures: OR = 0.58 (95%CI: 0.13 to 2.54)<br><br>Oral streptococcal IE group (n=151)<br>Upper GI procedures: OR = 0.43 (95%CI: 0.14 to 1.33)<br>Lower GI procedures: OR = 0.77 (95%CI: 0.26 to 2.29)<br>Urological procedures: OR = 0.19 (95%CI: 0.06 to 0.54)<br><br>*Multivariate analysis in patients with enterococcal IE:*<br>Urological procedures: adj OR = 8.56 (95%CI: 3.69 to 19.85) |
| **Analysis used** | Details of urological, upper and lower GI procedures were collected, including any procedures undertaken ≤1 year before the development of IE.<br><br>Univariate and multivariate analysis were performed. A logistic regression model was used for the multivariable analysis. Missing data patterns were identified and a multiple imputation method was used to complete the data set. |
| **Length of follow-up** | Not reported. |
| **Location** | Between 1 January 2001 and 31 December 2010, Leeds, UK. |
| **Source of funding** | Supported by the Leeds Charitable Trust. |
| **Comments** | |

1 **Table 62**

| | |
|---|---|
| **Bibliographic reference** | **Chen (2013): Dental Scaling and Risk Reduction in Infective Endocarditis: A Nationwide Population-Based Case-Control Study.**<br>**ID:** |
| **Study type** | Case-control study |
| **Aim** | To investigate whether the improvement of oral hygiene through dental scaling could reduce the risk of IE. |
| **Patient characteristics** | *Inclusion criteria:*<br>• Patients who were age 18 or older with newly diagnosed IE, from the National Health Insurance (NHI) Research Database (NHIRD), from January 1, 2000 to December 31, 2009.<br>• On the same index date, 10 patients (without IE) with matched age, sex, and significant underlying diseases, were selected to be the control group for each study patient. |
| **Number of patients** | Total = 8096<br>Cases = 736<br>Mean age = 55.40 years old (SD: 21.10); male = 60.2%; female = 39.8%.<br>Control = 7360<br>Mean age = 55.41 years old (SD: 21.08); male = 60.2%; female = 39.8%. |
| **Procedures** | Dental scaling |
| **Outcomes and effect estimates** | *Adjusted odds ratio of IE in patients receiving dental scaling:*<br>0 time in 2 years: adj OR = 1 (95%CI: n/a)<br>1 time in 2 years: adj OR = 0.845 (95%CI: 0.693 to 1.012)<br>At least 1 time per year: adj OR = 0.696 (95%CI: 0.542 to 0.894) |
| **Analysis used** | The frequencies of dental scaling and other dental procedures, including tooth extractions, root therapy, endodontic treatment, mouth or gingival surgery, and treatment of tooth abscess, within 2 years before the index date were analyzed and compared between the study and the control groups. Also further divided patients into 3 groups based on the frequency of dental scaling and compared the risk of IE between groups.<br>The risk of patients in developing IE was expressed as the odds ratio which was analyzed using logistic regression analysis. |
| **Length of follow-up** | Not reported. |
| **Location** | From January 1, 2000 to December 31, 2009, Taiwan. |
| **Source of funding** | Grants from the National Science Council (NSC98-2410-H-010-003-MY2), and Taipei Veterans General Hospital (V99C1-140, V99A-153, and V100D-002-3). |
| **Comments** | |

2 **Table 63**

| | |
|---|---|
| **Bibliographic reference** | **Ammar (2013); ID:**<br>**Case – Control study of potential culprit procedures for infective endocarditis in an Egyptian tertiary care centre.** |
| **Study type** | Case control study |
| **Aim** | To test the hypothesis that underlying medical conditions, not culprit procedures, are the most important risk factor for development of IE. |

| Bibliographic reference | **Ammar (2013); ID:**<br>**Case – Control study of potential culprit procedures for infective endocarditis in an Egyptian tertiary care centre.** |
|---|---|
| **Patient characteristics** | *Inclusion criteria:*<br>• 175 patients with definite IE according to modified Duke Criteria for diagnosis of IE from the IE database of the Cardiology Department at Cairo University Hospital and 175 control cases without IE collected from the Cairo University Hospital and the National Heart Institute, Outpatient Clinic, and Family Medicine Clinic.<br>• Control cases were matched to IE cases by age (±x years), sex, and medical comorbidities including underlying heart disease and prosthetic valves.<br>• A consented questionnaire was used to collect the clinical data from the control.<br>• The following history and clinical data were collected from both IE cases and controls including:<br>○ Age, sex, history of hospitalization (for at least 24 h) within the last 3 months for indication unrelated to a possible or definite diagnosis of IE, underlying valvular heart disease, congenital heart disease, prosthetic valves or intracardiac devices.<br>○ Co-morbid conditions: such as diabetes mellitus, renal impairment defined as GFR<60 ml/min/1.73 m2,11 renal dialysis, prior IE, hepatic disease, drug abuse and malignancy.<br>○ Potential culprit procedures including: upper respiratory tract procedures, upper and lower GI endoscopy, barium enema, gynecological surgery, urinary catheterization, cardiac catheterization, device implantation, peripheral and central intravenous lines and dental procedures (tooth extraction and any procedure involving manipulation of the gingiva).<br>○ The causative organism (if identified), in patients with confirmed IE. |
| **Number of patients** | Cases = 175<br>Gender: 102 males; 73 females; Mean age: 32.13 years old (SD: 13.76); known structural heart disease = 117/175<br><br>Control = 175<br>Gender: 103 males; 72 females; Mean age: 32.90 years old (SD: 12.12); known structural heart disease = 111/175 |
| **Procedures** | Dental procedures, gynaecological procedures, urinary catheterization |
| **Outcomes and effect estimates** | *Procedure-related risk factors:*<br>Dental procedures:<br>Cases = 6 (3.4%); control = 8 (4.6%), P>0.05<br><br>Gynaecological procedures:<br>Cases = 1 (0.6%); control = 4 (2.3%), P>0.05<br><br>Urinary catheterization:<br>Cases = 2 (1.1%); control = 6 (3.4%), P>0.05 |
| **Analysis used** | Unpaired student's t test for normally distributed, continuous variables and Pearson's chi-square test for categorical variables. Correlations between normally distributed variables were done using Pearson's correlation coefficient. A probability value (p value) less than 0.05 was considered significant. There was no correction for multiple testing. |
| **Length of follow-up** | Not reported |

| | |
|---|---|
| **Bibliographic reference** | **Ammar (2013); ID:**<br>**Case – Control study of potential culprit procedures for infective endocarditis in an Egyptian tertiary care centre.** |
| **Location** | From March 2005 till June 2008, Cairo, Egypt. |
| **Source of funding** | Not reported |
| **Comments** | |

1 **Table 64**

| | |
|---|---|
| **Bibliographic reference [from CG64]** | **Duval X, Alla F, Hoen B, et al. (2006) Estimated risk of endocarditis in adults with predisposing cardiac conditions undergoing dental procedures with or without antibiotic prophylaxis. Clinical Infectious Diseases. 42: e102–07. Ref ID: 10629** |
| **Study type** | Epidemiological study (cross sectional study) |
| **Aim** | To estimate the risk of endocarditis in adults with predisposing cardiac conditions (PPC) undergoing dental procedures with or without antibiotic prophylaxis. |
| **Patient characteristics** | Included: 25-84 yrs from the French population |
| **Number of patients** | n = 2805 interviewed adults,<br><br>n = 104 native valve PCC<br><br>n = 24 prosthetic valve PCC |
| **Procedures** | Dental procedures |
| **Outcomes and effect estimates** | Effect size:<br><br>**Prevalence of PCC and number of at-risk dental procedures**<br>n = 104 native valve PCC, n = 15 of which had undergone an at-risk dental procedure, unprotected in n = 12<br>n = 24 prosthetic valve PCC, n = 4 of which had undergone an at-risk dental procedure, unprotected in n = 2<br>Applying these to the adult French population, in 1999, resulted in the following estimates: n = 1,287,296 (CI; 999,196 to 1,575,396) had a known PCC, corresponding to 3.3% (CI; 2.6 to 4%) of the 39 million adults<br><br>In 1999, a total of 2,746,384 at-risk dental procedures (CI; 2,304,094 to 3,188,384) were performed in these adults, a rate of 2.1 procedures per subject per year<br>n = 1,704,195 (62%) of these procedures were performed without antibiotic prophylaxis<br><br>**Annual number of IE cases after at-risk dental procedures in adults with known PCC**<br>n = 12/182 cases of IE that occurred in adults with PCC in the 1999 survey occurred after an at-risk dental procedure and were due to an oral micro-organism (n = 10 unprotected)<br>With the estimated 1370 cases of IE, 714 would have occurred in adults with PCC, 44 attributable to dental procedures (37 without and 7 with antibiotic prophylaxis)<br><br>**Risk of IE after at-risk dental procedures in adults with known PCC** |

| Bibliographic reference [from CG64] | **Duval X, Alla F, Hoen B, et al. (2006) Estimated risk of endocarditis in adults with predisposing cardiac conditions undergoing dental procedures with or without antibiotic prophylaxis. Clinical Infectious Diseases. 42: e102–07. Ref ID: 10629** |
|---|---|
| | The estimated risk of IE was:<br>1 case per 46,000 (CI; 36,236 to 63,103) unprotected at-risk dental procedures<br>1 case per 54,300 (CI; 41,717 to 77,725) unprotected at-risk dental procedures in adults with native valve PCC<br>1 case per 10,700 (CI; 6,000 to 25,149) unprotected at-risk dental procedures in adults with prosthetic valve PCC<br>1 case per 149,000 (88,988 to 347,509) protected dental procedures, a 70% reduction in the risk compared with unprotected procedures<br><br>**Assessment of IE prophylaxis strategies intact**<br>Using the annual number of procedures and the risk estimates if antibiotics have been administrated in 100% of at-risk dental procedures [a] , n = 41 cases (CI; 29 to 53) of IE would have been prevented in those with native valve PCC and 39 cases (CI; 11 to 72) in those with prosthetic valve PCC in France in 1999<br><br>**Estimated incidence of IE**<br>Annual incidence 35 cases per million (CI; 32 to 39) in the entire 25-84yr French population<br>555 cases per million (CI; 520 to 588) in those with known PCC<br>980 cases per million (CI; 875 to 1090) in those with known prosthetic valve PCC<br>460 cases per million (CI; 415 to 500) in those with known native valve PCC<br>18 cases per million (CI; 16 to 21) in those without known PCC<br><br>An estimate of the number of IE cases that would have been prevented during 1-yr if antibiotic prophylaxis had been administered in 100% of cases of at-risk dental procedures.<br><br>(*Author's conclusion: antibiotic prophylaxis reduces the risk of IE after a dental procedure. However, because of the very limited risk of "spontaneous" IE after unprotected dental procedures in adults with known PCCs, a huge number of doses of prophylaxis must be prescribed to prevent a very low number of IE cases)* |
| **Analysis used** | Monte-Carlo simulation. |
| **Length of follow-up** | 1-year study 1999 |
| **Location** | France |
| **Source of funding** | Programme hospitalier de recherché clinique, the federation francaise de cardiologie, Aventis and SmithKilne Beecham Labs |
| **Comments** | To assess the risk of developing IE after an at-risk dental procedure using estimations of: the estimated annual number of IE cases that occur after at-risk dental procedures in adults with known predisposing cardiac conditions (PCC) [b] (numerator) [c] and the annual number of at-risk dental procedures performed in adults with known PCCs (denominator) [d] |

*(a) 2.7 administered antibiotic courses, corresponding to 2,228,545 for those with native valve PCC and 512,829 for those with prosthetic valve PCC*
*(b) PCC were defined according to the French recommendations for IE prophylaxis*
*(c) Data used was taken from a 1-yr French epidemiological study on IE in*
*(d) 1999Sample drawn from 2 studies ongoing in 1998, a structured and previously validated questionnaire was administered by phone interview to classify subjects as having a PCC or not*

1 **Table 65**

| | |
|---|---|
| **Bibliographic reference [from CG64]** | **Lacassin F, Hoen B, Leport C, Selton-Suty C, Delahaye F, Goulet V et al. Procedures associated with infective endocarditis in adults. A case control study.[see comment] 1013. European heart journal 1995;16:1968-74. Ref ID: 1013** |
| **Study type** | Case-control study |
| **Aim** | To investigate procedures associated with infective endocarditis in adults |
| **Patient characteristics** | Inclusion: cases: definite and probable IE defined according to revised Von Reyn's criteria with modifications; possible IE defined according to non revised Von Reyn's criteria<br><br>Exclusion: cases: patients younger than 15yrs, valve replacement within the previous year, prematurely dead, intravenous drug users, those with Coxiella burnetti IE (unlikely to be related to any procedure)<br><br>Cases: those without IE who satisfied the same exclusion criteria as the cases. Cases were recruited randomly from cardiology or medicinal wards either during a consultation for echocardiography or during hospitalisation in the same period of observations as cases.<br><br>Cases and controls were distributed into 3 groups of underlying cardiac conditions: native valve disease, prosthetic valve or no known cardiac disease<br><br>Each case was matched to one control as regards sex, age (±5yrs) and group of underlying cardiac conditions. The proportion of those with diabetes mellitus, or who consumed alcohol and tobacco did not differ between the 2 groups. Cases had significantly more often an infectious episode or a skin wound than controls (39% and 19% vs. 15% and 5% respectively) |
| **Number of patients** | Total = 171 pairs<br><br>n = 171 cases were interviewed as soon as possible after the diagnosis of IE<br><br>Following a pre-established list, they were requested to indicate all the procedures involving cutaneous and mucosal surfaces they had undergone within the 3mths prior to diagnosis<br><br>In case of medical consultation or procedure, the information was checked by the cited practitioner [b]<br><br>n = 171 controls were interviewed under the same conditions as cases using the same questionnaire form<br><br>Following a pre-established list, they were requested to indicate all the procedures involving cutaneous and mucosal surfaces they had undergone within the 3mths prior to diagnosis<br><br>In case of medical consultation or procedure, the information was checked by the cited practitioner |
| **Procedures** | Dental, urological, gastrointestinal procedures |

| Bibliographic reference [from CG64] | **Lacassin F, Hoen B, Leport C, Selton-Suty C, Delahaye F, Goulet V et al. Procedures associated with infective endocarditis in adults. A case control study.[see comment]<br>1013. European heart journal 1995;16:1968-74.<br>Ref ID: 1013** |
|---|---|
| **Outcomes and eefect estimates** | The relative risk of IE for each procedure, causative organisms, antibiotic prophylaxis<br>**Procedures**<br>*Univariate adjusted for other procedures:*<br>Any dental procedures: cases = 37 (22%); control = 33 (19%); OR = 1.2 (95%CI: 0.7 to 2.1)<br>Any urological procedures: cases = 6 (3.5%); control = 2 (11%); OR = 3.1 (95%CI: 0.6 to 15.7)<br>Any GI procedures: cases = 14 (8.2%); control = 8 (4.7%); OR = 1.2 (95%CI: 0.7 to 4.1)<br><br>n = 88 (51.5%) of cases and n = 70 (41%) of controls had undergone at least one procedure, the adjusted OR for the risk of IE related to a procedure 1.6 (1.01 to 2.53, 95%CI), p<0.05<br>Taking the frequency of the procedures in the control group (40%) as an estimation of the frequency in the general population, the risk of IE attributable ≥1 procedure (attributable risk) was 20%<br>Any dental procedure – no increased risk (cases n = 37 (22%), controls n = 33 (19%));<br>Dental extraction no higher risk of IE; scaling and root canal work showed a trend towards a higher risk (NS)<br><br>Any urological procedure – no increased risk (cases n = 6 (3.5%), controls n = 2 (1%))<br>Any GI procedure – no increased risk (cases n = 14(8.2%), controls n = 8 (4.7%))<br>Any surgical procedure – cases n = 11 [a] (6%), controls n = 2 (1%); adjusted OR for the risk of IE 4.7 (1.02 to 2.53, 95%CI)<br><br>All procedures, the mean number of procedures was significantly higher in cases than in controls (2.0 vs. 4.5, p<0.05)<br>The risk of IE increased with the number of procedures per case, RR for one procedure 1.2; 1.7 for two procedures; 3.6 for three or more procedures (p=0.005)<br>No control had had >1 dental procedure in the previous 3mths, n = 3 cases had undergone 2 procedures<br><br>**Multivariate analysis:**<br>Urological procedure: adj OR = 6.1 (95%CI: 0.9 to 39.7)<br>Scaling: adj OR = 2.7 (95%CI: 0.8 to 9.0)<br>Canal treatment: adj OR = 1.7 (95%CI: 0.5 to 5.2)<br><br>**Causative organism**<br>The only procedure associated with a risk for IE due to viridans streptococci was scaling (n = 9/50 in the cases; n = 2/50 in the controls, OR=5.25, p=0.025)<br>The only procedure associated with the subsequent occurrence of IE was surgery for staphylococcal IE (n = 4/27 in the cases; n = 0/27 in the controls, p=0.03)<br>In multivariate analysis, scaling was associated with a significant risk for IE due to viridans streptococci, independently of an infectious episode. Conversely, only infectious episodes contributed to the risk of staphylococcal infective endocarditis, the risk after skin wound and surgery being non-significant in this analysis |

| | |
|---|---|
| **Bibliographic reference [from CG64]** | **Lacassin F, Hoen B, Leport C, Selton-Suty C, Delahaye F, Goulet V et al. Procedures associated with infective endocarditis in adults. A case control study.[see comment]<br>1013. European heart journal 1995;16:1968-74.<br>Ref ID: 1013** |
| | **Antibiotic prophylaxis**<br>n = 8 cases of IE occurred in those who had received an appropriate antibiotic prophylaxis, (n = 4 PVE, n = 4 NVE). Procedures included multiple extractions within a single session (n = 3), scaling (n = 3), ENT procedure (n = 1) and urethrocystoscopy (n = 1)<br><br>n = 6 controls had received appropriate antibiotic prophylaxis (n = 2 PV disease, n = 4 NV disease) |
| **Analysis used** | Univariate and multivariate analyses. |
| **Length of follow-up** | 1st November 1990 to 31st October 1991, Public and private medical facilities in 3 regions in France |
| **Location** | France |
| **Source of funding** | Several grants from medical societies in France and from the following companies: Baxter, Dideco-Shiley, Eli-Lily, Medtronic, St Jude Medical Companies |
| **Comments** | |

*(a) Abdominal surgery N=3, soft tissue surgery N=6, gynaecological surgery N=2. Two of the 7 clean surgical procedures were done with antibiotic prophylaxis and five without antibiotic prophylaxis*

*(b) To adjust for factors which could potentially influence the risk of IE associated with procedures, the questionnaire requested items concerning general co-morbid conditions such as alcohol and tobacco consumption, and diabetes mellitus*

**Table 66**

| | |
|---|---|
| **Bibliographic reference [from CG64]** | **Strom BL, Abrutyn E, Berlin JA, Kinman JL, Feldman RS, Stolley PD et al. Risk factors for infective endocarditis: oral hygiene and nondental exposures. Circulation 2000;102:2842-8.<br>Ref ID: 31** |
| **Study type** | Case-control study |
| **Aim** | To investigate risk factors for infective endocarditis |
| **Patient characteristics** | Information was abstracted from medical records and obtained from structural telephone interviews with controls and endocarditis cases (medical records were requested to validate individual diagnosis and procedures, agreement between interviews and medical records exceeded 90%<br><br>Cases were more likely than controls to suffer from self-reported severe kidney disease, they were also more likely to report physician diagnosed diabetes. Cases did not differ from controls in history of living with pets, animal bites, smoking, menopausal status, history of rheumatoid arthritis, other autoimmune disease, thyroid disease, alcoholism, cancer, stroke, ischaemic heart disease, cardiomyopathy, arrhythmia, heart operation other than valve replacement, cardiac disease other than prior history of endocarditis, valvular heart disease, congenital heart disease, rheumatic fever, heart murmur<br><br>Cases and controls were similar with respect to age and sex, race, education, occupation, and dental insurance<br><br>Controls and case-patients were matched for age, sex, race, education, occupation and dental insurance |

| | |
|---|---|
| **Bibliographic reference [from CG64]** | **Strom BL, Abrutyn E, Berlin JA, Kinman JL, Feldman RS, Stolley PD et al. Risk factors for infective endocarditis: oral hygiene and nondental exposures. Circulation 2000;102:2842-8.**<br>**Ref ID: 31** |
| | Cases were more likely to have self-reported prior kidney disease, to report physician diagnosed diabetes |
| **Number of patients** | n = 416 enrolled potential case-patients<br><br>n = 287 community acquired IE not associated with IV drug use<br><br>n = 273 interviewed case-patients |
| **Procedures** | Pulmonary, Barium enema, lower and upper GI endoscopy, urinary catheterization, other genitourinary procedures. |
| **Outcomes and effect estimates** | **Medical procedures and therapies**<br>Multivariable adjusted OR (in previous 3 months):<br>Pulmonary procedures (inc. lung biopsy & bronchoscopy): cases = 3 (1.1%); control = 3 (1.1%); adj OR = 0.27 (95%CI: 0.01 to 5.46)<br>Barium enema: cases = 11 (4%); control = 1 (0.4%); adj OR = 11.9 (95%CI: 1.34 to 106)<br>Lower GI endoscopy: cases = 14 (5.1%); control = 8 (2.9%); adj OR = 1.95 (95%CI: 0.58 to 6.53)<br>Upper GI endoscopy: cases = 8 (2.9%); control = 4 (1.5%); adj OR = 1.36 (95%CI: 0.26 to 6.99)<br>Urinary catheterization cases = 12 (4.4%); control = 4 (1.5%); adj OR = 0.58 (95%CI: 0.11 to 3.10)<br>Gynecological surgery: cases =3 (1.1%); control = 0 (0.0%); adj OR = N/A<br>Other genitourinary procedures (inc. cystoscopy, lithotripsy, vasectomy) cases = 4 (1.5%); control = 3 (1.1%); adj OR = 0.61 (95%CI: 0.06 to 5.80)<br><br>Only barium enema remained significant after multivariate adjustment OR 11.9 (CI; 1.34 to 106), p=0.026 (review indicated that in some cases the procedure was performed as part of the workup for the illness finally diagnosed as IE, or for a comorbidity, accordingly this cannot be interpreted as indicating a causal relationship between the procedure and IE)(NS were pulmonary procedures, lower GI endoscopy, upper GI endoscopy, gynaecological surgery, urinary catheterisation, other genitourinary, cardiac procedure, other surgery, intravenous therapy, nasal-oxygen therapy)<br><br>Overall IV fluid administration was not associated with IE, when analysis was restricted to those with infected skin flora and their controls the unadjusted OR increased from 1.8 to 5.0(CI: 1.1 to 23), p=0.04. Adjusted [b] OR was 6.7 (CI; 1.1 to 41), p=0.04<br><br>Tests of interaction between procedures and antibiotic use provided no evidence that anti biotic use modified the risk associated with those procedures<br><br>**Prior infection as a risk factor**<br>An association between endocarditis and skin infection was NS with multivariate analysis [a]<br>The elevated OR for skin infection disappeared after the analysis was restricted to subjects with cardiac valvular abnormalities<br>When restricted to cases who were infected with skin flora and their matched controls the OR for skin infections increased markedly to 6.0 (CI; 1.3 to 27), p=0.019. |

| | |
|---|---|
| **Bibliographic reference [from CG64]** | **Strom BL, Abrutyn E, Berlin JA, Kinman JL, Feldman RS, Stolley PD et al. Risk factors for infective endocarditis: oral hygiene and nondental exposures. Circulation 2000;102:2842-8.**<br>**Ref ID: 31** |
| | UTIs were not associated with IE<br>Initially pneumonia showed an increase among cases, but this occurred in the month before study dates and may be an early manifestation of endocarditis<br><br>**Oral hygiene**<br>No association was found between IE and the frequency of routine dental care within the previous year, tooth brushing, or use of a toothpick, Water Pik or gum stimulator, there was no association between IE and complete denture prosthesis for edentulous mouths<br><br>There was no evidence that of a risk in having teeth vs. being edentulous, when this was repeated considering only cases affected with dental flora (n = 106 and matched controls) there was an increased risk associated with having teeth, adjusted OR 7.02 (CI; 1.25 to 2.14), p=0.03.<br>Edentulousness was associated with decreased risk compare with having teeth and not flossing, OR 0.11 (CI; 0.02 to 0.71), p=0.02 |
| **Analysis used** | Multivariable analysis |
| **Length of follow-up** | From August 1988 – November 1990 surveillance for IE in 54 hospitals |
| **Location** | Philadelphia |
| **Source of funding** | NIH grant |
| **Comments** | |

*(a) The elevated OR for skin infection disappeared after the analysis was restricted to subjects with cardiac valvular abnormalities*
*(b) Adjusted for cardiac valvular abnormality and diabetes*

# G.4 Review question 4

## Dental procedures

### Table 67

| | |
|---|---|
| **Bibliographic reference** | **Tuna (2012), ID: 165**<br>**Do antibacterial mouthrinses affect bacteraemia in third molar surgery? A pilot study.** |
| **Study type** | RCT |
| **Aim** | To evaluate the effects of mouthrinses containing 7.5% povidone iodine and 0.2% chlorhexidine on bacteraemia following impacted third molar surgery. |
| **Patient characteristics** | *Inclusion criteria:*<br>• Aged over 18 years requiring surgical removal of a third molar |

| Bibliographic reference | **Tuna (2012), ID: 165**<br>**Do antibacterial mouthrinses affect bacteraemia in third molar surgery? A pilot study.** |
|---|---|
| | • No systemic disorder nor any signs or symptoms of pericoronitis at the time of surgery nor during the previous month<br>• No known risk factor for bacterial endocarditis<br>• No antibiotic treatment during the previous 30 days<br>• Not using routine oral antiseptic mouthrinse nor suffering any type of congenital or acquired immunodeficiency<br>• Had no other disease or condition which could predispose to infections or bleeding.<br>*Exclusion criteria:*<br>• Patients with an oral hygiene index and gingival bleeding index (GBI) higher than 10%. |
| **Number of patients** | Total number = 34; control group = 10 (group of interest)<br>*[the other 24 patients had povidone iodine or chlorhexidine prophylaxis].*<br>Gender: 5 males; 5 females<br>Mean age: 26.8 years old (SD: 4.8) |
| **Procedures** | Third molar extraction.<br>• Peripheral venous blood samples were collected from each patient at baseline (before the injection of local anaesthesia with articaine and adrenaline), 1 minute and 15 minutes after completion of the extraction. |
| **Outcomes and effect estimates** | Incidence of bacteraemia:<br>Baseline= 5/10 (50%); 1st min = 4/10 (40%); 15th min = 3/10 (30%); McNemar's p = 0.810.<br><br>Types of bacteria:<br>1st min = *3 Streptococcus anginosus; Streptococcus gordonii; Streptococcus oralis; Streptococcus salivarius; Streptococcus mitis*<br>15th min = *Streptococcus salivarius; 2 Streptococcus anginosus; Streptococcus oralis; Staphylococcus epidermis* |
| **Analysis used** | • Every blood sample comprised 20 ml of blood which was divided into two bottles with anaerobic culture medium (10 ml) and aerobic culture medium (10 ml). Altogether, 60 ml of blood was obtained from each patient by a researcher who was blind to details of the study.<br>• After each sample was drawn, the angiocath needle and the line were flushed with 3 ml of saline. This procedure was repeated three times (baseline, 1 minute and 15 minutes postoperatively). All the blood culture bottles were processed in the BACTEC 9120 system (Becton Dickinson, NJ, USA) in the microbiology laboratory. |
| **Length of follow-up** | 7 days incubation of the blood samples. |
| **Location** | Yeditepe University, Faculty of Dentistry, Istanbul, Turkey. |
| **Source of funding** | Not reported. |
| **Comments** | |

1 **Table 68**

| | |
|---|---|
| **Bibliographic reference** | **DuVall (2013), ID: 80**<br>**The comparative efficacy of 0.12% chlorhexidine and amoxicillin to reduce the incidence and magnitude of bacteraemia during third molar extractions. Oral surgery, oral medicine and oral pathology.** |
| **Study type** | RCT |
| **Aim** | To compare the incidence and magnitude of bacteraemia of a 0.12% chlorhexidine pre-procedure rinse to the AHA and the ADA/AAOS recommended 2g amoxicillin antibiotic prophylaxis during third molar extractions. |
| **Patient characteristics** | *Inclusion criteria:*<br>• ASA I or II: healthy, no systemic disease<br>• Diagnosed/planned extraction #1, 16, 17, 32 under conscious sedation<br>• #17 and 32 required a mucogingival flap for extraction<br>• 18 years of age or older<br>• Previously received penicillin and/or amoxicillin without a hypersensitivity or allergic reaction<br>*Exclusion criteria:*<br>• ASA III or IV: poorly controlled systemic disease<br>• Known penicillin, amoxicillin or cephalosporin drug allergy<br>• Pregnant women<br>• Current immunosuppressed status<br>• Active viral disease<br>• Cardiac anomalies or another condition/situation requiring pre- or intra-operative use of antibiotics<br>• Antibiotic use within the previous two months<br>• Steroid therapy within the previous two months<br>• Chlorhexidine use or other oral antimicrobial rinses within the previous 2 months<br>• The routine use of an oral antiseptic at home<br>• Gingival tissue manipulation within 2 hours of the procedure<br>• 7 of the original 37 eligible subjects were excluded due to technical reasons (complications during blood draws and/or unavailable microbiological lab support). |
| **Number of patients** | Total number = 30; control group = 10 (group of interest)<br>*[the other 20 patients had amoxicilin or chlorhexidine prophylaxis].*<br>Gender (total): 23 males; 7 females<br>Mean age (total): 21.8 years old (range: 18 to 29)<br>*[no subgroups data]* |
| **Procedures** | Third molar extraction |

| Bibliographic reference | **DuVall (2013), ID: 80**<br>**The comparative efficacy of 0.12% chlorhexidine and amoxicillin to reduce the incidence and magnitude of bacteraemia during third molar extractions. Oral surgery, oral medicine and oral pathology.** |
|---|---|
| | 4 blood samples (BS) were obtained through IV access line for each patient in the following manner:<br>• Baseline (before placebo tablet)<br>• 1.5 min following initiation of the mucogingival flap #32<br>• 1.5 min following initiation of the mucogingival flap #17<br>• 10 min following initiation of the mucogingival flap #17 |
| **Outcomes and effect estimates** | *Incidence of bacteraemia (defined as at least one positive culture of the 4 BS per patient):*<br>6/10 (60%)<br><br>*Magnitude of bacteraemia (mean CFU/ml per BS with SD):*<br>BS1 = 0.00 (SD:0.00); BS2 = 1.26 (SD: 3.67); BS3 = 1.90 (SD: 5.36); BS4 = 0.45 (SD: 0.83); Kruskal-Wallis P = 0.031 |
| **Analysis used** | The Wampole ISOSTAT/ISOLATOR Microbial System was used for blodd culture.<br>No irrigation/flush with 10ml sterile saline solution was completed prior to BS1, but was completed prior to BS2 to BS4.<br>For each colony type the concentration/magnitude of the bacteria in the blodd was calculated in CFU/ml. |
| **Length of follow-up** | Aerobic: 2 days incubation; anaerobic: 4 days incubation. |
| **Location** | Patients presenting to the surgical centre, oral surgery clinic for third molar extractions under conscious sedation from June 2011 to December 2011 |
| **Source of funding** | Funding provided by the 59th Clinical Research Training Division, Lackland, AFB, TX |
| **Comments** | |

1 **Table 69**

| Bibliographic reference | **Lockhart (2008), ID: 457**<br>**Bacteremia Associated with Tooth Brushing and Dental Extraction.** |
|---|---|
| **Study type** | RCT |
| **Aim** | To compare the incidence, duration, nature and magnitude of endocarditis-related bacteraemia from single tooth extraction and tooth brushing, and to determine the impact of amoxicillin prophylaxis on single tooth extraction. |
| **Patient characteristics** | *Inclusion criteria:*<br>• Patients presented to our urgent care service with the need for extraction of at least one erupted tooth.<br>*Exclusion criteria:*<br>• less than ten teeth<br>• use of systemic antibiotics within the previous 2 weeks<br>• need for antibiotic prophylaxis based on current practice guidelines |

| Bibliographic reference | **Lockhart (2008), ID: 457**<br>**Bacteremia Associated with Tooth Brushing and Dental Extraction.** |
|---|---|
| | • active viral disease, immunocompromised, poorly controlled systemic disease<br>• history of penicillin allergy<br>• temperature greater than 100.5 degrees Fahrenheit<br>• facial cellulitis and manipulation of the gingival tissues (e.g., chewing, tooth brushing) within 1 hr prior to the study. |
| **Number of patients** | Total number = 290; control group = 96 (group of interest)<br>*[the other 194 patients either had amoxicilin prophylaxis or on brushing intervention].*<br>Mean age = 40.5 years old (SD: 10.9)<br>Gender = 51 males; 45 females.<br><br>*No. of blood samples:*<br>Baseline = 89<br>After surgery at 1.5 min = 84; 5 min = 84; 20 min = 83; 40 min = 83; 60 min = 82 |
| **Procedures** | Tooth extraction.<br><br>6 blood samples (BS) were drawn as follow:<br>The baseline blood sample (20 mL) was then drawn and 7-8 mL was inoculated directly into both aerobic and anaerobic BACTEC® bottles for bacterial culturing. Subsequent blood draws of 20 mL were taken at 1.5 min and at 5 min after the initiation of surgery. Additional blood samples (20 mL) were drawn 20, 40, and 60 min following the end of the procedure. |
| **Outcomes and effect estimates** | *Incidence and duration of bacteraemia:*<br>Baseline = 0/89 (0%); 1.5 min = /84 (45%); 5 min = 42/84 (50%); 20 min = 8/83 (10%); 40 min = 4/83 (5%); 60 min = 4/82 (5%)<br><br>*IE-related bacterial species identified:*<br>Overall those with (viridans) streptococci = 106/151 (70%)<br><br>*Individual IE-related species identified:*<br>*Actinomyces meyeri/odontolyticus*<br>*Capnocytophaga sp.*<br>*Eikenella corrodens*<br>*Fusobacterium nucleatum*<br>*Granulicatella adiacens*<br>*Haemophilus aphrophilus*<br>*Lactobacillus salivarius*<br>*Neisseria elongata* |

| Bibliographic reference | **Lockhart (2008), ID: 457**<br>**Bacteremia Associated with Tooth Brushing and Dental Extraction.** |
|---|---|
| | *Neisseria flavescens*<br>*Neisseria mucosa/sicca*<br>*Peptostreptococcus micros*<br>*Prevotella melaninogenica*<br>*Prevotella oralis*<br>*Propionibacterium acnes*<br>*Staphylococcus epidermidis*<br>*Streptococcus anginosus*<br>*Streptococcus constellatus*<br>*Streptococcus cristatus*<br>*Streptococcus gordonii*<br>*Streptococcus intermedius*<br>*Streptococcus mitis*<br>*Streptococcus mutans*<br>*Streptococcus oralis*<br>*Streptococcus salivarius*<br>*Streptococcus sanguinis*<br>*Veillonella parvula* |
| **Analysis used** | Blood samples were cultured in BACTEC Plus Aerobic/F and LYTIC/10 Anaerobic/F (Becton, Dickinson, Sparks, MD). Bacterial colonies were isolated on both selective and non-selective media such as blood agar, Chocolate agar and MacConkey II agar for aerobes, and on anaerobic blood agar. All false-positive bottles (i.e., bottles that were signaled positive but the subculture was negative) were further incubated for the total of 2 weeks. Bottles with positive cultures were also kept for two weeks and subcultured periodically to ensure recovery of additional species. |
| **Length of follow-up** | 2 weeks incubation. |
| **Location** | USA |
| **Source of funding** | This study was supported by NIDCR/NIH Grant # R01 DE13559-01. |
| **Comments** | |

1 **Table 70**

| Bibliographic reference | **Assaf (2007), ID: 687**<br>**Effect of the Diode Laser on Bacteremia Associated with Dental Ultrasonic Scaling: A Clinical and Microbiological Study.** |
|---|---|
| **Study type** | Split-mouth trial |

| Bibliographic reference | **Assaf (2007), ID: 687**<br>**Effect of the Diode Laser on Bacteremia Associated with Dental Ultrasonic Scaling: A Clinical and Microbiological Study.** |
|---|---|
| **Aim** | To evaluate the potential use of diode lasers (DLs) to reduce bacteraemia associated with ultrasonic scaling (US). |
| **Patient characteristics** | *Inclusion criteria:*<br>• adults who presented for treatment to the clinics with the diagnostic criteria of plaque-induced generalized chronic gingivitis.<br>• systemically healthy and required to have at least 20 teeth and no history of periodontal therapy.<br>*Exclusion criteria:*<br>• Those who were smoking, had antibiotic therapy within the previous 3 months, subgingival restorations, use of antiseptic mouthwash, history of infective endocarditis, congenital or acquired cardiac defects, cardiac prosthesis, haematological disorders, immune defects, corticosteroid or immunosuppressive medication, or any systemic conditions that might affect the periodontium and the treatment protocol. |
| **Number of patients** | Total number = 22<br>Gender: 14 females; 8 males<br>Age range: from 21 years to 50 years<br>Mean age: 31.8 years for females; 33 years for males. |
| **Procedures** | Ultrasonic scaling (US) with or without diode lasers (DL) (on all patients, split-mouth design)<br><br>On treatment day, a blood sample of 10 mL was drawn just before and 3 min after initiation of US on the control side. Following the completion of US on the control side, laser energy was applied to the gingival crevices of the teeth present on the experimental side (DL+US). Thirty minutes later,blood was drawn again just before and 3 min after initiation of US in the previously lased teeth. Clinical assessment was repeated 4 weeks after treatment. |
| **Outcomes and effect estimates** | *Incidence of bacteraemia (those with positive culture):*<br>US: Baseline = 0/22 (0%); 3 min = 15/22 (68%)<br>US+DL: Baseline = 0/22 (0%); 3 min = 8/22 (36%); RR = 1.87 (95%CI: 1.01 to 3.49)<br><br>*Individual bacterial identified:*<br>*Streptococcus mitis*<br>*Streptococcus salivarius*<br>*Streptococcus sanguis*<br>*Prevotella intermedia and P. nigrescens*<br>*Prevotella melaninogenica*<br>*Capnocytophaga spp.*<br>*Haemophilus spp.*<br>*Bacteroides spp.* |

| Bibliographic reference | **Assaf (2007), ID: 687**<br>**Effect of the Diode Laser on Bacteremia Associated with Dental Ultrasonic Scaling: A Clinical and Microbiological Study.** |
|---|---|
| | *Fusobacterium spp.* |
| **Analysis used** | Blood samples of 10 mL were drawn from the patient through an antecubital vein using strict aseptic technique via a 22-gauge sterile plastic cannula. Samples were then incubated at 37°C for 14 days. Results were considered positive when the blood–broth mixture in the bottles had risen above the sleeve of the growth indicator device. |
| **Length of follow-up** | 14 days incubation. |
| **Location** | Faculty of Dentistry of Yeditepe University, Turkey. |
| **Source of funding** | Not reported. |
| **Comments** | |

1 **Table 71**

| Bibliographic reference | **Cherry (2007), ID: 1075**<br>**Effect of rinsing with povidone–iodine on bacteraemia due to scaling: a randomized-controlled trial.** |
|---|---|
| **Study type** | RCT |
| **Aim** | To investigate rinsing with povidone–iodine on bacteraemia caused by ultrasonic scaling. |
| **Patient characteristics** | *Inclusion criteria:*<br>• adults to have plaque induced gingivitis, as defined by the American Academy of Periodontology, involving five adjacent teeth (FDI teeth 31–35).<br>*Exclusion criteria:*<br>• allergy to iodine, significant medical problems (e.g. diabetes), known infection with the human immunodeficiency virus, cardiac defects or other conditions requiring prophylactic antibiotic cover<br>• pregnancy<br>• having taken antibiotics in the last 3 months or currently taking corticosteroid or immunosuppressive medications or having received periodontal treatment within the previous 6 months.<br><br>Patients were instructed not to brush for at least 30 min before their appointment to avoid the possibility of any tooth brushing-induced bacteraemia. |
| **Number of patients** | Total = 60; control group = 30 (group of interest)<br>*[the other 30 patients had povidone–iodine wash prophylaxis].*<br>Mean age: 43.9 years old (SD: 20.8)<br>Gender: 7 males; 23 females |
| **Procedures** | Ultrasonic scaling. |

| Bibliographic reference | **Cherry (2007), ID: 1075**<br>**Effect of rinsing with povidone–iodine on bacteraemia due to scaling: a randomized-controlled trial.** |
|---|---|
| | 10 ml of blood was sampled as a baseline measurement immediately following rinsing with either NaCl or POV–I and before scaling commenced, to ensure the absence of a pre-existing bacteraemia. 10 ml of blood was sampled 30 s after scaling was commenced and a further 10 ml of blood was sampled at the completion of 2 min of scaling. |
| **Outcomes and effect estimates** | Overall, a positive bacteraemia of oral origin was found in 33% of the patients in the group.<br><br>*Incidence of bacteraemia:*<br>Baseline = 0/30 (0%); 30s = 4/30 (13%); 2 min = 9/30 (30%)<br><br>4 of the 9 bacteraemic patients were al bacteraemic at 30s.<br>24 isolates were identified, with 11 of these were Viridans group streptococci (42%). |
| **Analysis used** | A lysocentrifugation tube was inoculated with each blood sample immediately following collection and then centrifuged at room temperature for 10 min at 5000 g.<br>The CHBA plates were incubated for 7 days at 351C, 5% $CO_2$ in a $CO_2$ incubator; the Chromogenic agar plates were incubated for 7 days in ambient atmosphere at 37C; and the BHV plates were incubated for 7 days in an anaerobic cabinet at 37C, 10% $CO_2$, 80% $N_2$, 10% $H_2$. |
| **Length of follow-up** | 7 dyas incubation. |
| **Location** | Westmead Centre for Oral Health, Australia. |
| **Source of funding** | Not reported. |
| **Comments** | |

1 **Table 72**

| Bibliographic reference | **Morozumi (2010), ID: 381**<br>**Effects of irrigation with an antiseptic and oral administration of azithromycin on bacteraemia caused by scaling and root planning.** |
|---|---|
| **Study type** | RCT |
| **Aim** | To investigate the effects of irrigation with an essential oil-containing antiseptic (EO) and oral administration of azithromycin (AZM) on bacteraemia caused by scaling and root planing. |
| **Patient characteristics** | *Inclusion criteria:*<br>• Adults who had >20 teeth, moderate to severe chronic periodontitis<br>*Exclusion criteria:*<br>• Had congenital valve defects or other risk factors for IE; low level of haematocrit; high risk of cardiovascular disease and diabetes; allergy to macrolides |

| Bibliographic reference | **Morozumi (2010), ID: 381**<br>**Effects of irrigation with an antiseptic and oral administration of azithromycin on bacteraemia caused by scaling and root planning.** |
|---|---|
| | • Had taken systemic antibiotics, anti-inflammatory drugs, immunosuppressive drugs within 3 months before the study<br>• Had received periodontal treatment within the previous 6 months, regularly used an oral irrigation device or mouthrinse, had an incompatible dentition. |
| **Number of patients** | Total = 30; Control group = 10 (group of interest)<br>Gender: 8 males; 2 females<br>Mean age: 55.4 years old (SD:9.3) |
| **Procedures** | Scaling and root planing<br><br>At baseline, peripheral blood and subgingival plague were collected. The second sample of peripheral blood was taken 6 min after the initiation of SRP. |
| **Outcomes and effect estimates** | *Prevalence of bacteraemia:*<br>Baseline = 0/10 (0%); 6 min = 9/10 (90%)<br><br>*Individual bacteria identified:*<br>alpha-*Streptococcus*<br>beta-*Streptococcus*<br>*Streptococcus constellatus*<br>*Streptococcus mutans* |
| **Analysis used** | Blood was obtained by venepuncture in the antecubital fossa. Each sample comprised 10 ml of blood, which was obtained using a 22-gauge butterfly and safety lock blood collection set and 30 ml syringe.<br>The collected blood samples were inoculated into an anaerobic culture bottle that could cover both anaerobic and aerovic bacteria. Bottles were incubated and continuously monitored over 6 days. |
| **Length of follow-up** | 6 days incubation. |
| **Location** | Between Jan 2006 and Oct 2008, Niigata University Medical & Dental Hospital, Japan. |
| **Source of funding** | Not reported. |
| **Comments** | |

1 **Table 73**

| Bibliographic reference | **Pineiro (2010), ID: 395**<br>**Bacteraemia following dental implants' placement.** |
|---|---|
| **Study type** | RCT |

| Bibliographic reference | **Pineiro (2010), ID: 395**<br>**Bacteraemia following dental implants' placement.** |
|---|---|
| **Aim** | To investigate the prevalence, duration and aetiology of bacteraemias following the placement of implants as well as the prophylactic efficacy of a chlorhexidine digluconate mouthrinse. |
| **Patient characteristics** | *Inclusion criteria:*<br>• Adults suitable for oral rehabilitation using osseointegrated implants.<br>*Exclusion criteria:*<br>• Less than18 years of age, use of antibiotics in the previous 3 months, routine use of oral antiseptics, immunodeficiency and any other disease that could predispose them to infections or bleeding complications. |
| **Number of patients** | Total = 50; control group = 30 (group of interest)<br>*[the other 20 patients had chlorhexidine prophylaxis].*<br>Mean age: 55 years old (SD: 13.5)<br>Gender: 8 males; 22 females |
| **Procedures** | Dental implant placement<br><br>All patients received intravenous sedation with midazolam and propofol, together with infiltrative local anaesthesia by injection of an average of four cartridges (1.8ml per cartridge) of 2% lidocaine with epinephrine.<br><br>A peripheral venous blood sample (10 ml) was collected from each patient before the start of the surgical procedure to determine the prevalence of bacteraemia before intervention (baseline). Further peripheral blood samples (10 ml) were taken 30 s after insertion of the last implant and at 15 min after the completion of suturing of themucoperiosteal flap to determine the prevalence and duration of bacteraemia secondary to implant placement. |
| **Outcomes and effect estimates** | *Incidence of bacteraemia:*<br>Baseline = 1/30 (3.3%); 30 s = 2/30 (6.6%); 15 min = 1/30 (3.3%)<br><br>*Individual bacterial identified:*<br>*Streptococcus viridans (anginosus group)*<br>*Streptococcus viridans (mitis group)*<br>*Neisseria cinerea*<br>*Streptococcus viridans (mitis group)* |
| **Analysis used** | After disinfection with alcohol and povidone iodine, an intravenous catheter was inserted into the antecubital fossa or on the dorsumof the hand.<br>Each sample was inoculated in equal measure into containers with aerobic and anaerobic culture media (Bactec plus, Becton Dickinson) and immediately transported to the laboratory.<br>The blood samples were processed using the Bactec 9240. A Gram stain was performed on each positive blood culture. Positive |

| Bibliographic reference | **Pineiro (2010), ID: 395**<br>**Bacteraemia following dental implants' placement.** |
|---|---|
| | aerobic blood cultures were subcultured on blood agar, on chocolate agar in an atmosphere with 5–10% $CO_2$ and on MacConkey agar in an aerobic atmosphere. The same protocol was used for positive anaerobic blood cultures, although also including subculture on Schaedler agar incubated in an anaerobic atmosphere. |
| **Length of follow-up** | Incubation period not reported. |
| **Location** | Spain. |
| **Source of funding** | This work was supported by the Xunta de Galicia (grant PGIDT 08CSA010208PR and grant RH 107/05, Research Intensification), Spain. |
| **Comments** | |

1 **Table 74**

| Bibliographic reference | **Yagci (2013), ID: 112**<br>**Relationship between odontogenic bacteremia and orthodontic stripping.** |
|---|---|
| **Study type** | Before-and after study. |
| **Aim** | To evaluate the prevalence of bacteraemia associated with an orthodontic stripping procedure. |
| **Patient characteristics** | *Inclusion criteria:*<br>• Adults and children with a Class I molar relationship with minimal anterior crowding and in the permanent dentition<br>• with adequate oral hygiene<br>• with plaque scores of 0 or 1.<br>*Exclusion criteria:*<br>• with a history of congenital heart disease, rheumatic fever, hypertrophic cardiomyopathy, subacute bacterial endocarditis, aortic or mitral stenosis, prosthetic heart valves, bleeding disorders, or diabetes mellitus; immune suppressed or pregnant patients and patients who had used an antiseptic mouthwash or antibiotics within the last 3 months. |
| **Number of patients** | Total = 29<br>Gender: 22 female, 7 male<br>Mean age: 18.2 years old (SD: 3.4, range, 14.7-24.3) |
| **Procedures** | Orthodontic stripping.<br><br>Patients were instructed not to eat anything or brush their teeth during the 2 hours preceding the stripping.<br>All blood samples were collected from the patients under sterile conditions at 2 time points: before and soon after stripping. |
| **Outcomes and effect estimates** | *Prevalence of bacteraemia:*<br>Baseline = 0/29 (0%)<br>Post stripping = 1/29 (3.4%) [*Streptococcus sanguis*] |

| Bibliographic reference | **Yagci (2013), ID: 112**<br>**Relationship between odontogenic bacteremia and orthodontic stripping.** |
|---|---|
| **Analysis used** | A sterile plastic cannula of 20 g and a sterile syringe were used, and an initial blood sample of 10 $cm^3$ was collected before treatment. Soon after completing the stripping procedure, the valve of the cannula was reopened, and a second blood sample of 10 $cm^3$ was taken with a new syringe.<br>The blood samples were injected into aseptic culture flasks containing 50 $cm^3$ of brain-heart infusion broth and incubated at 37C for 5 days. |
| **Length of follow-up** | 5 days incubation. |
| **Location** | The Department of Orthodontics, Erciyes University, Turkey. |
| **Source of funding** | Not reported. |
| **Comments** | |

1 **Table 75**

| Bibliographic reference | **Sonbol (2009), ID: 545**<br>**Prevalence, intensity and identity of bacteraemia following conservative dental procedures in children.** |
|---|---|
| **Study type** | RCT |
| **Aim** | To investigate the prevalence, intensity and microbial identity of bacteraemia following conservative dental procedures. |
| **Patient characteristics** | *Inclusion criteria:*<br>• children and adolescents heavier than 17.5 kg undergoing general anaesthesia for dental treatment.<br>*Exclusion criteria:*<br>• with chronic medical disorders, predisposing cardiac lesions, known viral carriage, haemorrhagic disorders and difficult veins |
| **Number of patients** | Total = 205 (at randomisation)<br>Gender: 102 boys; 103 girls<br>Mean age: 10.8 years old (SD: 3.67), range 4.00–17.5 years old.<br><br>43 were withdrawn with final total number of 162 children.<br>Rubber dam and clamp: N=41<br>Fast drill: N=40<br>Slow drill: N=40<br>Matrix band and wedge: N=41 |
| **Procedures** | 1. Rubber dam and clamp: a clamp was placed on either a single, fully erupted maxillary or mandibular primary or permanent molar.<br>2. Fast drill: either a carious primary or permanent molar tooth was drilled for 1 min using a high-speed handpiece and a diamond bur with water irrigation. |

| Bibliographic reference | **Sonbol (2009), ID: 545**<br>**Prevalence, intensity and identity of bacteraemia following conservative dental procedures in children.** |
|---|---|
| | 3. Slow drill: either a carious primary or permanent molar tooth was drilled for 1 min using a slow-speed handpiece and a number 4 rosehead bur.<br>4. Matrix band and wedge: a matrix band was placed on either a mandibular or maxillary primary or permanent molar. A wooden wedge was pushed between the matrix band and the adjacent tooth.<br><br>Blood samples of 6 ml pre-procedure and then another 6 ml 30 s after the procedure were drawn. |
| **Outcomes and effect estimates** | *Prevalence of bacteraemia:*<br>Rubber dam and clamp: Baseline = 12/41 (29%); post-procedure = 22/41 (54%); p=0.01<br>Fast drill: Baseline = 6/40 (15%); post-procedure = 9/40 (22%); p=0.5<br>Slow drill: Baseline = 4/40 (10%); post-procedure = 9/40 (22%); p=0.2<br>Matrix band and wedge: Baseline = 13/41 (32%); post-procedure = 27/41 (66%); p=0.001<br><br>*Intensity of bacteraemia (detectable ≥0.33 CFU/ml):*<br>*Anaerobic:*<br>Rubber dam and clamp: Baseline = 7/41 (17%); post-procedure = 17/41 (41%); p=0.005<br>Fast drill: Baseline = 4/40 (10%); post-procedure = 7/40 (18%); p=0.6<br>Slow drill: Baseline = 2/40 (5%); post-procedure = 9/40 (23%); p=0.02<br>Matrix band and wedge: Baseline = 9/40 (23%); post-procedure = 18/40 (45%); p=0.002<br>*Aerobic:*<br>Rubber dam and clamp: Baseline = 6/41 (15%); post-procedure = 16/41 (39%); p=0.001<br>Fast drill: Baseline = 4/40 (10%); post-procedure = 5/40 (13%); p=0.4<br>Slow drill: Baseline = 2/40 (5%); post-procedure = 1/40 (3%); p=1.0<br>Matrix band and wedge: 6/40 (15%); post-procedure = 21/40 (53%); p=0.0001<br><br>A total of 628 bacterial isolates were recovered from the membrane filters of which 53 were from baseline blood samples and 575 from postprocedure samples.<br>*Streptococcus* spp.: baseline = 3.8%; post-procedure = 52%<br>*Staphylococcus* spp.: baseline = 49%; post-procedure = 18.3% |
| **Analysis used** | • Following attainment of general anaesthesia, a 21-gauge Y-cannula was placed in a vein in either the right or left antecubital fossa using aseptic technique. Using a separate sterile syringe, 6 ml blood was withdrawn and placed immediately into a sterile universal bottle containing 1.23 ml 0.35% of sodium polyanetholesulfonate solution to prevent clotting and to inactivate the natural antibacterial action of the blood.<br>• Thirty seconds after the procedure, a further 6 ml blood was withdrawn and placed into a second sterile universal bottle containing 1.23 ml 0.35% SPS solution. |

| Bibliographic reference | **Sonbol (2009), ID: 545**<br>**Prevalence, intensity and identity of bacteraemia following conservative dental procedures in children.** |
|---|---|
| | • Two equal volumes of the solution were poured into a disposable, sterile filtration unit. One filter was incubated aerobically and the other filter was incubated in an anaerobic chamber, for 10 days. |
| **Length of follow-up** | 10 days incubation. |
| **Location** | UK |
| **Source of funding** | Not reported. |
| **Comments** | |

1 **Table 76**

| Bibliographic reference | **Zhang (2013), ID: 155**<br>**Effects of irrigation with an antiseptic and oral administration of azithromycin on bacteraemia caused by scaling and root planning.** |
|---|---|
| **Study type** | Before-and-after study |
| **Aim** | To investigate incidence, magnitude and bacterial diversity of bacteraemia due to flossing compared with scaling and root planing (SRP) |
| **Patient characteristics** | *Inclusion criteria:*<br>• had radiographic evidence of inter-proximal bone loss viewed on an orthopantomogram<br>• required to be >21 years old, with a diagnosis of chronic periodontitis<br>• have a palpable vein in an antecubital fossa<br>• at least one quadrant (qualified quadrant) with a minimum of five teeth with two or more inter-proximal sites with probing depths ≥5 mm, not at the same tooth.<br>*Exclusion criteria:*<br>• had significant medical conditions (e.g. diabetes), immune deficiency, congenital or acquired cardiac defects or other conditions requiring antibiotic cover, haematological disorders, pregnancy, infection, history of taking antibiotics in the past 3 months, or taking immunosuppressive or corticosteroid medication. |
| **Number of patients** | Total = 30<br>Gender: 12 males and 18 females<br>Mean age: 47 years old (SD: 9.5) |
| **Procedures** | Scaling and root planning (SRP)<br><br>Patients were instructed not to brush or floss their teeth, chew any food or perform any intraoral manipulations for at least 1 h before the experimental visits.<br>A 20 ml blood sample was obtained as a baseline at the beginning of prior to SRP. Another 20 ml of blood was sampled at 5 min after the initiation of SRP, and at 30 s and 10 min after the completion of SRP. |

| Bibliographic reference | **Zhang (2013), ID: 155**<br>**Effects of irrigation with an antiseptic and oral administration of azithromycin on bacteraemia caused by scaling and root planning.** |
|---|---|
| **Outcomes and effect estimates** | The term total bacteraemia (TB) is used to describe positive bacteraemia samples comprising any genus of oral bacteria, whilst VSB describes positive bacteraemia samples in which any bacteria of the genus viridans streptococci was present, either in combination with other oral bacteria or as the only bacteria in the blood sample.<br><br>*Prevalence of bacteraemia:*<br>Baseline TB = 3/30 (10%); 5 min after initiation = 10/30 (33.3%); 30 s post = 5/30 (16.7%); 10min post = 2/30 (6.7%)<br>Baseline VSB = 0/30 (0%); 5 min after initiation = 6/30 (20%); 30 s post = 2/30 (6.7%); 10min post = 0/30 (0%)<br><br>*Magnitude of bacteraemia (mean CFU/ml):*<br>TB: 5 min after initiation = 2.2 (SD: 3.2); 30 s post = 2.1 (SD: 3.8); 10min post = 1.0 (SD: 1.1)<br>VSB: 5 min after initiation = 0.4 (SD: 0.2); 30 s post = 0.3 (SD: 0.1); 10min post = 0.0 |
| **Analysis used** | Blood samples was obtained from each patient via a vein in the antecubital fossa using a 25 mm/22 gauge cannula which was left in place during each experimental visit to avoid multiple insertions of a needle.<br>Two lysocentrifugation tubes (10 ml each) were inoculated with each 20 ml blood sample immediately following collection and were transferred to the laboratory immediately.<br>Inoculation of cultures was performed in a Class II biosafety laminar flow cabinet to reduce the risk of contamination. The plates were incubated for 7 days. |
| **Length of follow-up** | 7 days incubation. |
| **Location** | Westmead Centre for Oral Health, Sydney, Australia. |
| **Source of funding** | Not reported. |
| **Comments** | |

1 **Table 77**

| Bibliographic reference [from CG64] | **Lucas VS, Omar J, Vieira A, Roberts GJ. The relationship between odontogenic bacteraemia and orthodontic treatment procedures 9668. European Journal of Orthodontics 2002;24:-301. Ref ID: 9668** |
|---|---|
| **Study type** | RCT |
| **Aim** | To investigate the relationship between odontogenic bacteraemia and orthodontic treatment procedures |
| **Patient characteristics** | Inclusion: mean age 13.5yrs (range 9.2 to 17.9), n = 64 males, n = 78 females<br><br>Indices were recorded for bacterial dental plaque and gingival inflammation. A separate score was recorded for the teeth involved in the orthodontic procedure |

| Bibliographic reference [from CG64] | Lucas VS, Omar J, Vieira A, Roberts GJ. The relationship between odontogenic bacteraemia and orthodontic treatment procedures 9668. European Journal of Orthodontics 2002;24:-301. Ref ID: 9668 |
|---|---|
| **Number of patients** | Total = 142 (n = 81 undergoing GA, n = 61 receiving treatment in the O/P department)<br><br>n = 39 upper alginate impression<br>n = 42 separator<br>n = 25 fit/placement of band<br>n = 36 archwire adjustment |
| **Procedures** | Upper alginate impression, separator, fit/placement of band, archwire adjustment.<br><br>Blood samples: baseline sample and 30 second sample taken after the orthodontic procedure |
| **Outcomes and effect estimates** | Prevalence and intensity of bacteraemia following 4 orthodontic procedures.<br>**Prevalence of bacteraemia**<br>Upper alginate impression: Baseline = 9/39 (23%); post-procedure = 12/39 (31%)<br>Separator: Baseline = 12/42 (27%); post-procedure = 15/42 (36%)<br>Fit/placement of band: Baseline = 9/25 (36%); post-procedure = 11/25 (44%)<br>Archwire adjustment: Baseline = 12/36 (23%); post-procedure = 7/36 (31%)<br>There was NS difference in the number of positive blood cultures between baseline and the dentogingival manipulations<br>There was NS association between the mean plaque and gingivitis scores and the number of positive blood cultures for any of the procedures<br><br>**Intensity of bacteraemia (mean and SD cfu per ml of blood)**<br>Upper alginate impression: Baseline = 0.2 (0.7); post-procedure = 0.3 (0.6), p>0.05<br>Separator: Baseline = 0.9 (0.2); post-procedure = 2.2 (9.1), p<0.02<br>Fit/placement of band: Baseline = 0.1 (0.2); post-procedure = 0.3 (0.6), p>0.05<br>Archwire adjustment: Baseline = 0.2 (0.7); post-procedure = 0.04 (0.1), p>0.05<br><br>The mean total number of aerobic and anaerobic bacteria isolated from the blood samples (cfu of bacteria per ml of blood) was significantly greater following the placement of a separator (p<0.02)<br>There was NS difference in the mean number of aerobic or anaerobic, or the combined total bacteria isolated from the blood samples between baseline and an upper alginate impression or placement of a band or archwire adjustment<br><br>**Identity of bacteria**<br>The identity of bacteria isolated from blood cultures were similar to those following dental operative procedures, these included S. gordonii, S. sanguis, S. salivarius, S. vestibularis and coagulase negative staphylococci |

| | |
|---|---|
| **Bibliographic reference [from CG64]** | **Lucas VS, Omar J, Vieira A, Roberts GJ. The relationship between odontogenic bacteraemia and orthodontic treatment procedures 9668. European Journal of Orthodontics 2002;24:-301. Ref ID: 9668** |
| **Analysis used** | Microbiology:<br>6ml per sample, inoculated into sodium polyanethol sulphonate and added to the lysing solution and 3ml of a proprietary streptokinase-streptodornase compound and incubated at 37˚C for 10mins. One plate was incubated aerobically and the other anaerobically for 10days, from day3 they were checked daily for bacterial growth |
| **Length of follow-up** | Not reported. |
| **Location** | London |
| **Source of funding** | Not stated |
| **Comments** | |

1 **Table 78**

| | |
|---|---|
| **Bibliographic reference [from CG64]** | **Roberts GJ, Gardner P, Longhurst P, Black AE, Lucas VS. Intensity of bacteraemia associated with conservative dental procedures in children.[see comment]. British Dental Journal 2000;188:95-8.**<br>**Ref ID: 460** |
| **Study type** | RCT [a] |
| **Aim** | To explore the intensity of bacteraemia. |
| **Patient characteristics** | Inclusion: healthy children receiving dental treatment under general anaesthetic,<br>Exclusion: those who had taken antibiotics within the previous month, known viral carriage and haemorrhagic disorders |
| **Number of patients** | Total = 257 children<br>n = 141 male, n = 116 female, mean age 9yrs 1mth (range 2yrs to 19yrs 6mths)<br><br>n = 54 baseline (no procedure)<br>n = 51 rubber bam placement<br>n = 49 slow drill<br>n = 47 fast drill<br>n = 56 matrix band and wedge |
| **Procedures** | Rubber dam placement<br>Matrix band<br>Slow drill<br>Fast drill<br><br>Blood samples: before procedure, 30 s after procedure. |

| | |
|---|---|
| **Bibliographic reference [from CG64]** | **Roberts GJ, Gardner P, Longhurst P, Black AE, Lucas VS. Intensity of bacteraemia associated with conservative dental procedures in children.[see comment]. British Dental Journal 2000;188:95-8.**<br>**Ref ID: 460** |
| **Outcomes and effect estimates** | *Prevalence of bacteraemia:*<br>Positive blood cultures: baseline n = 5/54 (9.3%); rubber dam placement n = 16/51 (31.4%); slow drill n=6/49 (12.2%); fast drill n = 2/47 (4.3%; matrix band and wedge n = 18/56 (32.1%)<br>Significant differences in the number of positive cultures for:<br>- baseline vs. rubber dam placement (p<0.005)<br>- baseline vs. matrix band (p<0.003)<br>- rubber dam placement vs. slow drill (p<0.02)<br>- rubber dam placement vs. fast drill (p<0.001)<br>- slow drill vs. matrix band (p<0.02)<br>- fast drill vs. matrix band (p<0.0001)<br><br>NS difference:<br>- baseline vs. slow drill; baseline vs. fast drill; rubber dam placement vs. matrix band; slow drill vs. fast drill<br><br>Intensity of bacteraemia<br>There was NS differences between any of the groups in the cfu (colony forming units per/ml of blood)<br><br>Micro-organisms<br>The organisms isolated are typical of those associated with bacteraemia of dental origin<br><br>Exploration by each group of samples did not reveal showed NS relation between plaque accumulation, gingival inflammation, gingival bleeding and the presence or absence of bacteraemia |
| **Analysis used** | Blood cultures<br><br>Microbiology:<br>Two commercial blood culture systems were used; the Bactec radiometric system and the Bactec 760, a 3ml volume of blood was inoculated into each of the aerobic and anaerobic bottles. Bacteria were speciated using standard methods, streptococci were speciated using API Strep 20. A further 1.5ml was inoculated into the Isolator system vial |
| **Length of follow-up** | Not reported |
| **Location** | GOSH and Guy's and St Thomas' Hospital Trust, London. |
| **Source of funding** | Not stated |

| | |
|---|---|
| **Bibliographic reference [from CG64]** | **Roberts GJ, Gardner P, Longhurst P, Black AE, Lucas VS. Intensity of bacteraemia associated with conservative dental procedures in children.[see comment]. British Dental Journal 2000;188:95-8.**<br>**Ref ID: 460** |
| **Comments** | |

1 *(a) randomisation by random number table*

2 **Table 79**

| | |
|---|---|
| **Bibliographic reference [from CG64]** | **Roberts GJ, Jaffray EC, Spratt DA, Petrie A, Greville C, Wilson M et al. Duration, prevalence and intensity of bacteraemia after dental extractions in children. Heart (British Cardiac Society) 2006;92:1274-7.**<br>**Ref ID: 2375** |
| **Study type** | RCT |
| **Aim** | To investigate the duration, prevalence and intensity of bacteraemia after dental extractions. |
| **Patient characteristics** | Inclusion: children attending Eastman Dental Hospital for treatment under general anaesthetic,<br>Exclusion: antibiotic usage within the previous month, viral carriage, haemorrhagic disorders and body weight less than 17.5kg<br><br>An orodontic examination was carried out according to the WHO criteria for dental caries, plaque and gingivitis were assessed<br><br>Age, plaque index, gingivitis index, number of teeth present at the start of the operation and number of teeth extracted were all similar between the various groups |
| **Number of patients** | Total = 500<br>Mean age of the children was 7.6yrs (range 3.4 to 18.9)<br><br>Children were allocated to one of the time groups in random permuted blocks; 10sec, 30sec, 1min, 2min, 4min, 7.5min, 15min, 30min, 45min, 1hr |
| **Procedures** | Dental extraction |
| **Outcomes and effect estimates** | *Intensity of bacteraemia (cfu/6ml sample):*<br>10sec; before extraction median 2.9 (range 0 to 46); after extraction median 9.8 (range 0 to 149), p=0.001<br>30sec; before extraction median 0.5 (range 0 to 4); after extraction median 2.6 (range 0 to 17), p=0.001<br>1min; before extraction median 0.4 (range 0 to 4); after extraction median 16.4 (range 0 to 247), p=0.003<br>2min; before extraction median 1.2 (range 0 to 23); after extraction median 8.1 (range 0 to 162), p=0.009<br>4min; before extraction median 0.4 (range 0 to 4); after extraction median 1.7 (range 0 to 15), p=0.002<br>7.5min; before extraction median 0.4 (range 0 to 4); after extraction median 1.2 (range 0 to 14), p=0.002<br>15min; before extraction median 1.7 (range 0 to 53); after extraction median 1.9 (range 0 to 33), NS<br>30min; before extraction median 0.3 (range 0 to 6); after extraction median 0.6 (range 0 to 8), not determined |

| | |
|---|---|
| **Bibliographic reference [from CG64]** | **Roberts GJ, Jaffray EC, Spratt DA, Petrie A, Greville C, Wilson M et al. Duration, prevalence and intensity of bacteraemia after dental extractions in children. Heart (British Cardiac Society) 2006;92:1274-7.**<br>**Ref ID: 2375** |
| | 45min; before extraction median 0.7 (range 0 to 3); after extraction median 2.4 (range 0 to 46), NS<br>1hr; before extraction median 1.0 (range 0 to 28); after extraction median 2.1 (range 0 to 49), NS<br><br>The intensity was significantly greater at the post-extraction time than at the pre-extraction time up to and including 7.5min; however by 15min and beyond, the difference was NS<br><br>The odds of having a positive culture were significantly greater in the post-extraction time than in the pre-extraction time (OR>1) at each time point up to an including a post-procedure time of 7.5min but not beyond this time<br><br>The genera most often detected were Streptococcus, Actinomyces and Staphylococcus [a]<br><br>(it is appropriate to estimate that dental bacteraemia is quenched within about 12min of completing dental extractions) |
| **Analysis used** | Percentage prevalence of positive cultures, intensity of bacteraemia, speciation of the organism isolated<br><br>Microbiology:<br>The samples were processed automatically in the Bactec 9480, for the lysis filtration samples the blood was processed by a well-established method, positive cultures from both broth culture and lysis filtration were isolated and identified. Negative controls were processed with every 10th run of broth culture and each run of lysis filtration and identify contamination |
| **Length of follow-up** | Not reported. |
| **Location** | UK. |
| **Source of funding** | British heart foundation grant |
| **Comments** | |

*(a) Some of the staphylococci may be contaminants, it is not possible to identify the skin as a source of contamination without carrying out DNA typing of the isolates and matching them to skin swabs taken at the time of the blood sample*

**Table 80**

| | |
|---|---|
| **Bibliographic reference [from CG64]** | **Roberts GJ, Simmons NB, Longhurst P, Hewitt PB. Bacteraemia following local anaesthetic injections in children. British Dental Journal 1998;185:295-8.**<br>**Ref ID: 2440** |
| **Study type** | RCT |

| | |
|---|---|
| **Bibliographic reference [from CG64]** | **Roberts GJ, Simmons NB, Longhurst P, Hewitt PB. Bacteraemia following local anaesthetic injections in children. British Dental Journal 1998;185:295-8.**<br>**Ref ID: 2440** |
| **Aim** | To estimate odontogenic bacteraemia. |
| **Patient characteristics** | Inclusion: healthy children attending for dental extractions under general anaesthetic, average age 8yrs 7mths (differences between the baseline and test groups was<br>NS)<br><br>Exclusion: children who had had antibiotics within the previous month, those with a history of Hepatitis B or HIV |
| **Number of patients** | Total = 143 children<br>n = 50 baseline, blood taken before any dento-gingival manipulation<br>n = 32 buccal infiltration<br>n = 32 modified intraligamental<br>n = 29 conventional intraligamental |
| **Procedures** | Local anaesthetic injections (buccal infiltration, modified intraligamental, conventional intraligamental)<br><br>Blood samples: taken 30sec after injection |
| **Outcomes and effect estimates** | *Prevalence of bacteraemia:*<br>Positive blood cultures:<br>- baseline n = 4/50 (8.0%; 0.5 to 15.5% 95% CI)<br>- buccal infiltration n = 5/32 (15.6%; 2.8 to 28.5%, 95% CI)<br>- modified intraligamental n = 16/32 (50.0%; 29.2 to 64.5% 95% CI)<br>- conventional intraligamental n = 28/29 (96.6%; 75.2 to 99.2%, 95% CI)<br><br>Significant differences:<br>- baseline vs. modified intraligamental ($p<0.0001$)<br>- baseline vs. conventional intraligamental ($p<0.0001$)<br>- buccal infiltration vs. modified intraligamental ($p<0.003$)<br>- buccal infiltration vs. conventional intraligamental ($p<0.0001$)<br>- modified intraligamental vs. conventional intraligamental ($p<0.0001$)<br><br>NS differences:<br>- baseline vs. buccal infiltration |

| | |
|---|---|
| **Bibliographic reference [from CG64]** | **Roberts GJ, Simmons NB, Longhurst P, Hewitt PB. Bacteraemia following local anaesthetic injections in children. British Dental Journal 1998;185:295-8.**<br>**Ref ID: 2440** |
| | Colony forming units (cfu):<br>The results for infiltration, modified intraligamental and the baseline were always zero. Positive cultures were only obtained in those who had had a conventional intraligamental injection, mean value 252cfu/ml, with a range of 0 to 3018cfu/ml<br><br>Micro-organisms isolated<br>The organisms isolated are typical of those associated with bacteraemia of dental or oral origin<br><br>Peridontal indices and bacteraemia<br>There was no positive association between the presence of plaque on the tooth surface adjacent to the conventional intraligamental injection, similarly there was no association with gingivitis |
| **Analysis used** | Blood cultures<br>Microbiology:<br>Two commercial blood culture systems were used; the Bactec radiometric system and the Bactec 760, a 3ml volume of blood was inoculated into each of the aerobic and anaerobic bottles. Bacteria were speciated using standard methods, streptococci were speciated using API Strep 20. A further 1.5ml was inoculated into the Isolator system vial |
| **Length of follow-up** | |
| **Location** | Guy's Dental Hospital, London |
| **Source of funding** | Not stated |
| **Comments** | |

1 **Table 81**

| | |
|---|---|
| **Bibliographic reference [from CG64]** | **Tomas I, Alvarez M, Limeres J, Potel C, Medina J, Diz P. Prevalence, duration and aetiology of bacteraemia following dental extractions. ORAL DIS 2007;13:56-62.**<br>**Ref ID: 27** |
| **Study type** | RCT |
| **Aim** | To investigate the prevalence, duration and aetiology of bacteraemia following dental extractions. |
| **Patient characteristics** | Inclusion: patients, who for behavioural reasons, underwent dental extractions under general anaesthesia; n = 29(55%) male and n = 24(45%) female, mean age 26.1±12.3yrs (range 8 to 52yrs)<br><br>Exclusion: patients who had taken antibiotics in the 3mths prior to the study (including antibiotic prophylaxis for the surgical procedure in the present series), routine use of oral antiseptics, patients suffering from any type of congenital or acquired |

| Bibliographic reference [from CG64] | **Tomas I, Alvarez M, Limeres J, Potel C, Medina J, Diz P. Prevalence, duration and aetiology of bacteraemia following dental extractions. ORAL DIS 2007;13:56-62.**<br>**Ref ID: 27** |
|---|---|
| | immunodeficiency |
| **Number of patients** | Total = 106 (Control group = 53, group of interest)<br>Oral health scale<br>n = 10 (19%) were grades 0-1, n = 21(40%) were grade 2 and n = 22(41%) were grade 3 |
| **Procedure** | Dental extractions<br><br>Blood samples: baseline (after nasotracheal intubation and before local anaesthetic injection), 30sec after final dental extraction, 15min and 1hr after finishing the surgical procedure |
| **Outcomes** | Bacteraemia, factors related to the development of bacteraemia<br>*Bacteraemia*<br>At baseline, 5/53 (9.4%) had positive blood cultures, at 30sec 51/53 (96.2%), at 15min 34/53 (64.2%) and at 1hr 11/53 (20%)<br><br>Of the 209 pairs of blood culture bottles were used, n = 100 were positive, a single bacterium was identified in n = 71 of the positive blood cultures, two bacteria in n = 26, three bacteria to n = 2 and four in the remaining blood culture<br>n = 133 bacterial strains were isolated of which n = 10(7.5%) were aerobes, n = 110(82.7%) were facultative and n = 13(9.8%) were obligate anaerobes<br>The most frequent were Streptococcus spp. (63.8%), particularly S. viridans, followed by Staphylococcus spp. (11.25) and Neisseria spp. (7.5%)<br><br>Factors related to the development of bacteraemia<br>Analysis of the factors potentially contributing to bacteraemia at 30sec was not performed as there were only n = 2 patients with negative blood cultures<br>Female gender and gingival inflammation <3 were significantly related to bacteraemia at 15min, the risk of bacteraemia was x5 higher in females than in males (OR 5.385; 1.356 to 21.378, 95%CI), and x5 higher in patients with gingival inflammation <3 compared with those with grade 3 (OR 0.186; 0.047 to 0.737, 95%CI)<br><br>At 15min the following were NS related to bacteraemia; age, levels of plaque and calculus, presence of periodontal pockets, dental mobility, number of decayed teeth, presence of submucous abscesses and/or periapical lesions and number of teeth extracted<br><br>None of the variables showed significant association with bacteraemia at the 1ht time point |
| **Analysis used** | Microbiology:<br>Bottles with aerobic and anaerobic culture media were processed in Bactec 9240, each positive culture was gram stained, |

| Bibliographic reference [from CG64] | **Tomas I, Alvarez M, Limeres J, Potel C, Medina J, Diz P. Prevalence, duration and aetiology of bacteraemia following dental extractions. ORAL DIS 2007;13:56-62.**<br>**Ref ID: 27** |
|---|---|
| | Bacteria isolated were identified using biochemical tests provided by the Vitek system |
| **Length of follow-up** | Not reported. |
| **Location** | Santiago de Compostela University Hospital, Spain |
| **Source of funding** | Grant from Xunta de Galicia |
| **Comments** | |

1

2 **Upper and lower respiratory tract procedures**

3 **Table 82**

| Bibliographic reference | **Sharif-Kashani (2010), ID: 368**<br>**Incidence of Fever and Bacteraemia Following Flexible Fiberoptic Bronchoscopy: A Prospective Study** |
|---|---|
| **Study type** | Before-and-after study |
| **Aim** | To determine the incidence of bacteraemia and fever following FB. |
| **Patient characteristics** | *Inclusion criteria:*<br>• adults who were scheduled for FB with different indications were enrolled in the study.<br>*Exclusion criteria:*<br>• had immunosuppressant states including diabetes mellitus and low white blood cell count; receiving antibiotic therapy within a week prior to the FB; current active infection; fever >38°C during 48 hours prior to the FB and concurrent treatment with a systemic steroids. |
| **Number of patients** | Total = 85<br>Gender: 69 males (81%); 16 females (19%)<br>Mean age: 57 years old (SD: 28); range: 34-90 years old. |
| **Procedures** | Flexible fiberoptic bronchoscopy<br><br>Three aerobic and anaerobic cultures for venous blood and lavage fluid were drawn just prior, immediately following and 20 min after bronchoscopy using 10 cc of venous blood samples and bronchoalveolar lavage (BAL) specimens. |
| **Outcomes and effect estimates** | *Prevalence and duration of bacteraemia:*<br>Baseline: 0/85 (0%); Immediately after FB: 7/85 (8%); 20 min after FB: 1/85 (1%) |

| Bibliographic reference | **Sharif-Kashani (2010), ID: 368**<br>**Incidence of Fever and Bacteraemia Following Flexible Fiberoptic Bronchoscopy: A Prospective Study** |
|---|---|
| | *Individual bacteria identified:*<br>*Staphylococcus coagulase negative*<br>*Staphylococcus coagulase positive*<br>*Citrobacter freundii*<br>*Streptococcus viridans* |
| **Analysis used** | Blood specimens were injected in a dual culture (aerobic and anaerobic) medium bottle and bottles were incubated in a BabT-Alert incubator for 7 days at temperature of 35-37 °C.<br>Positive cultures were considered if one bacteria growth concentration was more than 10 4 cfu/mL and also visual examination of blood cultures indicated bacterial growth by rapid development of turbidity in the medium within up to 7 days after inoculation and incubation. |
| **Length of follow-up** | 7 days incubation. |
| **Location** | Between October 2006 and March 2007, National Research Institute of Tuberculosis and Lung Disease, Tehran, Iran. |
| **Source of funding** | Not reported. |
| **Comments** | |

1 **Table 83**

| Bibliographic reference | **El Batrawy (2014), ID: 776**<br>**Bacteraemia associated with bronchoscopy.** |
|---|---|
| **Study type** | Before-and-after study |
| **Aim** | To assess the incidence of bacteraemia following bronchoscopy to determine whether the use of prophylactic antibiotics is warranted in patients at risk of endocarditis. |
| **Patient characteristics** | *Inclusion criteria:*<br>• adults and children who underwent bronchoscopy during the study period<br>*Exclusion criteria:*<br>• Patients with current respiratory tract infection or febrile illnesses and those receiving antibiotic therapy within a week prior to the bronchoscopy |
| **Number of patients** | Total = 45<br>Overall mean range: 8 to 65 years old.<br>Adults: gender: 29 males; 7 females (total = 36)<br>Adults mean age: 48 years old (SD: 13.75)<br>Children: gender: 4 males; 5 females (total = 9)<br>Children mean age: 12.3 years old (SD: 2.8) |

| Bibliographic reference | **El Batrawy (2014), ID: 776**<br>**Bacteraemia associated with bronchoscopy.** |
|---|---|
| **Procedures** | Bronchoscopy (rigid or flexible).<br><br>Blood sampling: three 10 mL blood samples were taken from the anti-cubical fossa one immediately before and two after bronchoscopy 10 min apart under complete aseptic conditions.<br>True bacteraemia was defined as episodes in which two post bronchoscopy positive blood cultures yielded the same organisms. |
| **Outcomes and effect estimates** | *Prevalence of bacteraemia:*<br>Baseline = 0/45; 10 min after = 0/45; 20 min after = 0/45 |
| **Analysis used** | The 10 mL venous blood samples were inoculated, at bed side, onto the BACTECTM PLUS Aerobic/F blood culture medium which usually contains nutritive elements for microorganisms, anticoagulant, and resins for the adsorption of antibiotics. Bottles were then transported immediately to the Microbiology Laboratory for further processing.<br>After 18–24 h incubation, plates were examined for the presence of any relevant growth. If no growth appeared after 18–24 h incubation, plates were re-incubated for additional 48 h and re-examined thereafter. If no evidence of microbial growth exists bottles were discarded and reports were discharged as no growth after 5 days incubation. |
| **Length of follow-up** | 5 days incubation. |
| **Location** | Chest Department, Thoracic Surgery Department and<br>Microbiology Laboratory of Ain Shams University Hospitals,<br>Cairo, Egypt. |
| **Source of funding** | Not reported. |
| **Comments** | |

1 **Table 84**

| Bibliographic reference | **Saayman (2009), ID: 505**<br>**Bacteraemia following single-stage percutaneous dilatational tracheostomy.** |
|---|---|
| **Study type** | Before-and-after study |
| **Aim** | The aim of the current study is to establish the incidence of bacteraemia in consecutive ICU patients undergoing PDT with a single dilator technique. |
| **Patient characteristics** | *Inclusion criteria:*<br>• ventilated adult ICU patients requiring PDT were included.<br>*Exclusion criteria:*<br>• if the patient's advocate refused assent, survival was expected to be less than 24-h, patients were under age 18 years of age or immunosuppressed. |
| **Number of patients** | Total = 118; Non-antibiotics group = 57 (group of interest) |

| Bibliographic reference | **Saayman (2009), ID: 505**<br>**Bacteraemia following single-stage percutaneous dilatational tracheostomy.** |
|---|---|
| | Overall gender: 43 females and 75 males (subgroup not available)<br>Overall age range: 19–88 years of age (median 61) (subgroup not available) |
| **Procedures** | Single-stage percutaneous dilatational tracheostomy.<br><br>Peripheral venous blood cultures were performed using full aseptic conditions immediately prior to the procedure (pre-tracheostomy). A second set of peripheral venous blood cultures were taken immediately after securing the tracheostomy tube (post-tracheostomy). The time between the insertion of the tracheostomy tube and sampling was no more than 15 min. |
| **Outcomes and effect estimates** | *Prevalence of bacteraemia:*<br>Baseline = 0/57 (0%); post PDT = 5/57 (8.7%)<br><br>*Individual bacteria identified:*<br>*Coagulase Negative Staphylococcus*<br>*S. milleri*<br>*H. influenza*<br>*Candida spp.*<br>*Enterobacter* |
| **Analysis used** | Povidone-iodine solution (10% w/v) was applied to the skin and 20 ml of blood withdrawn from a peripheral vein and 10 ml inserted into aerobic and anaerobic blood culture bottles respectively.<br>Incubation of pre- and post-cultures was performed using the BACTEC system until positive or for up to 5 days. Blood cultures were recorded as positive if growth of one or more significant organisms were identified. |
| **Length of follow-up** | 5 days incubation. |
| **Location** | Adult Critical Care, University Hospital of Wales, Cardiff, UK. |
| **Source of funding** | Not reported. |
| **Comments** | |

1 **Table 85**

| Bibliographic reference | **Yokoyama (2014), ID: 74**<br>**Randomized clinical trial of the effect of perioperative synbiotics versus no synbiotics on bacterial translocation after oesophagectomy.** |
|---|---|
| **Study type** | RCT |
| **Aim** | To investigate the effect of perioperative symbiotic administration on the incidence of bacterial translocation to mesenteric lymph nodes (MLNs) and the occurrence of postoperative bacteraemia. |

| | |
|---|---|
| **Bibliographic reference** | **Yokoyama (2014), ID: 74**<br>**Randomized clinical trial of the effect of perioperative synbiotics versus no synbiotics on bacterial translocation after oesophagectomy.** |
| **Patient characteristics** | *Inclusion criteria:*<br>• adult patients with oesophageal cancer scheduled to undergo oesophagectomy.<br>*Exclusion criteria:*<br>• oesophagectomy without a planned MLN dissection (no thoracotomy or median sternotomy), cancers that needed a two-step procedure, and age over 80 years. |
| **Number of patients** | Total number = 42; control group = 21 (group of interest)<br>Gender: 18 males; 8 females<br>Mean age: 66 years old (range: 25 to 77 years old) |
| **Procedures** | Oesophagectomy.<br><br>Blood samples (1ml) were collected into a test tube on the morning of the operation after induction of anaesthesia and just before laparotomy (baseline), and on post-operative day 1.<br>Patients in the control group consumed an ordinary diet without synbiotics before surgery. |
| **Outcomes and effect estimates** | *Prevalence of bacteraemia:*<br>Baseline = 5/21 (24%); post-operative day 1 = 12/21 (57%) |
| **Analysis used** | The samples were held at room temperature for 5min until storage at −80◦C. Bacterial detection in blood samples collected on post-operative day 1 was correlated with bacterial detection in the MLN-2 samples. |
| **Length of follow-up** | Not reported. |
| **Location** | Between January 2008 and August 2011, Nagoya University Hospital, Japan. |
| **Source of funding** | Not reported. |
| **Comments** | |

1 **Table 86**

| | |
|---|---|
| **Bibliographic reference [from CG64]** | **Ho H, Zuckerman MJ, Wassem C. A prospective controlled study of the risk of bacteremia in emergency sclerotherapy of esophageal varices. [Review] [44 refs]. Gastroenterology 1991;101:1642-8.**<br>**Ref ID: 829** |
| **Study type** | Before-and-after study |
| **Aim** | To determine the frequency of bacteraemia after endoscopy. |
| **Patient characteristics** | Inclusion: patients admitted for upper GI bleeding or elective oesophageal variceal sclerotherapy (EVS)<br><br>Exclusion: had received any antibiotics in the last 2 weeks before admission |

| Bibliographic reference [from CG64] | **Ho H, Zuckerman MJ, Wassem C. A prospective controlled study of the risk of bacteremia in emergency sclerotherapy of esophageal varices. [Review] [44 refs]. Gastroenterology 1991;101:1642-8.**<br>**Ref ID: 829** |
|---|---|
| | The emergency endoscopy and sclerotherapy groups were comparable in age and sex distribution |
| **Number of patients** | Total = 72 (n = 126 endoscopies)<br><br>n = 36 (n = 37 sessions) emergency endoscopy group<br>n = 36 sclerotherapy groups<br>(n = 14 the emergency EVS group, n = 33 sessions)<br>(n = 36 the elective EVS group, n = 56 sessions) |
| **Procedures** | Emergency endoscopy, elective EVS, emergency EVS<br><br>Blood samples:<br>Before endoscopy, at 5min and 30min after the procedure |
| **Outcomes and effect estimates** | Blood cultures<br>Positive blood cultures were found in n = 30/378 cultures (7.9%), of these n = 11 were considered to be potentially significant<br><br>*Prevalence of bacteraemia:*<br>Emergency endoscopy group blood cultures:<br>Baseline = 0/37 (0%); 5 min = 2/37 (5%); 30 min = 3/37 (8%)<br>Total n = 5 positive , the incidence of endoscopy-related bacteraemia was considered to be 11% (n = 4) with a predominance of skin flora<br><br>Elective EVS sclerotherapy:<br>Baseline = 3/33 (9%); 5 min = 1/33 (3%); 30 min = 4/33 (12%)<br>Total n = 8 positive blood cultures (n = 3 drawn before endoscopy), no significant bacteraemia was noted and no patients had signs or symptoms of infection<br><br>Emergency EVS sclerotherapy;<br>Baseline = 7/56 (13%); 5 min = 5/56 (9%); 30 min = 5/56 (9%)<br>Total n = 17 positive blood cultures (n = 7 drawn before endoscopy), n = 4 (7.1%) sessions had significant pre-endoscopic blood cultures and n = 5 (8.9%) sessions had six significant post-endoscopic blood cultures<br>n = 8/17 (47%) testing positive for E coli, Campylobacter coli, Pseudomonas fluorescens, Bacteroides fragilis, or they were polymicrobial with Clostridium. The other n = 9/17 (53%) positive blood culture results were with oral and skin flora |

| | |
|---|---|
| **Bibliographic reference [from CG64]** | **Ho H, Zuckerman MJ, Wassem C. A prospective controlled study of the risk of bacteremia in emergency sclerotherapy of esophageal varices. [Review] [44 refs]. Gastroenterology 1991;101:1642-8.**<br>**Ref ID: 829** |
| | In this group there were positive blood cultures in n = 8/56 (14%) of sessions, excluding those with the same organisms identified pre and post procedure, bacteraemia was n = 6/56 (11%), this was significant bacteraemia in n = 3/56 (5.4%)<br><br><u>Differences in bacteraemia between groups</u><br>There were NS differences in the positive blood culture results in:<br>- the post endoscopy groups between: emergency EVS vs. emergency endoscopy; emergency EVS vs. elective EVS; elective EVS vs. emergency endoscopy<br>- within groups (post endoscopic vs preendoscopic); elective EVS; emergency EVS<br>The difference within groups (post endoscopic vs preendoscopic) in the emergency group was significant p=0.03<br><br>There was no difference in postendoscopic bacteraemia compared with preendoscopic bacteraemia in emergency alone, or for elective ECS or emergency EVS<br><br><u>Analysis of significant bacteraemia:</u><br>There was NS differences in the significant bacteraemia in the postendoscopy groups; emergency EVS vs. emergency endoscopy; emergency EVS vs. elective EVS; elective EVS vs. emergency endoscopy |
| **Analysis used** | Microbiology:<br>5ml per sample inoculated into each Trypiticase Soy Broth for both aerobic and anaerobic, bacterial growth was monitored for 7days with Bactec 360 Microscan system |
| **Length of follow-up** | Not reported. |
| **Location** | Texas, US. |
| **Source of funding** | Not stated |
| **Comments** | |

1 **Table 87**

| | |
|---|---|
| **Bibliographic reference [from CG64]** | **Melendez LJ, Chan KL, Cheung PK, Sochowski RA, Wong S, Austin TW. Incidence of bacteremia in transesophageal echocardiography - a prospective-study of 140 consecutive patients. J AM COLL CARDIOL 1991;18:1650-4. Ref ID: 9109** |
| **Study type** | Before-and-after study |
| **Aim** | To investigate the incidence of bacteraemia in transesophageal echocardiography |
| **Patient characteristics** | Inclusion: consecutive ambulatory patients scheduled for transoesophageal echocardiography (TOE) at 2 tertiary hospitals |

| | |
|---|---|
| **Bibliographic reference [from CG64]** | **Melendez LJ, Chan KL, Cheung PK, Sochowski RA, Wong S, Austin TW. Incidence of bacteremia in transesophageal echocardiography - a prospective-study of 140 consecutive patients. J AM COLL CARDIOL 1991;18:1650-4. Ref ID: 9109** |
| | Age 53±15yrs (range 19 to 84yrs), n = 69 male, n = 71 female, n = 34 patients with a valve prosthesis<br><br>Exclusion: those with a potential source of bacteraemia (known or suspected bacterial infection, indwelling urinary catheter, multiple venipuncture sites, recent surgery or trauma)<br><br>None of the patients received prophylactic antibiotic agents before or after transoesophageal echocardiography |
| **Number of patients** | Total = 140 |
| **Procedure** | Transoesophageal echocardiography (TOE)<br><br>Blood samples: immediately before the procedure, within 5mins after termination of the procedure, 1hr after the procedure |
| **Outcomes and effect estimates** | *Prevalence of bacteraemia:*<br>Baseline = 4/140 (2.9%); 5 min = 2/140 (1.4%); 1 hour = 2/140 (1.4%)<br>Blood cultures were positive in n = 4 patients before TOE, in n = 2 in immediately after (bacteria species, coagulase negative staphylococci) and in n = 2 late samples (bacteria species, coagulase negative staphylococci, Propionibacterium), both these organisms were considered to be likely contaminants<br><br>There was no correlation between difficulty in intubation and a positive blood culture, or between a positive culture and the presence of an indwelling intravenous line<br><br>The relative risks of bacteraemia immediately after and 1hr after TOE were NS different from baseline<br><br>All patients were contacted 12 weeks after transoesophageal echocardiography, none had developed bacterial endocarditis or other infections requiring the administration of antimicrobial therapy |
| **Analysis used** | Blood cultures<br><br>Microbiology: 10ml per sample, 5ml were inoculated into aerobic and anaerobic culture, cultures were assessed for bacterial growth with use of a semiautomated instrument (Bactec 460) that detects carbon dioxide generated by bacterial metabolism, cultures were considered negative if no bacterial growth was observed after 7days. |
| **Length of follow-up** | 12 weeks |
| **Location** | 2 tertiary hospitals, Canada |
| **Source of funding** | Not stated |
| **Comments** | |

1 **Table 88**

| | |
|---|---|
| **Bibliographic reference [from CG64]** | **Roudaut R, Lartigue CM, Texier-Maugein J, Dallocchio M. Incidence of bacteraemia or fever during transoesophageal echocardiography: A prospective study of 82 patients. European Heart Journal 1993;14:936-40.Ref ID: 3797** |
| **Study type** | Before-and-after study |
| **Aim** | To investigate the incidence of bacteraemia or fever during transoesophageal echocardiography |
| **Patient characteristics** | Inclusion: patients referred from transoesophageal echocardiography<br><br>Exclusion: had received antibiotics before the procedure, was febrile, had any suspicion of infective endocarditis<br>The mean procedure duration was 19min and no complications occurred<br><br>There was NS differences in the clinical characteristics of the two groups, n = 8 patients had prosthetic heart valves |
| **Number of patients** | Total = 82<br>n = 44 (group I)<br>n = 38 (group II) |
| **Procedures** | Transoesophageal echocardiography<br><br>Blood samples:<br>- group I blood cultures taken before procedure, immediately after the procedure, 15min after procedure<br>- group II blood cultures taken before procedure, during procedure (10min after the first attempt to introduce the endoscope), immediately after procedure [c]<br>Rectal temperature of the n = 62 hospitalised patients was measured twice a day for a mean of 6 days after the procedure. |
| **Outcomes and effect estimates** | Incidence of bacteraemia:<br>Group I: Baseline = 0/44 (0%); immediately after = 1/44 (2.3%); 15 min after = 0/44 (0%)<br>Group II: Baseline = 0/38 (0%); 10 min into the procedure = 1/38 (2.6%); immediately after = 0/38 (0%)<br>n = 2/82 (2.4%) patients had a single positive blood culture (Corynebacteria from a group I patient at the end of the procedure, Staphylococcus epidermis from a group II patient during the procedure from the second patient) [a]<br><br>Incidence of fever:<br>The rectal temperate rose above 37.5Cin n = 9 patients within the first 24hr after examination but returned to normal within the subsequent 24hr (maximum temperature observed was 38.4C)<br><br>Follow-up:<br>A third (34%) of the patients were seen within the first months after the procedure, average follow-up 4mths<br>No sign of endocarditis was detected in these patients [b] |

| | |
|---|---|
| **Bibliographic reference [from CG64]** | **Roudaut R, Lartigue CM, Texier-Maugein J, Dallocchio M. Incidence of bacteraemia or fever during transoesophageal echocardiography: A prospective study of 82 patients. European Heart Journal 1993;14:936-40.Ref ID: 3797** |
| **Analysis used** | Microbiology:<br>Aerobic and anaerobic blood culture bottles (BCB system roche) were inoculated and incubated for 10days at 37˚C |
| **Length of follow-up** | A third (34%) were examined a few months later to evaluate any occurrence of endocarditis |
| **Location** | France |
| **Source of funding** | Not stated |
| **Comments** | |

*(a) the smear samples from the surface of the endoscope after the procedure were positive in N=29/38 (79%), the organisms were essentially haemolytic Streptococcus or Neisseria*
*(b) for those who were lost to follow-up the authors assumed that patients would have been referred back to them in the event of an episode of endocarditis*
*(c) in addition in group II cotton swabs were used to take smear samples from the surface of the endoscope after the procedure*

**Table 89**

| | |
|---|---|
| **Bibliographic reference [from CG64]** | **Shyu K-G, Hwang J-J, Lin S-C, Tzou S-S, Cheng J-J, Kuan P et al. Prospective study of blood culture during transesophageal echocardiography. American Heart Journal 1992;124:1541-4. Ref ID: 3820** |
| **Study type** | Before-and-after study |
| **Aim** | To ascertain the incidence and significance of bacteraemia associated with transesophageal echocardiography. |
| **Patient characteristics** | Inclusion: patients undergoing transoesophageal echocardiography, n = 66 male, n = 66 women, ranging in age from 17 to 73yrs (mean age 44.6yrs)<br><br>Exclusion: absence of fever (<37.5C) within 3days of the procedure, no leukocytosis (total white cell count <10000/mm3), no use of antibiotics for 3days before the procedure, other evidence of infection from clinical record review<br>No procedure related complications were noted in any of the n = 132 patients |
| **Number of patients** | n = 132 (n = 135 procedures) |
| **Procedures** | Transesophageal echocardiography<br><br>Blood samples: 30 to 60mins before the procedure, immediately after, 180 to 240mins after the procedure[b] |
| **Outcomes and effect estimates** | The mean time (±SD) of introducing the endoscope into the oesophagus was 50.1(±64.8)secs, the insertion time was less than 30sec in n = 61 procedures, 30 to 60sec in n = 52 procedures, and >60sec in n = 22 procedures<br>The mean procedure time was 10.2(±4.3)mins<br><br>*Prevalence of bacteraemia:*<br>Baseline (pre-): 3/270 (1.1%); immediately after = 0/270 (0%); 180 to 240 min after = 1/270 (0.4%) |

| Bibliographic reference [from CG64] | Shyu K-G, Hwang J-J, Lin S-C, Tzou S-S, Cheng J-J, Kuan P et al. Prospective study of blood culture during transesophageal echocardiography. American Heart Journal 1992;124:1541-4. Ref ID: 3820 |
|---|---|
| | Blood cultures [a]<br>n = 3/270 pre-echocardiographic cultures were positive, the n = 3 patients were asymptomatic and subsequent cultures were negative<br><br>None of the blood samples obtained immediately after the procedure was positive<br><br>n = 2/270 cultures from n = 1 patient 4hrs after the procedure were positive<br><br>No evidence of endocarditis was subsequently found in these patients and the positive cultures were considered to be transient bacteraemia, no positive blood samples were obtained in n = 21 patients with prosthetic valves<br><br>Throat swabs<br>n = 135 throat swabs, the majority of isolated microorganisms were Neisseria species and Streptococcus viridans, these are normal flora of the oral cavity. The microorganisms isolated from blood cultures were different to those isolated from the throat swab (post procedure, Staphylococcus epidermidis) |
| **Analysis used** | Microbiology:<br>blood cultures were incubated at 35˚C for 7days, aerobic culture vials were tested twice on days 1 and 2 and once on days 3 through 7, anaerobic culture vials were tested once on days 1 through 7. Positive vials were subcultured on appropriate media and gram staining was performed |
| **Length of follow-up** | Not reported. |
| **Location** | October 1990 to August 1991, National Taiwan University Hospital |
| **Source of funding** | Not stated |
| **Comments** | |

*(a) The threshold of the growth value indicating a positive result was set at 25 to 30, a change in growth value of >10 to 15 between two consecutive readings was also indicative of a positive result*
*(b) A cotton swab took smear samples from the throat 30 to 60mins before the procedure*

**Table 90**

| Bibliographic reference [from CG64] | Yildirim I, Okur E, Ciragil P, Aral M, Kilic MA, Gul M. Bacteraemia during tonsillectomy. Journal of Laryngology & Otology 2003;117:619-23. Ref ID: 238 |
|---|---|
| **Study type** | Before-and-after study |
| **Aim** | To investigate bacteraemia during tonsillectomy |

| Bibliographic reference [from CG64] | Yildirim I, Okur E, Ciragil P, Aral M, Kilic MA, Gul M. Bacteraemia during tonsillectomy. Journal of Laryngology & Otology 2003;117:619-23. Ref ID: 238 |
|---|---|
| **Patient characteristics** | Inclusion: patients with a history of recurrent episodes of acute tonsillitis or obstructive symptoms due to tonsillar hypertrophy who had been admitted for elective tonsillectomy, randomly classified into two groups, n = 28 male, n = 36 female<br><br>Exclusion: any cardiovascular risk factors, had received antibiotic therapy for at least 20days before the operation |
| **Number of patients** | Total = 64<br><br>n = 33, group I<br>Blood samples: pre-operative (after intubation), early post-operative (within 2mins after tonsillectomy) and post-operative (60mins after tonsillectomy)<br>Tonsillar surface and deep tissue cultures were taken<br><br>n = 31, group II<br>Blood samples: pre-operative (after intubation), post-operative (15 and 60mins after tonsillectomy)<br>Tonsillar surface and deep tissue cultures were taken |
| **Procedures** | Tonsillectomy<br>Blood samples:<br>Group I: pre-operative (after intubation), early post-operative (within 2mins after tonsillectomy) and post-operative (60mins after tonsillectomy)<br>Group II: pre-operative (after intubation), post-operative (15 and 60mins after tonsillectomy) |
| **Outcomes and effect estimates** | Blood cultures<br>Group I: Baseline = 0/33 (0%); 2 min = 9/33 (27.3%); 60 min = 0/33 (0%)<br>Group II: Baseline = 0/31 (0%); 15 min = 2/31 (6.5%); 60 min = 0/31 (0%)<br><br>All of the pre-operative blood cultures were negative<br>Group I, bacterial growth was observed in n = 9/33 (27.3%) blood cultures taken within 2mins of tonsillectomy<br>Group II, bacterial growth was observed in n = 2/31 (6.5%) blood cultures taken within 15mins after tonsillectomy, the difference between the two groups was significant, p=0.027 (organisms identified both groups; E. coli, Staph sureus, H. influenzae, unclassified streptococci, GABHS , Streph viridans, Strep pneumoniae<br><br>The organisms isolated from the tonsillar surface did not always correspond with the organisms isolated from the deep tissue specimens. Staphylococcus aureus was the most commonly grown organism in the core of the tonsillar tissue and/or surface culture (n = 18), followed by GABHS (n = 14), Haemophilus influenzae (n = 11) and Streptococcus pneumoniae (n = 10)<br><br>The patients with bacteraemia did not have any clinical signs and/or symptoms of a serious infection and were discharged |

| Bibliographic reference [from CG64] | **Yildirim I, Okur E, Ciragil P, Aral M, Kilic MA, Gul M. Bacteraemia during tonsillectomy. Journal of Laryngology & Otology 2003;117:619-23. Ref ID: 238** |
|---|---|
| | without hospitals. |
| **Analysis used** | Microbiology:<br>6ml (those under 10yrs), 16-18ml )those >10yrs), half of the samples inoculated into an aerobic culture bottle, half into an anaerobic culture bottle, blood culture bottles were incubated within the Bactec 9050 automatic blood culture system, routine bacteriological inoculations were performed from the bottles in which bacterial growth took place, aerobic microorganisms were identified by standard lab methods, anaerobic were identified by using OXOID An-identdiscs |
| **Length of follow-up** | Not reported |
| **Location** | Turkey |
| **Source of funding** | Kahramanmaras Sutcu University Research Fund |
| **Comments** | |

1 **Table 91**

| Bibliographic reference [from CG64] | **Zuccaro G, Jr., Richter JE, Rice TW, Achkar E, Easley K, Lewis J et al. Viridans streptococcal bacteremia after esophageal stricture dilation.[see comment]. Gastrointestinal Endoscopy 1998;48:568-73.**<br>**Ref ID: 5981** |
|---|---|
| **Study type** | Cohort study |
| **Aim** | To determine the frequency and duration of bacteraemia associated with esophageal stricture dilation. |
| **Patient characteristics** | Inclusion: consecutive patients with dysphagia presenting for upper endoscopy and stricture dilation, without valvular[a] disease . Patients, n = 73 male, n = 30 female; controls, n = 32 male, n = 18 female<br><br>Exclusion: <18yrs old, received antibiotics within 2wks before the procedure, anaemic |
| **Number of patients** | Total = 153 patients<br>n = 103 with dysphagia having upper endoscopy and stricture dilation<br>n = 50 control, without dysphagia or oesophageal disease undergoing upper endoscopy for reasons unrelated to swallowing disorders |
| **Procedures** | Esophageal stricture dilation<br><br>Blood samples: pre-procedure, 5, 20 and 30mins after the procedure |
| **Outcomes and effect estimates** | *Prevalence of bacteraemia (viridans streptococcus):*<br>Baseline (before) = 0/103 (0%); 1 min = 19/81 (23%); 5 min = 16/96 (17%); 20-30 min = 3/63 (5%) |

| Bibliographic reference [from CG64] | **Zuccaro G, Jr., Richter JE, Rice TW, Achkar E, Easley K, Lewis J et al. Viridans streptococcal bacteremia after esophageal stricture dilation.[see comment]. Gastrointestinal Endoscopy 1998;48:568-73.**<br>**Ref ID: 5981** |
|---|---|
| | All blood cultures performed before the procedure were negative.<br>Viridans streptococcal bacteraemia occurred in n = 22/103 (21.4%; 13.4 to 29.3%, 95%CI) after stricture dilation, compared with n = 1/50 (2%; 0.06 to 10.7%, 95%CI) control patients, p=0.001<br><br>n = 19/81 (23%) blood cultures obtained 1min after stricture dilation were positive for viridans streptococcus, compared with n = 16/96 (17%) obtained 5min after dilation, and n = 3/63 (5%) obtained 20 to 30min after dilation<br><br>Of the n = 19 bacteraemic patients at 1min, n = 14/19 (74%) were still bacteraemic at 5min and n = 2/19 were still bacteraemic at 20 to 30mins<br><br>Benign strictures were dilated in n = 80 and malignant in n = 15, of the n = 103 patients n = 96 underwent endoscopy immediately before dilation<br>Time after dilation:<br>1min; n = 81 blood cultures obtained; n = 24 positive cultures; organisms cultured, viridans streptococcus (n = 19), coagulase negative staph (n = 3), neisseria species (n = 3), diptheroids (n = 2), other (n = 3)<br>5min; n = 96 blood cultures obtained; n = 17 positive cultures; organisms cultured, viridans streptococcus (n = 16), coagulase negative staph (n = 3), neisseria species (n = 1), diptheroids (n = 1)<br>20to30min; n = 63 blood cultures obtained; n = 4 positive cultures; organisms cultured, viridans streptococcus (n = 3), coagulase negative staph (n = 1)<br><br>Stricture diameter<br>Stricture diameter before dilation appeared to be the single most predictive factor for viridans streptococcal bacteraemia, n = 13/96 had strictures which precluded passage of the endoscope before dilation of these bacteraemia occurred in N/13 (62%), the other n = 83/96 had strictures which allowed the passage of the endoscope before dilation of these n = 12/83 (14%); p=0.001, OR 9.5 (2.7 to 33.8, 95%CI)<br><br>There was NS difference in the rate of viridans streptococcal bacteraemia among patients with benign versus malignant strictures, passage of single versus multiple dilators, presence or absence of oesophagitis, use of antisecretory therapy, or the presence or absence of periodontal disease<br><br>No patients experienced fever, chills, or other symptoms/signs of clinically significant bacteraemia in the recovery room. All those with bacteraemia were follow-up by telephone and no adverse events related to transient bacteraemia were reported |
| **Analysis used** | Microbiology: 20ml sample, 10ml inoculated into commercially prepared blood culture bottles, the bottles were then incubated |

| | |
|---|---|
| **Bibliographic reference [from CG64]** | **Zuccaro G, Jr., Richter JE, Rice TW, Achkar E, Easley K, Lewis J et al. Viridans streptococcal bacteremia after esophageal stricture dilation.[see comment]. Gastrointestinal Endoscopy 1998;48:568-73.**<br>**Ref ID: 5981** |
| | for 5days ion the BacT/Alert instrument, when a blood culture bottle became positive by the BacT/Alert signal or growth on the subculture plate it was removed from the BacT/Alert and a gram stain performed |
| **Length of follow-up** | 9mth study period |
| **Location** | USA |
| **Source of funding** | Not stated |
| **Comments** | |

1

2 **Upper and lower GI tract – colorectal procedures**

3 **Table 92**

| | |
|---|---|
| **Bibliographic reference** | **Min (2008), ID: 617**<br>**Low frequency of bacteraemia after an endoscopic resection for large colorectal tumours in spite of extensive submucosal exposure.** |
| **Study type** | Before-and-after study |
| **Aim** | To evaluate the frequency of bacteraemia associated with an EMR or ESD for colon lesions |
| **Patient characteristics** | *Inclusion criteria:*<br>• adult patients admitted for endoscopic resection of colonic adenoma or adenocarcinoma.<br>*Exclusion criteria:*<br>• indications for antibiotic prophylaxis as determined by the American Society for Gastrointestinal Endoscopy or European Society for Gastrointestinal Endoscopy guidelines<br>• antibiotic use within 1 week before the procedure<br>• possible signs of any infection at the time of the procedure (body temperature >37C, heart rate >90 beats/min, or respiratory rate >20 breaths/min), and an inability to get informed consent. |
| **Number of patients** | Total = 40 (conventional EMR = 30; EMR-P = 3; ESD = 7)<br>Gender: 28 males; 12 females<br>Median age of 60.0 years old (range 44 to 80 years old) |
| **Procedures** | Endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD)<br><br>Blood cultures were obtained immediately before, 5 minutes after, and 30 minutes after the procedure. |

| Bibliographic reference | **Min (2008), ID: 617**<br>**Low frequency of bacteraemia after an endoscopic resection for large colorectal tumours in spite of extensive submucosal exposure.** |
|---|---|
| **Outcomes and effect estimates** | *Prevalence of bacteraemia:*<br>Baseline = 0/40 (0%); 5 min = 0/40 (0%); 30 min = 1/40 (2.5%)<br><br>*Individual bacteria identified:*<br>Coagulase-negative *Staphylococcus*. |
| **Analysis used** | To ensure accurate timing of the blood cultures, a 20-gauge angiocatheter was placed in a vein in the antecubital space before the procedure and was used for blood sampling.<br>20 ml of blood were collected through this catheter and then equally distributed into commercially available aerobic/anaerobic blood culture bottles. Before the second and the third blood cultures, the angiocatheter was flushed with sterile non-bacteristatic 0.9% sodium chloride solution.<br>For the second and third blood cultures, an initial 5 ml of blood was collected and discarded. After that, another 20 ml was collected and then equally distributed into culture bottles. All samples were incubated for 5 days. |
| **Length of follow-up** | 5 days incubation. |
| **Location** | Between October 2006 and March 2007, Samsung Medical Centre, Korea. |
| **Source of funding** | Study support by a grant from the In-Sung Foundation for Medical Research (CA68461). |
| **Comments** | |

1 **Table 93**

| Bibliographic reference | **Chun (2012), ID: 238**<br>**Prospective Assessment of Risk of Bacteraemia Following Colorectal Stent Placement.** |
|---|---|
| **Study type** | Before-and-after study |
| **Aim** | To evaluate the risk of bacteraemia and infectious complications after stent insertion for colorectal obstruction. |
| **Patient characteristics** | *Inclusion criteria:*<br>• adult patients with colorectal obstruction who needed stent insertion.<br>*Exclusion criteria:*<br>• those with conditions for which ASGE guidelines recommend antibiotic prophylaxis<br>• antibiotic use within 1 week before the anticipated procedure<br>• body temperature >38C<br>• bleeding tendency, and declined participation or inability to give informed consent. |
| **Number of patients** | Total = 64<br>Gender: 35 males; 29 females |

| Bibliographic reference | **Chun (2012), ID: 238**<br>**Prospective Assessment of Risk of Bacteraemia Following Colorectal Stent Placement.** |
|---|---|
| | Mean age: 68.8 years old (SD: 10.8) |
| **Procedures** | Colorectal stent placement.<br><br>The first set of blood sample was taken immediately before the procedure, and the second set was taken 30 min after colorectal stent insertion. |
| **Outcomes and effect estimates** | *Prevalence of bacteraemia:*<br>Baseline = 0/64 (0%); 30 min = 4/64 (6%)<br><br>*Individual bacteria identified:*<br>*Bacteroides fragilis*<br>*Escherichia coli*<br>*Klebsiella spp.* |
| **Analysis used** | The skin site was cleaned with 70% isopropyl alcohol solution and air-dried for 30 s. The area was then cleaned with 10% povidone-iodine solution for 60 s and allowed to air-dry for another 60 s. The 20-gauge angiocatheter then was inserted. Two sets of blood cultures were obtained.<br>Before the second blood culture, the angiocatheter was flushed with sterile non-bacteriostatic 0.9% sodium chloride solution.<br>20 ml of blood was collected through the indwelling angiocatheter and then equally distributed into aerobic/anaerobic culture media sets. Cultures were observed for 5 days. |
| **Length of follow-up** | 5 days incubation. |
| **Location** | Between May 2009 and April 2011, Seoul St. Mary's Hospital, Korea. |
| **Source of funding** | Not reported. |
| **Comments** | |

1 **Table 94**

| **Bibliographic reference [from CG64]** | **Weickert U, Vetter S, Burkhardt U, Eickhoff A, Buhl A, Riemann JF. Bacteremia after diagnostic conventional laparoscopy and minilaparoscopy: a prospective study in 100 patients. Journal of Clinical Gastroenterology 2006;40:701-4. Ref ID: 42** |
|---|---|
| **Study type** | Before-and-after study |
| **Aim** | To investigate bacteraemia rates caused by conventional diagnostic laparoscopy. |
| **Patient characteristics** | Inclusion: patients having undergone diagnostic laparoscopy, mean age 53.5yrs(range 19 to 81yrs), n = 59 male, n = 41 female<br><br>Exclusion: <18yrs, fever or other signs of infection with 14days before laparoscopy, antibiotics within 14days before laparoscopy, conditions for which current guidelines recommend antibiotic prophylaxis, immunosuppressant therapy |

| | |
|---|---|
| **Bibliographic reference [from CG64]** | **Weickert U, Vetter S, Burkhardt U, Eickhoff A, Buhl A, Riemann JF. Bacteremia after diagnostic conventional laparoscopy and minilaparoscopy: a prospective study in 100 patients. Journal of Clinical Gastroenterology 2006;40:701-4. Ref ID: 42** |
| **Number of patients** | Total = 100 patients<br>n = 50 (convention laparoscopy); n = 50 (mini-laparoscopy) |
| **Procedures** | Conventional laparoscopy and mimi-laparoscopy<br><br>Blood samples: immediately before laproscopy and within 5mins after the procedure |
| **Outcomes and effect estimates** | *Prevalence of bacteraemia:*<br>Baseline (before): 0/100 (0%); 5 min after = 4/100 (4%)<br>There was no bacterial growth in 100 blood cultures drawn before laparoscopy, bacterial growth occurred in n = 4 blood cultures taken immediately after laparoscopy, all bacteria found were gram-positive<br><br>No difference was found between patients with and without positive blood cultures, none of the patients developed fever or other signs of infection in the follow-up, n = 1 patient received oral antibiotics for 5 days |
| **Analysis used** | Microbiology:<br>20ml sample, kept in commercially available aerobic/anaerobic blood culture bottles (BD Bactec 9000 system), blood cultures were incubated at 35˚C for 7days |
| **Length of follow-up** | 7 days incubation |
| **Location** | Germany |
| **Source of funding** | Not stated |
| **Comments** | |

1 **Table 95**

| | |
|---|---|
| **Bibliographic reference [from CG64]** | **Kullman E, Borch K, Lindstrom E, et al. (1992) Bacteremia following diagnostic and therapeutic ERCP. Gastrointestinal Endoscopy 38: 444–49. Ref ID: 10028** |
| **Study type** | Before-and-after study |
| **Aim** | To investigate the level of bacteraemia following diagnostic and therapeutic ERCP. |
| **Patient characteristics** | Inclusion: median age 66 yrs (range 26–92 yrs), n = 104 female, n = 76 male<br><br>Exclusion: those with signs of localised or general infection, antibiotic treatment with the preceding 7 days, treatment with corticosteroids or other immunosuppressive drugs, history or signs of endocarditis or valvular heart disease |

| Bibliographic reference [from CG64] | **Kullman E, Borch K, Lindstrom E, et al. (1992) Bacteremia following diagnostic and therapeutic ERCP. Gastrointestinal Endoscopy 38: 444–49. Ref ID: 10028** |
|---|---|
| **Number of patients** | Total = 180 patients (n = 194 examinations)<br>Diagnostic ERCP n = 115 participants (n = 126 procedures)<br>Therapeutic ERCP n = 65 participants (n = 68 procedures) |
| **Procedures** | Diagnostic and therapeutic ERCP<br><br>Blood samples: before the examination, 5min after cannulation and at 5 and 15 min after the end of examination. |
| **Outcomes and effect estimates** | *Prevalence of bacteraemia:*<br>Diagnostic ERCP:<br>Baseline (before) = 1/126 (0.8%); during = 10/126 (7.9%); after 5 min =12/126 (9.5%); after 15 min = 14/126 (11.1%)<br>Therapeutic ERCP:<br>Baseline (before) = 0/68 (0%); during = 10/68 (14.7%); after 5 min =10/68 (14.7%); after 15 min = 13/68 (19.1)<br><br>Overall:<br>n = 19/126 (15%) of diagnostic procedures and n = 18/68 (27%) of therapeutic procedures were associated with bacteraemia during and/or within 15min after the endoscopy, NS between the groups<br><br>There was NS difference in the frequency of bacteraemia between diagnostic ERCP and biliary manometry or between endoscopic sphincterotomy and endoprosthesis<br><br>Of the n = 37 bacteraemic patients, n = 9 had polymicrobial bacteraemia with 16 detected groups of microorganisms. Different Streptococci, mainly α-haemolytic, were the most common, they were identified in n = 14(38%) of the bacteraemic patients either alone or with other species<br><br>There was no correlation between the occurrence of bacteraemia and the age of participants or the duration of the endoscopic procedure<br><br>During follow-up for 4 to 26mths of bacteraemic patients none developed clinically overt endocarditis<br><br>There was no correlation of bacteraemia with subsequent fever, pancreatitis, or sepsis in patients with partial or complete obstruction of the pancreaticobiliary system due to stones, strictures or cancer |
| **Analysis used** | Microbiology:<br>A 2-phase blood culture system, one aerobic and one anaerobic flask was inoculated with 4ml of blood and each incubated at |

| Bibliographic reference [from CG64] | **Kullman E, Borch K, Lindstrom E, et al. (1992) Bacteremia following diagnostic and therapeutic ERCP. Gastrointestinal Endoscopy 38: 444–49. Ref ID: 10028** |
|---|---|
| | 37˚C, the flasks were inspected for bacterial growth twice daily for 2 days and then once daily for an additional 8days. When growth was observed or suspected a gram stain was done. Subcultures were performed on blood-agar, hematin-agar and anaerobic blood-agar plates, which were incubated at 37˚C in air, carbon dioxide and in an anaerobic box |
| **Length of follow-up** | 4 to 6 months |
| **Location** | University Hospital, Sweden |
| **Source of funding** | Not stated |
| **Comments** | |

1 **Table 96**

| Bibliographic reference [from CG64] | **London MT, Chapman BA, Faoagali JL, Cook HB. Colonoscopy and bacteraemia: an experience in 50 patients. New Zealand Medical Journal 1986;99:269-71. Ref ID: 952** |
|---|---|
| **Study type** | Before-and-after study |
| **Aim** | To investigate the incidence of bacteraemia during colonoscopy. |
| **Patient characteristics** | Inclusion: patients undergoing colonoscopy, n = 24 males, n = 26 females, mean age 58.8yrs (range 22 to 80yrs)<br><br>Exclusion: patients with evidence of infection or who had taken antibiotics in the previous 2 weeks<br><br>Biopsies, often multiple were taken from n = 26 patients, n = 19 had neither a biopsy or a polypectomy<br><br>n = 45 were prepared for colonoscopy by a whole gut lavage usually 8 litres of an isotonic solution, n = 5 were prepared with soap and water enemas |
| **Number of patients** | Total = 50 (204 blood samples) |
| **Procedure** | Colonoscopy<br><br>Blood sample: before insertion (baseline); 5 min after insertion; 5 min after removal |
| **Outcomes and effects estimates** | Blood cultures<br>Baseline =<br>n = 204 blood cultures from n = 50 patients, n = 6 positive blood cultures from n = 5 patients (n = 2 patients had samples positive prior to colonoscopy not from later samples)<br>In n = 2 patients the positive culture was considered to be directly related to the colonoscopy, the blood samples were collected at the limit of insertion of the colonoscope and were for Bacteroides fragilis and Bacillus sp. (these n = 2 patients were from the n = 7 group with carcinoma of the colon) |

| | |
|---|---|
| **Bibliographic reference [from CG64]** | **London MT, Chapman BA, Faoagali JL, Cook HB. Colonoscopy and bacteraemia: an experience in 50 patients. New Zealand Medical Journal 1986;99:269-71. Ref ID: 952** |
| | Positive blood cultures were in n = 4/45 patients who had whole gut lavage and in n = 1/5 who had an enema |
| **Analysis used** | Blood cultures<br><br>Microbiology: 7-10ml was inoculated into 40ml BBL(vacutainer) supplemented broth, cultures were incubated at 30˚C for 3wks and examined daily, aerobic and anaerobic subcultures were made at 24hrs, 6days, 14days and 21days and the cultures identified |
| **Length of follow-up** | Not reported |
| **Location** | New Zealand |
| **Source of funding** | Not stated |
| **Comments** | |

1

# G.52 Review question 5

3 **Table 97**

| | |
|---|---|
| **Bibliographic reference** | **Lucas,VS., Gafan, G., Dewhurst, S., Roberts, GJ. (2008). Prevalence, intensity and nature of bacteraemia after toothbrushing. Journal of Dentistry. 36: 481-487** |
| **Study type** | RCT*<br><br>*randomisation performed using random number table |
| **Aim** | To estimate the prevalence, intensity and microbial identity of bacteraemia associated with toothbrushing |
| **Patient characteristics** | <u>Inclusion criteria</u><br>- Children and adolescents aged between 3 and 17 years, having dental treatment (extractions only) under general anaesthesia at the Eastman Dental Hospital<br><br><u>Exclusion criteria</u><br>- Weight less than 17.5kg<br>- The use of antibiotics within the preceding month because of changes in the oral flora<br>- Medical condition requiring antibiotic prophylaxis eg: cardiac anomalies<br>- Systemic disease eg: insulin dependent diabetes<br>- Known cases of HIV and hepatitis because changes in the oral flora |

<table>
<tr><td>Bibliographic reference</td><td>Lucas,VS., Gafan, G., Dewhurst, S., Roberts, GJ. (2008). Prevalence, intensity and nature of bacteraemia after toothbrushing. Journal of Dentistry. 36: 481-487</td></tr>
<tr><td></td><td>- Poor veins<br><br><u>Other characteristics</u><br>- Mean age (SD): 7.9 years (3.3), range: 3.2 to 17.3 years<br>- Gender: 85 boys (60%), 56 girls (40%)</td></tr>
<tr><td>Number of patients</td><td>N=141 included from a total sample of 183 (exclusion reasons included failed venepuncture, refusal to participate, change in treatment plan or unfit for general anaesthesia)<br><br>Subjects randomised to the following toothbrushing groups:<br><br>1. Manual Oral B 30: n=32<br>2. Braun electric (rotary movement): n=35<br>3. Sonicare (oscillating movement): n=33<br>4. Dental handpiece and rubber cup: n=41</td></tr>
<tr><td>Outcomes</td><td>3. Bacteraemia levels/intensity/bacterial counts per uni volume at one or more timepoints following the everyday activity – reported in study as intensity of bacteraemia, recorded as the number of colony forming units of bacteria per millilitre of blood (cfu/ml)<br>4. Duration of bacteraemia following everyday activity – not reported in study<br>5. Number/incidence/odds of having positive blood samples before and after everyday activity – reported in study as the prevalence of bacteraemia in each group, recorded as the number of positive blood cultures and expressed as the percentage prevalence</td></tr>
<tr><td>Predictors/risk factors and effect estimates</td><td><u>Predictor of interest to this question</u><br>- Toothbrushing (for 1 minute)- carried out as an isolated procedure before any extractions, thus removing the potential for confounding bacteraemia from other procedures<br><br><u>Effect estimates</u><br>1. Bacteraemia levels/intensity at one or more timepoints following the procedure – reported in study as intensity of bacteraemia, recorded as the number of colony forming units of bacteria per millilitre of blood (cfu/ml)
<table>
<tr><th colspan="10">Aerobic intensity of detectable bacteraemia (cfu/ml blood)</th></tr>
<tr><th colspan="5">Baseline</th><th colspan="5">30 seconds after toothbrushing</th></tr>
<tr><th></th><th>Mean</th><th>SD</th><th>Median</th><th>Range</th><th>Mean</th><th>SD</th><th>Median</th><th>Range</th><th>Significance, p</th></tr>
<tr><td>Oral B 30</td><td>0.05</td><td>0.21</td><td>0</td><td>0 to 1.17</td><td>0.39</td><td>1.34</td><td>0</td><td>0 to 0.67</td><td>>0.05</td></tr>
</table></td></tr>
</table>

| Bibliographic reference | Lucas,VS., Gafan, G., Dewhurst, S., Roberts, GJ. (2008). Prevalence, intensity and nature of bacteraemia after toothbrushing. Journal of Dentistry. 36: 481-487 |
|---|---|

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| (n=32) | | | | | | | | | |
| Braun electric (n=35) | 0.05 | 0.11 | 0 | 0 to 0.50 | 0.28 | 1.15 | 0 | 0 to 6.83 | >0.05 |
| Sonicare electric (n=33) | 0.02 | 0.06 | 0 | 0 to 0.17 | 0.51 | 2.35 | 0 | 0 to 13.3 | **0.03** |
| Dental handpiece and rubber cap (n=41) | 0.02 | 0.07 | 0 | 0 to 0.3 | 1.00 | 3.10 | 0 | 0 to 15.2 | **0.001** |

| **Anaerobic intensity of detectable bacteraemia (cfu/ml blood)** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Baseline | | | | 30 seconds after toothbrushing | | | | |
| | Mean | SD | Median | Range | Mean | SD | Median | Range | Significance, p |
| Oral B 30 (n=32) | 0.01 | 0.04 | 0 | 0 to 0.17 | 0.46 | 1.8 | 0 | 0 to 8.83 | >0.05 |
| Braun electric (n=35) | 0.02 | 0.07 | 0 | 0 to 0.33 | 0.11 | 0.43 | 0 | 0 to 2.50 | >0.05 |
| Sonicare electric (n=33) | 0.04 | 0.10 | 0 | 0 to 0.50 | 0.79 | 3.68 | 0 | 0 to 20.83 | >0.05 |
| Dental handpiece and rubber cap (n=41) | 0.008 | 0.04 | 0 | 0 to 0.17 | 0.94 | 2.87 | 0 | 0 to 13.83 | **0.005** |

2. **Duration of bacteraemia following everyday activity** – not reported in study

<table>
<tr><td>Bibliographic reference</td><td>Lucas,VS., Gafan, G., Dewhurst, S., Roberts, GJ. (2008). Prevalence, intensity and nature of bacteraemia after toothbrushing. Journal of Dentistry. 36: 481-487</td></tr>
<tr><td></td><td>3. Number/incidence/odds of having positive blood samples before and after everyday activity – reported in study as the prevalence of bacteraemia in each group, recorded as the number of positive blood cultures and expressed as the percentage prevalence
<table>
<tr><th>Toothbrush</th><th>Baseline</th><th>30 seconds after brushing for 1 minute</th><th>Significance</th></tr>
<tr><td>Oral B 30</td><td>7 (22%)</td><td>6 (19%)</td><td>ns</td></tr>
<tr><td>Braun electric</td><td>9 (26%)</td><td>12 (34%)</td><td>ns</td></tr>
<tr><td>Sonicare electric</td><td>9 (27%)</td><td>11 (33%)</td><td>ns</td></tr>
<tr><td>Dental handpiece and rubber cap</td><td>6 (15%)</td><td>15 (37%)</td><td>p=0.02</td></tr>
</table></td></tr>
<tr><td>Analysis used</td><td>1. All data were tested for normality using the Shapiro-Wilk test and found to be not normally distributed<br>2. Categorical data were analysed using the McNemar test<br>Continuous variables were analysed using the Wilcoxon Rank Sum Test</td></tr>
<tr><td>Length of follow-up</td><td>Measurements taken at baseline and 30 seconds after toothbrushing</td></tr>
<tr><td>Location</td><td>UK (London)</td></tr>
<tr><td>Source of funding</td><td>Not reported</td></tr>
<tr><td>Comments</td><td><u>Clinical procedure and microbiological assessment of bacteraemia</u><br>- Following induction of general anaesthesia, either a laryngeal mask (n=138) or nasotracheal intubation (n=3) was used<br>- The first 0.5ml of blood withdrawn through the cannula was discarded to void any skin contaminants<br>- 6ml of blood was taken before toothbrushing (baseline) for each group of subjects.<br>- A second 6ml sample was taken 30 seconds after toothbrushing<br>- All blood samples processed in a laminar flow cabinet within 1 hour of collection. Blood and sodium polyanethol sulphonate (SPS) added to lysing solution.<br>- Sample divided into two equal volumes –each inoculated onto Brain Heart Infusion Agar, one plate incubated aerobically and the other anaerobically for 10 days.<br>- From day 3, each filter checked daily for bacterial growth using a stereo microscope.<br>- For each batch of blood samples, two separate blank filters were placed onto infusion agar.<br>- Bacteria characterised initially by gram staining. Bacterial colonies were subjected to Catalase and Oxidase testing and presumptive Staphylococcus spp. and Streptococcus spp. to a coagulase test.<br>- Bacterial colonies further identified using commercial carbohydrate fermentation and enzyme hydrolysis tests.</td></tr>
</table>

| Bibliographic reference | Lucas,VS., Gafan, G., Dewhurst, S., Roberts, GJ. (2008). Prevalence, intensity and nature of bacteraemia after toothbrushing. Journal of Dentistry. 36: 481-487 |
|---|---|
| | Microbial identity of organisms identified in study<br>- Oral Streptococcus spp. comprised 2 and 15% at baseline and 30 seconds after toothbrushing respectively.<br>- Coagulase negative Staphylococcus spp. comprised 12 and 24% at baseline and after toothbrushing respectively<br>- Other bacteria included Lactobacillus spp, Actinomyces spp, Neisseria spp. and Micrococcus spp<br>- No obligate anaerobes were detected<br><br>Study limitations: assessed using checklist for prognostic studies from Hayden et al., 2006<br>- Study participation: period of recruitment not reported, sample size calculation not reported, highly selected population with pre-existing dental disease<br>- Study attrition: no major limitations<br>- Prognostic factor measurement: details of toothbrushing intervention not reported eg: whether it was performed by one or more investigators and whether standardised procedures were used or not.<br>- Outcome measurement: no major limitations, outcomes well defined, raw data not reported for all outcomes therefore no further analyses possible in some cases.<br>- Confounding measurement and account: no major limitations, toothbrushing carried out as an isolated procedure before any extractions, thus removing potential for confounding bacteraemia from other procedures, blood samples processed within one hour of collection.<br>- Analysis: no major limitations, methods described. |

1 **Table 98**

| Bibliographic reference | Lockhart, PB., Brennan, MT., Sasser, HC., Fox, PC., Paster, BJ., Bahrani-Mougeot, FK. (2008). Bacteremia associated with toothbrushing and dental extraction. Circulation. 117: 3118-3125 |
|---|---|
| Study type | Double blind randomised* controlled trial<br>*randomly assigned using computer-generated list with a block size of 12 to 1 of 3 interventions |
| Aim | To compare the incidence, duration, nature and magnitude of endocarditis-related bacteremia from single-tooth extraction and toothbrushing and to determine the impact of amoxicillin prophylaxis on single tooth extraction |
| Patient characteristics | Inclusion criteria<br>- Patients presenting to urgent care service with the need for extraction of at least 1 erupted tooth<br>Exclusion criteria<br>- Fewer than 10 teeth<br>- Use of systemic antibiotics within the previous 2 weeks<br>- Need for antibiotic prophylaxis based on current practice guidelines |

| Bibliographic reference | Lockhart, PB., Brennan, MT., Sasser, HC., Fox, PC., Paster, BJ., Bahrani-Mougeot, FK. (2008). Bacteremia associated with toothbrushing and dental extraction. Circulation. 117: 3118-3125 |
|---|---|
| | - Active viral disease<br>- Immunocompromised<br>- Poorly controlled systemic disease<br>- History of penicillin allergy<br>- Temperature >100.5F<br>- Facial cellulitis<br>- Manipulation of the gingival tissues (eg: chewing, toothbrushing) within one hour before the study<br><br><u>Other characteristics</u><br>1. Age in years, mean (SD)<br>Brushing group: 39.7 (11.7)<br>Extraction-amoxicillin group: 39.7 (10.5)<br>Extraction-placebo group: 40.5 (10.9)<br><br>2. Male, n (%)<br>Brushing group: 55 (56)<br>Extraction-amoxicillin group: 61 (64)<br>Extraction-placebo group: 51 (53)<br><br>3. Ethnicity, n (%)<br>Brushing group: white – 27 (28), black – 68 (69), Hispanic – 2 (2), Other – 1 (1)<br>Extraction-amoxicillin group: white – 18 (19), black – 73 (76), Hispanic – 3 (3), Other – 2(2)<br>Extraction-placebo group: white – 23 (24), black- 73 (76), Hispanic – 1 (1), Other – 0 (0)<br><br>4. Diabetes, n (%)<br>Brushing group: 5 (5)<br>Extraction-amoxicillin group: 9 (9)<br>Extraction-placebo group: 8 (8)<br><br>5. Surgery type, n (%)<br>Brushing group: -<br>Extraction-amoxicillin group: simple – 83 (87), complex – 9 (9), missing – 4 (4)<br>Extraction-placebo group: simple – 70 (73), complex – 18 (19), missing – 8 (8) |

<table>
<tr><td>Bibliographic reference</td><td>Lockhart, PB., Brennan, MT., Sasser, HC., Fox, PC., Paster, BJ., Bahrani-Mougeot, FK. (2008). Bacteremia associated with toothbrushing and dental extraction. Circulation. 117: 3118-3125</td></tr>
<tr><td></td><td></td></tr>
<tr><td>Number of patients</td><td>N=290<br>Subjects randomised to the following groups:<br>1. Toothbrushing n=98<br>2. Single tooth extraction with amoxicillin prophylaxis n=96<br>3. Single tooth extraction with an identical placebo (placebo not defined) n=96<br><br>Power calculation: assuming a significance level of 0.05, 80 subjects per study arm would yield power of 90% to detect a difference in cumulative incidences of at least 20% (prior work suggested that the incidence of bacteraemia from single tooth extraction would range between 70% and 100%. No consenus available on incidence after toothbrushing).</td></tr>
<tr><td>Outcomes</td><td>1. Bacteraemia levels/intensity/bacterial counts per unit volume at one or more timepoints following the everyday activity – reported in study as magnitude of bacteraemia<br>2. Duration of bacteraemia following everyday activity – reported in study as a) overall duration of bacteraemia b) duration of bacteraemia from endocarditis-related bacterial species<br>3. Number/incidence/odds of having positive blood samples before and after everyday activity – reported in study as a) overall incidence of bacteraemia at any of the 6 draws b) overall incidence of bacteraemia at the time of the procedures and c) incidence of bacteraemia from endocarditis related bacterial species</td></tr>
<tr><td>Predictors/risk factors and effect estimates</td><td><u>Predictor of interest to this question</u><br>- Toothbrushing: brushing arm subjects brushed all surfaces of the teeth adjacent to the gingiva with a new toothbrush without toothpaste for 2 minutes, timed as 30 seconds for each of the maxillary and mandibular quadrants of teeth. Subjects randomised to the brushing group had their dental extraction accomplished at the end of study period, after the last blood straw or on a subsequent visit (hence, no potential for confounding of bacteremia from other procedures)<br><br><u>Effect estimates</u><br>1. Bacteraemia levels/intensity/bacterial counts per unit volume at one or more timepoints following the everyday activity/procedure – reported in study as magnitude of bacteraemia – all analysed samples were below the detection threshold of $10^4$ CFU per millilitre of blood<br>2. Duration of bacteraemia following everyday activity/procedure – reported in study as a) overall duration of bacteraemia b) duration of bacteraemia from endocarditis-related bacterial species<br><br>
<table>
<tr><th colspan="3">f) overall duration of bacteraemia</th></tr>
<tr><td></td><td>Number of subjects (%) bacteraemic at 40 minutes after activity/procedure</td><td>Number of subjects (%) bacteraemic at 60 minutes after activity/procedure</td></tr>
</table>
</td></tr>
</table>

| Bibliographic reference | Lockhart, PB., Brennan, MT., Sasser, HC., Fox, PC., Paster, BJ., Bahrani-Mougeot, FK. (2008). Bacteremia associated with toothbrushing and dental extraction. Circulation. 117: 3118-3125 |
|---|---|

| | | |
|---|---|---|
| Toothbrushing group | - | 9 (9) |
| Extraction-amoxicillin group | 2 (2) | - |
| Extraction-placebo group | - | 2 (2) |

| **g) duration of bacteraemia from endocarditis-related bacterial species** | |
|---|---|
| | Number of subjects (%) bacteraemic at 60 minutes after activity/procedure |
| Toothbrushing group | 2 (2) |
| Extraction-amoxicillin group | - |
| Extraction-placebo group | 5 (5) |

**3. Number/incidence/odds of having positive blood samples before and after everyday activity –** reported in study as a) overall incidence of bacteraemia at any of the 6 draws b) overall incidence of bacteraemia at the time of the procedures and c) incidence of bacteraemia from endocarditis related bacterial species

| **c) overall incidence of bacteraemia* at any of the 6 draws** | |
|---|---|
| Toothbrushing group | 32% |
| Extraction-amoxicillin group | 56% |
| Extraction-placebo group | 80% |
| $x^2$ | p<0.0001 |

| **d) overall incidence of bacteraemia* at the time of the procedures** | |
|---|---|
| Toothbrushing group | 28% |
| Extraction-amoxicillin group | 56% |
| Extraction-placebo group | 79% |
| $x^2$ | Not reported |

*'All baseline blood cultures were negative with the exception of 3 instances, likely from skin contamination eg: Staphylococcus epidermis'

| **h) cumulative incidence of bacteraemia** from endocarditis related bacterial species from all 6 blood draws** |
|---|

| Bibliographic reference | **Lockhart, PB., Brennan, MT., Sasser, HC., Fox, PC., Paster, BJ., Bahrani-Mougeot, FK. (2008). Bacteremia associated with toothbrushing and dental extraction. Circulation. 117: 3118-3125** |
|---|---|

| | |
|---|---|
| Toothbrushing group | 23% |
| Extraction-amoxicillin group | 33% |
| Extraction-placebo group | 60% |
| $X^2$ | p<0.0001 |

| **i) incidence of positive cultures** from endocarditis related bacterial species in the first 5 minutes of activity/procedure*** | |
|---|---|
| Toothbrushing group | 19% |
| Extraction-amoxicillin group | 33% |
| Extraction-placebo group | 58% |
| $X^2$ | p=not reported |

| **j) incidence of positive cultures** from endocarditis related bacterial species at 20 minutes*** | |
|---|---|
| Toothbrushing group | 1% |
| Extraction-amoxicillin group | 1% |
| Extraction-placebo group | 10% |
| $X^2$ | p=0.001 |

**All baseline blood cultures were negative, with the exception of one patients (with 2 species) in the brushing group
***The pattern observed at 20 minutes persisted to 40 minutes (numbers not reported).

| | |
|---|---|
| **Analysis used** | - For analysis of incidence, each patient was assessed at each blood draw and coded as positive for any bacterium that was common to the list of 275 bacterial species reported to cause IE. Comparison by study arm at each blood draw and a summary comparison by study arm that combined all draws were made with Chi square tests.<br>- Duration of bacteraemia was defined as the number of blood draws at which any target organism was cultured.<br>- Intercurrent negative findings were rare (n=2), were judged to be spurious and were considered positive for analysis.<br>- Duration of specific intervals by study arm was compared with $x^2$ tests.<br>- Statistical significance of 0.05 was used in all cases. |
| **Length of follow-up** | 60 minutes after completion of brushing or extraction |
| **Location** | USA |
| **Source of funding** | Supported by National Institute of Dental and Craniofacial Research/National Institutes of Health grant |

| Bibliographic reference | **Lockhart, PB., Brennan, MT., Sasser, HC., Fox, PC., Paster, BJ., Bahrani-Mougeot, FK. (2008). Bacteremia associated with toothbrushing and dental extraction. Circulation. 117: 3118-3125** |
|---|---|
| **Comments** | Clinical procedure and microbiological assessment of bacteraemia<br><br>a) Procedures<br>- Baseline blood samples drawn (20ml) and 7 to 8ml inoculated directly into both aerobic and anaerobic BACTEC bottles for bacterial culturing<br>- Extraction began one hour after ingestion of amoxicillin or placebo<br>- Brushing arm subjects brushed all surfaces of the teeth adjacent to the gingiva with a new toothbrush without toothpaste for 2 minutes, timed as 30 seconds for each of the maxillary and mandibular quadrants of teeth.<br>- Subsequent blood draws of 20ml were taken at 1.5 minutes and at 5 minutes after the initiation of surgery or brushing.<br>- Additional blood samples (20ml) were drawn at 20, 40 and 60 minutes after the end of the procedure. 2mls of blood was drawn into a new syringe and discarded before each of the 6 blood draws and the catheter was flushed with 2ml of saline from a new syringe after each blood draw.<br><br>b) Bacterial isolation and identification<br>- Blood samples were cultured in BACTEC Plus Aerobic/F and LYTIC/10 Anaerobic/F. All false-positive bottles were further incubated for a total of 2 weeks.<br>- Bottles with positive cultures were kept for 2 weeks and subcultured periodically to ensure recover of additional species.<br>- The 16S ribosomal RNA sequencing method was used for bacterial identification.<br>- Bacterial lysates were used as templates in PCR with 16S rRNA universal primers according to standard protocols.<br>- Identification of strains was based on comparisons of the first 500 bases with Database Project and GenBank by BLAST.<br>- For those strains that were potentially new species, full 1500-base pair sequences were obtained.<br>- Investigators involved in bacterial culturing and identification were blinded as to subject randomisation.<br><br>c) Quantification of bacteria in blood<br>- Sensitive, real time quantitative PCR was used to quantify bacteria<br>- Bacterial DNA was isolated from patient blood draws and from blood seeded with known quantities of several common oral pathogens.<br>- For real time quantitative PCR, TaqMan technology and probes and universal 16S rRNA primers conserved among oral pathogens were used with the Smart Cycler system. Standard curves were established for the seeded pathogens and calculated the levels of bacteria in subject blood cultures.<br>- The sensitivity of the method was 25 CFU per PCR, which corresponds to $10^3$ to $10^4$ CFU per millilitre of blood.<br><br>Microbial identity of organisms identified in study<br>a) overall nature of bacteraemia |

| Bibliographic reference | Lockhart, PB., Brennan, MT., Sasser, HC., Fox, PC., Paster, BJ., Bahrani-Mougeot, FK. (2008). Bacteremia associated with toothbrushing and dental extraction. Circulation. 117: 3118-3125 |
|---|---|
| | 98 different bacterial species, the most common which belonged to Streptococcus (49%), Prevotella (9%), Actinomyces (5%) and Fusobacterium (5%)<br><br>b) nature of bacteraemia from endocarditis related bacterial species<br>10 (31%) of the 32 IE associated oral bacterial species were viridans streptococci. 13 (48%) of 27 positive cultures in the brushing group were viridans streptococci compared with 23 (49%) of 47 in the extraction-amoxicillin group and 106 (70%) of 151 in the extraction-placebo group. With the exception of one subject in the placebo group, polymicrobial blood cultures occurred within the first 5 minutes of the procedure – 2%, 6% and 29% in the brushing, extraction-amoxicillin and extraction-placebo group respectively.<br><br>Study limitations: assessed using checklist for prognostic studies from Hayden et al., 2006<br>- Study participation: highly selected population with pre-existing dental disease<br>- Study attrition: no major limitations<br>- Prognostic factor measurement: no major limitations<br>- Outcome measurement: although the incidence and duration of bacteraemia at various other time points are reported, this is in graphical form without accompanying numbers and therefore could not be extracted. For magnitude of bacteraemia, study seems to have pre-set a threshold for detection.<br>- Confounding measurement and account: no major limitations, toothbrushing carried out as an isolated procedure before any extractions, thus removing potential for confounding bacteraemia from other procedures, unclear if blood samples processed immediately.<br>- Analysis: no major limitations |

1

2 **Table 99**

| Bibliographic reference | Jones, DJ., Munro, CL., Grap, MJ., Kitten, T., Edmond, M. (2010). Oral care and bacteraemia risk in mechanically ventilated adults. Heart Lung. 39 (60): S57 –S65 |
|---|---|
| **Study type** | Prospective pre- and post-test design (without a control group) |
| **Aim** | To determine 1) the incidence of transient bacteraemia related to toothbrushing in mechanically ventilated critically ill adults 2) the relationship of oral microbial cultures and dental plaque scores to the incidence of transient bacteraemia, clinical outcomes and indicators of infection and 3) the relationships among patient characteristics and clinical outcomes |
| **Patient characteristics** | Inclusion criteria<br>- Subjects from the surgical trauma, medical respiratory and neuroscience intensive care units<br>- Mechanical ventilation<br>- Age greater than 18 years |

| Bibliographic reference | Jones, DJ., Munro, CL., Grap, MJ., Kitten, T., Edmond, M. (2010). Oral care and bacteraemia risk in mechanically ventilated adults. Heart Lung. 39 (60): S57 –S65 |
|---|---|
| | - Intubated less than 24 hours<br>- Invasive catheter in place less than 24 hours to decrease the likelihood of organisms already present in the line<br>- No documented evidence of clinical bloodstream infection prior to enrolment<br>- Having at least one tooth<br>- Haemoglobin greater than 7g/dl<br>Exclusion criteria<br>- Edentulous patients were excluded because dental plaque assessments could not be assessed in patients with no teeth<br>- Patients with haemoglobin level less than 7g/dl (to reduce risks of repeated blood sample collection)<br><br>Other characteristics<br>1. Gender, %<br>Male: 63, Female: 37<br><br>2. Age in years, mean (SD)<br>46 (17)<br><br>3. ICU, %<br>Surgical trauma – 37<br>Medical respiratory – 33<br>Neuroscience – 30<br><br>4. Ethnicity, %<br>Hispanic - 3, Non-Hispanic – 97% |
| **Number of patients** | A sample of 30 subjects were enrolled |
| **Outcomes** | 1. **Bacteraemia levels/intensity/bacterial counts per unit volume at one or more timepoints following the everyday activity –** not reported in study<br>2. **Duration of bacteraemia following everyday activity** – not reported in study<br>3. **Number/incidence/odds of having positive blood samples before and after everyday activity –** reported in study as incidence of transient bacteremia by positive blood cultures before and after toothbrushing (1 minute and 30 minutes post intervention) |
| **Predictors/risk factors and effect estimates** | **Predictor of interest to this question**<br>Toothbrushing – all subjects received a toothbrushing intervention twice daily. Performed using standardized protocol. Mouth divided into 4 quadrants, every tooth in each quadrant brushed for 5 strokes on lingual, buccal and biting surfaces using a soft pediatric toothbrush and toothpaste (Biotene toothpaste). Palate and tongue were also brushed. Each quadrant, |

| Bibliographic reference | **Jones, DJ., Munro, CL., Grap, MJ., Kitten, T., Edmond, M. (2010). Oral care and bacteraemia risk in mechanically ventilated adults. Heart Lung. 39 (60): S57 –S65** |
|---|---|
| | palate and tongue were rinsed with a total of 15ml mouthwash (Biotene) and a moisturising gel (Oral Balance) was applied to all soft surfaces of the oral cavity and lips. Toothbrushing was for 2 minutes twice a day over 48 hours performed by the principal investigator.<br>**Effect estimate**<br>None of the subjects had evidence of transient bacteremia before or after toothbrushing |
| **Analysis used** | n/a (no data found for outcome of interest in study) |
| **Length of follow-up** | 48 hours or until extubation if extubated prior to 48 hours |
| **Location** | USA |
| **Source of funding** | Supported by National Institutes of NIH/NINR |
| **Comments** | Clinical procedure and microbiological assessment of bacteraemia<br>- Bacteremia measured by quantitiative blood cultures with specific surveillance for the following bacteria: viridans Streptococci, S.aureus, P aeruginosa, Enterococcus spp, Klebsiella pneumoniae, and Candida spp.<br>- Blood cultures obtained for all subjects immediately preceding the first intervention, 1 minute post intervention and 30 minutes post intervention at both the first intervention and the last scheduled toothbrushing intervention (48 hours after first intervention).<br>- Blood samples plated on three plates and incubated for 7 days.<br><br>Microbial identity of organisms identified in study<br>None identified from blood cultures (all 30 subjects had one set of useable blood culture data, 80% were extubated prior to day 3 and so a second set of blood cultures not obtained. 6 subjects remained intubated for greater than 48 hours and so second set of blood cultures was obtained at the last intervention.<br><br>Study limitations: assessed using checklist for prognostic studies from Hayden et al., 2006<br>- Study participation: study dates not reported, no comparison group so not possible to determine relative levels of bacteremia associated with different activities (and therefore which groups may need prophylaxis) as opposed to just toothbrushing, no sample size calculation<br>- Study attrition: no major limitations<br>- Prognostic factor measurement: no major limitations<br>- Outcome measurement: no major limitations<br>- Confounding measurement and account: subjects also given Biotene mouthwash which could contain active ingredients and therefore have reduced bacteremia levels.<br>- Analysis: no major limitations |

1 **Table 100**

| | |
|---|---|
| **Bibliographic reference** | **Lucas V, Roberts GJ, Lucas V, Roberts GJ. Odontogenic bacteremia following tooth cleaning procedures in children 891. Pediatric dentistry 2000;22:96-100. *[included in CG64]*** |
| **Study type** | RCT* (Not blinded, 1991 to 1994)<br>*randomisation using random number tables |
| **Aim** | To investigate the prevalence and intensity of odontogenic bacteraemia from tooth cleaning procedures in children and adolescents |
| **Patient characteristics** | Inclusion criteria<br>- Children referred for dental treatment (Guy's Dental Hospital or Great Ormond Street Hospital) under general anaesthetic (GA)<br>Exclusion criteria<br>- Antibiotics within the previous month<br>- Haemorrhagic disorders<br>- Known viral carriage<br>Other characteristics<br>n = 79 male, n = 76 female, aged 21mths to 16yrs, 11mths |
| **Number of patients** | N = 155 recruited and randomised to following groups:<br>1. Toothbrushing: n= 52<br>2. Professional cleaning with a rubber cup: n= 53<br>3. Scaling: n=50<br>4. Control group (no cleaning procedures): n= 50 subjects for reference from study by Roberts et al., 1998a |
| **Outcomes** | Study reports on prevalence of bacteraemia following activity, intensity of bacteraemia following activity and incidence of positive blood cultures (see effect estimates section for details) |
| **Predictors/risk factors and effect estimates** | **Predictor of interest to this question**<br>Home care toothbrushing (no further details)<br><br>**Effect size**<br><br>**Positive blood cultures**<br>There was NS difference in the number of positive blood samples in the groups studied [toothbrushing – 20/52 (39%), dental flossing (data from De Leo et al., 1974) – 6/7 (86%), dental polishing – 13/53 (25%), dental scaling – 20/50 (40%), dental extractions (data from Roberts et al., 1998b) – 17/44 (39%)]. Chi square= 3.623, p=0.305 (excluding dental flossing), Chi square= 3.623, p=0.305 (excluding dental flossing and extractions)<br><br>**Intensity of bacteraemia**<br>There was NS difference in the intensity of bacteraemia (colony forming units per millilitre of blood, mean (SD), range) in |

| | |
|---|---|
| **Bibliographic reference** | **Lucas V, Roberts GJ, Lucas V, Roberts GJ. Odontogenic bacteremia following tooth cleaning procedures in children 891. Pediatric dentistry 2000;22:96-100. *[included in CG64]*** |
| | any of the 3 cleaning groups [toothbrushing – 32.2 (231), 0 to 1666, dental flossing – no data, dental polishing – 15.9 (83.5), 0 to 557, dental scaling – 2.2 (13.2), 0 to 93, dental extractions (from Roberts et al., 1998) – 0.23 (0.8), 0 to 4] |
| **Analysis used** | - Data tested for orality using the Shapiro-Wilk test and found not to be normally distributed<br>- Comparisons between the procedure group were made using the Kruskall-Wallis test |
| **Length of follow-up** | Measurement up to 30 seconds after intervention |
| **Location** | London |
| **Source of funding** | Not reported |
| **Comments** | Microbiology<br>A single 8ml blood sample was taken from each patient 30 seconds after the procedure. 3ml volume of blood was inoculated into each of the aerobic and anaerobic bottles, two commercial broth culture systems were used: the Bactec 460 radiometric system and the Bactec 760, bacteria were identified using standard laboratory methods and the oral streptococci were further identified using API Strep20. A further 1.5ml was inoculated into the Isolator system vial which estimates the intensity of bacteraemia by lysis centrifugation and gives cfu/ml of blood.<br><br>Bacteria isolated<br>There were similar to bacteria isolated from blood cultures following dental operative procedures, these included S. mitis, S. sanguis and coagulase negative staphylococci (the bacteria isolated from the baseline group included S. sanguis, coagulase negative staphylococci and Oerskovia species)<br><br>(authors conclude that even the professional cleaning procedures with a rubber cap and scaling should be carried out with benefit of pre-procedure antibiotic prophylaxis)<br><br>Study limitations: assessed using checklist for prognostic studies by Hayden et al., 2006<br>- Study participation: sample size calculation not reported, highly selected population with pre-existing dental disease<br>- Study attrition: no major limitations<br>- Prognostic factor measurement: home based toothbrushing, unclear if standardised procedures were advised or not and for how long intervention was carried out.<br>- Outcome measurement: no major limitations<br>- Confounding measurement and account: no major limitations<br>- Analysis: no major limitations |

1 **Table 101**

| | |
|---|---|
| **Bibliographic reference** | **Bhanji S, Williams B, Sheller B, et al. (2002) Transient bacteremia induced by toothbrushing: a comparison of the Sonicare toothbrush with a conventional toothbrush. Pediatric Dentistry 24: 295–99. *[included in CG64]*** |

| Bibliographic reference | **Bhanji S, Williams B, Sheller B, et al. (2002) Transient bacteremia induced by toothbrushing: a comparison of the Sonicare toothbrush with a conventional toothbrush. Pediatric Dentistry 24: 295–99.** ***[included in CG64]*** |
|---|---|
| **Study type** | RCT*<br>(Not blinded)<br>*Randomisation method not reported |
| **Aim** | To compare the incidence of bacteraemia resulting from the use of the Sonicare brush and manual brushing |
| **Patient characteristics** | Inclusion criteria<br>- children receiving dental care under general anaesthesia at Children's Hospital and Regional Medical Centre<br>- between the ages of 2 and 6 yrs<br>- had no medical conditions requiring antibiotic prophylaxis for dental treatment<br>- had not received antibiotic therapy within the past 30 days<br>- had no sinus tracts associated with dental abscesses<br>- had no conditions altering alveolar ridge or gingival anatomy<br><br>Exclusion criteria<br>- positive blood cultures before toothbrushing<br><br>Other characteristics<br>Not reported |
| **Number of patients** | N = 50 children<br><br>Subjects randomised to the following groups:<br>1. Sonicare electric toothbrushing: n= 25<br>2. Manual toothbrushing: n=25 |
| **Outcomes** | The following outcome was reported in the study: positive blood cultures after brushing (see effect estimates section for details) |
| **Predictors/risk factors and effect estimates** | **Predictor of interest to this question**<br>Toothbrushing: teeth brushed for a timed one-minute interval with the Sonicare electric toothbrush (high frequency brushing, 31,000 brush strokes per minute) or manually.<br><br>**Effect estimates**<br>Incidence of positive blood cultures after* brushing, n (%, 95%CI)<br>Manual group (n=24): 11/24 (46, 26 to 66)<br>Sonicare group (n=23): 18/23 (78, 62 to 95)<br>p=0.022 |

| | |
|---|---|
| **Bibliographic reference** | **Bhanji S, Williams B, Sheller B, et al. (2002) Transient bacteremia induced by toothbrushing: a comparison of the Sonicare toothbrush with a conventional toothbrush. Pediatric Dentistry 24: 295–99.** ***[included in CG64]*** |
| | *3 patients had positive blood cultures before toothbrushing and were excluded |
| **Analysis used** | - Proportion of subjects with positive cultures after toothbrushing in the two groups was compared using Chi-Square test and logistic regression |
| **Length of follow-up** | Measurement 30 seconds after brushing |
| **Location** | USA |
| **Source of funding** | Washington Dental Service Foundation, Phillips Oral Healthcare Corporation |
| **Comments** | Study limitations: assessed using checklist for prognostic studies by Hayden et al., 2006<br><br>- Study participation: study dates not reported, baseline characteristics (eg: gender, mean age etc) not reported, highly selected population with pre-existing dental disease<br>- Study attrition: no major limitations<br>- Prognostic factor measurement: no major limitations<br>- Outcome measurement: no major limitations<br>- Confounding measurement and account: no major limitations<br>- Analysis: no major limitations<br>Microbiology methods<br>- 30 seconds after toothbrushing, 1ml of blood was drawn and discarded. A second samples was collected and distributed to culture vials.<br>- 10 ml drawn per sample, divided into 3ml into an aerobic vial and 7 ml into an anaerobic vial, vials were incubated for 5 days using BacTec9240, positive vials were gram stained, isolated on agar media and analysed<br>Microbial identity of positive cultures<br><br>- Gram stain results of positive cultures were mainly gram positive cocci in chains (n=23).<br>- Gram negative cocci: n=5<br>- Gram positive rods: n=3<br>- Gram negative rods: n=1 |

1 **Table 102**

| | |
|---|---|
| **Bibliographic reference** | **Roberts GJ, Holzel HS, Sury MR, Simmons NA, Gardner P, Longhurst P. Dental bacteremia in children. SO: Pediatric cardiology 1997;18:24-7.** ***[included in CG64]*** |
| **Study type** | RCT* (1991 to 1993)<br>*randomisation was using random number tables, there were three exceptions, extractions which could only be performed if clinically needed, mucoperiosteal flap because of its relative infrequency was studied each time it was needed for treatment |

| Bibliographic reference | **Roberts GJ, Holzel HS, Sury MR, Simmons NA, Gardner P, Longhurst P. Dental bacteremia in children. SO: Pediatric cardiology 1997;18:24-7. *[included in CG64]*** |
|---|---|
| | of the patient, the third was the cardiac group all of whom had antibiotic prophylaxis and therefore formed a separate group of patients |
| **Aim** | To investigate the frequency of odontogenic bacteremia following common dental procedures in children |
| **Patient characteristics** | Inclusion<br>- children referred to Guy's Dental Hospital or GOSH for dental treatment under general anaesthetic,<br>Exclusion<br>- there were no exclusion criteria<br>Other characteristics<br>- n = 383 male, n = 352 female, mean age: 9yrs 3mths |
| **Number of patients** | n = 735<br>Group A – nonmanipulation group; baseline and dental examination<br>Group B – cleaning procedures; toothbrushing, polishing and scaling<br>Group C – minimal manipulation group; intraligamental injection and nasotracheal tube<br>Group D – conservative dentistry procedures; rubber dam placement, slow drill, fast drill, and matrix band placement<br>Group E – oral surgery group; single extractions, multiple extractions, and mucoperisoteal flaps<br>Group F – groups having antibiotic prophylaxis; cardiac patients<br><br>(Number for each of the above groups not reported however results for each of the above interventions has been reported separately – see effect estimates section) |
| **Outcomes** | Study reports on percentage of positive blood culture after procedure (see effect estimates section) |
| **Predictors/risk factors and effect estimates** | **Predictor of interest to this question**<br>Toothbrushing: the dentist brushed the teeth with a new toothbrush for one minute with normal vigor. Blood samples taken 30 seconds after.<br><br>**Effect size**<br><br>**Positive blood cultures, n/N (%):**<br>- baseline n = 5/53 (9.4%)<br>- dental examination n = 9/53 (17.0%)<br>- toothbrushing n = 20/52 (38.5%)<br>- polishing teeth n = 13/53 (24.5%)<br>- scaling teeth n = 20/50 (40.0%) |

| Bibliographic reference | Roberts GJ, Holzel HS, Sury MR, Simmons NA, Gardner P, Longhurst P. Dental bacteremia in children. SO: Pediatric cardiology 1997;18:24-7. *[included in CG64]* |
|---|---|
| | - intraligamental injection n = 28/29 (96.6%)<br>- nasotracheal tube n = 3/31 (9.7%)<br>- rubber dam placement n = 15/51 (29.4%)<br>- slow drill n = 6/47 (12.8%)<br>- fast drill n = 2/47 (4.3%)<br>- matrix band placement n = 18/56 (32.1%)<br>- single extraction n = 17/44 (38.7%)<br>- multiple extractions n = 30/59 (50.9%)<br>- mucoperiosteal flap n = 20/51 (39.2%)<br>- cardiac patients n = 6/59 (10.2%)<br><br>**Comparison of proportions compared to baseline (95% CI):**<br>- dental examination -5.3 to 20.49%<br>- toothbrushing 12.8 to 45.4%<br>- polishing teeth 0.7 to 29.4%<br>- scaling teeth 14.0 to 47.2%<br>- intraligamental injection 76.9 to 97.3%<br>- nasotracheal tube -6.5 to 13.2%<br>- rubber dam placement 4.8 to 35.1%<br>- slow drill -8.9 to 15.6%<br>- fast drill -5.2 to 4.8%<br>- matrix band placement 7.4 to 38.0%<br>- single extraction 12.5 to 45.9%<br>- multiple extractions 24.2 to 58.6%<br>- mucoperiosteal flap 13.4 to 46.2%<br><br>NS; dental examination, nasotracheal tube, slow drill, fast drill, |
| **Analysis used** | Results are expressed as the percentage of samples that yielded bacteria. Statistical calculations were made using Stata. |
| **Length of follow-up** | Measurement 30 seconds after procedure |
| **Location** | UK |
| **Source of funding** | Not stated |
| **Comments** | Study limitations: assessed using checklist list for prognostic studies from Hayden et al., 2006 |

| Bibliographic reference | Roberts GJ, Holzel HS, Sury MR, Simmons NA, Gardner P, Longhurst P. Dental bacteremia in children. SO: Pediatric cardiology 1997;18:24-7. *[included in CG64]* |
|---|---|
| | - Study participation: highly selected population with pre-existing dental disease<br>- Study attrition: no major limitations<br>- Prognostic factor measurement: no major limitations<br>- Outcome measurement: no major limitations<br>- Confounding measurement and account: no major limitations<br>- Analysis: no major limitations<br>Microbiology methods<br>Blood samples: one sample taken 30sec after each procedure<br>Two commercial blood culture systems were used; the Bactec radiometric system and the Bactec 760, a 3ml volume of blood was inoculated into each of the aerobic and anaerobic bottles. Bacteria were speciated using standard methods, streptococci were speciated using API Strep 20<br><br>Microbial identity of organisms identified<br>A total of 365 organisms were isolated (across all procedures), 212 (58%) were viridans streptococci |

# G.6 Review question 6a

**Table 103**

| Bibliographic reference | Horstkotte D, Rosin H, Friedrichs W, Loogen F (1987) Contribution for choosing the optimal prophylaxis of bacterial endocarditis. Eur Heart J. 8: 379–81. |
|---|---|
| **Study type** | Retrospective cohort study |
| **Aim** | To compare the benefit of antibiotic prophylaxis with the results of a patient group in which retrospective questioning showed that invasive procedures had been performed without any prophylaxis |
| **Patient characteristics** | Both patient groups showed a nearly similar distribution in the site of implantation and the type of prosthesis including a similar relationship between mechanical (84%) and biological (16%) valves<br><br>Exclusion: other procedures that could have caused bacteraemia of febrile conditions during a 6-month period before the procedure in question and before the onset of symptoms of endocarditis |
| **Number of Patients** | n = 533 |
| **Intervention** | Group A, 229 patients with prosthetic heart valves in whom 287 diagnostic and therapeutic procedures were performed using |

| Bibliographic reference | Horstkotte D, Rosin H, Friedrichs W, Loogen F (1987) Contribution for choosing the optimal prophylaxis of bacterial endocarditis. Eur Heart J. 8: 379–81. |
|---|---|
| | a prophylactic antibiotic regime as follows;<br>For patients with prosthetic heart valves without penicillin allergy<br>- expected bacteraemia caused by cocci (dental procedures, diagnostic and therapeutic procedures involving oropharynx and respiratory tract): 2 mega units penicillin G i.v. + 1g streptomycin i.m* 30 to 60 mins before procedure (*no i.m injection in patients receiving anticoagulant therapy) and 1 mega unit penicillin V p.o. after 6 and 12 hours.<br>- expected bacteraemia caused by enterobacteria (abdominal surgery, gastrointestinal interventions, diagnostic and therapeutic interventions involving the urogenital tract): 1g ampicillin i.v + 80mg gentamicin i.v. 30 to 60 mins before procedure and repeated injection after 6 and 8 hours.<br>For patients with prosthetic heart valves with penicillin allergy<br>- expected bacteraemia caused by cocci (dental procedures, diagnostic and therapeutic procedures involving oropharynx and respiratory tract): 1.0 to 1.5g erythromycin p.o 60 to 90 mins before procedure and 0.5g erythromycin p.o after 6 and 12 hours<br>- expected bacteraemia caused by enterobacteria (abdominal surgery, gastrointestinal interventions, diagnostic and therapeutic interventions involving the urogenital tract): ca 1.0g cephalosporin i.m* + 80mg gentamicin i.v. 60 mins before (no i.m injection in patients receiving anticoagulant therapy) and repeated injection after 8 hours. |
| **Comparison** | Group B, 304 (out of n = 1898 patients questioned) subjects with prosthetic heart valves in whom 390 procedures were performed who gave reliable information that they had undergone one of the procedures regarded as requiring endocarditis prophylaxis without having received any antibiotic regimen |
| **Length of follow up** | Not reported |
| **Location** | Germany |
| **Outcomes measures and effect size** | Incidence of prosthetic valve endocarditis*<br>- In group A no PVE was observed (0/287, 0%).<br>- In group B, 6 cases of PVE (6/390, 1.5%) occurred within 14 days after the intervention which corresponds to an incidence of 1.5 cases per 100 procedures.<br>- The highest incidence of PVE (n = 2/39 procedures, 5.1%) occurred after urological procedures, followed by oropharyngeal surgery (2.6%) and gynaecological (2.2%). Streptococci and enterococci were identified as causative organisms for PVE after oral, urological or gynaecological procedures.<br>- 2 cases of PVE occurred in 117 dental procedures, both of which occurred after tooth extraction.<br>- A further case of enterococcal PVE occurred after spontaneous passage of a renal calculus without having undergone any invasive intervention.<br><br>*Two more patients in group B developed prosthetic valve endocarditis 8 and 13 weeks respectively after the initial intervention however PVE was considered related to the diagnostic or therapeutic procedure only if symptoms of endocarditis occurred within 2 weeks. |
| **Source of funding** | Not reported |
| **Comments** | **Study limitations** |

| Bibliographic reference | **Horstkotte D, Rosin H, Friedrichs W, Loogen F (1987) Contribution for choosing the optimal prophylaxis of bacterial endocarditis. Eur Heart J. 8: 379–81.** |
|---|---|
| | - Retrospective nature; reliant on patient's memory for data regarding interventional procedures undergone and whether prophylaxis was received or not – no indication that data provided by subject was verified in any way.<br>- Unclear how similar the interventional procedures the 2 groups underwent were; numbers not reported<br>- Unclear whether confounding factors were taken into account<br>- Baseline characteristics: age, gender not reported<br>- Power calculation not reported |

1 **Table 104**

| Bibliographic reference | **Lacassin F, Hoen B, Leport C, Selton-Suty C, Delahaye F, Goulet V et al. Procedures associated with infective endocarditis in adults. A case control study. European heart journal 1995;16:1968-74.** |
|---|---|
| **Study type** | Case-control |
| **Aim** | To assess the relative risk of infective endocarditis associated with various procedures (medical, surgical and dental) and the protective efficacy of antibiotic prophylaxis by a case-control study |
| **Patient characteristics** | **Inclusion**<br>- cases: definite, probable or possible cases of IE identified from a prospective epidemiological survey conducted in all private and public medical facilities of three regions in France. Definite and probable IE defined according to revised Von Reyn's criteria with modifications to include echocardiographic and macroscopic findings for definite and probable cases. Definite endocarditis was defined on macroscopic or microbiological findings at operation or necropsy. Probable endocarditis was defined as 1) persistently positive blood cultures (at least two cultures obtained with 2 of 2 positive, 3 of 3 positive or at least 70% of cultures positive if 4 or more cultures obtained) with underlying heart disease plus echocardiographic vegetation or with vascular phenomena plus echocardiographic vegetation. Possible IE defined according to non-revised Von Reyn's criteria.<br><br>Controls: those without IE who satisfied the same exclusion criteria as the cases. Controls were recruited randomly from cardiology or medicinal wards either during a consultation for echocardiography or during hospitalisation in the same period of observations as cases.<br><br>**Exclusion:** cases: patients younger than 15yrs, valve replacement within the previous year, prematurely dead, intravenous drug users, those with Coxiella burnetti IE (unlikely to be related to any procedure)<br><br>**Characteristics:**<br>Cases and controls were distributed into 3 groups of underlying cardiac conditions: native valve disease, prosthetic valve or no known cardiac disease. Each case was matched to one control as regards sex, age (±5yrs) and group of underlying cardiac conditions. The proportion of those with diabetes mellitus, or who consumed alcohol and tobacco did not differ between the 2 groups. Cases had significantly more often an infectious episode or a skin wound than controls (39% and 19% |

| Bibliographic reference | Lacassin F, Hoen B, Leport C, Selton-Suty C, Delahaye F, Goulet V et al. Procedures associated with infective endocarditis in adults. A case control study. European heart journal 1995;16:1968-74. |
|---|---|
| | vs. 15% and 5% respectively)<br><br>Age in years, mean (SD)<br>Cases: 58 (15)<br>Controls: 58 (15)<br><br>Male/female, n<br>Cases: 113/58<br>Controls: 113/58<br><br>Native valve disease, n (%)<br>Cases: 66 (38.5)<br>Controls: 66 (38.5)<br><br>Prosthetic valve, n (%)<br>Cases: 41 (24)<br>Controls: 41 (24)<br><br>No known cardiac disease, n (%)<br>Cases: 64 (37.5)<br>Controls: 64 (37.5)<br><br>Duration of previous cardiac disease in months, mean (SD)<br>Cases: 12.5 (13)<br>Controls: 13 (15) |
| **Number of Patients** | n = 171 pairs |
| **Intervention** | Cases of definite, probable or possible IE that were requested to indicate all procedures (medical, surgical or dental) they had undergone within the 3 months prior to their diagnosis of IE. In the case of medical consultation or procedure, the information was checked by the cited practitioner. The use of antibiotics* was documented for the type, dosage, duration and administration schedule.<br><br>Antibiotics*<br>*regimen not described. To check whether the antibiotic regimen was appropriate for prophylaxis of IE, two independent investigators reviewed the use of antibiotics in each case and each control and compared it to the recommendations of the |

| Bibliographic reference | **Lacassin F, Hoen B, Leport C, Selton-Suty C, Delahaye F, Goulet V et al. Procedures associated with infective endocarditis in adults. A case control study. European heart journal 1995;16:1968-74.** |
|---|---|
| | European Society of Cardiology that at the time of this study, was used in France. Cases were interviewed as soon as possible after the diagnosis of IE. |
| **Comparison** | Controls without IE who were interviewed under the same conditions as cases using the same questionnaire form. |
| **Length of follow up** | 1st November 1990 to 31st October 1991 |
| **Location** | France |
| **Outcomes measures and effect size** | <u>Protective efficacy of antibiotic prophylaxis in subjects with underlying valvular disease (prosthetic or native) who had undergone a dental procedure</u><br>Among those with known heart disease who had a dental procedure (n = 48), 6/26 (23%) of the cases and 6/22 (27%) of the controls had received appropriate antibiotics.<br><br>Therefore:<br>- Number of patients with antibiotics who had IE = 6<br>- Number of patients with antibiotics who had no IE = 6<br>- Number of patients without antibiotics who had IE = 20<br>- Number of patients without antibiotics who had no IE = 16<br>Relative risk of developing endocarditis in those given prophylaxis compared to those without prophylaxis (95%CI): [6/12]/[20/36] = 0.9 (0.48 to 1.7)*<br>*Calculated by reviewer |
| **Source of funding** | Several grants from medical societies in France and from the following companies: Baxter, Dideco-Shiley, Eli-Lily, Medtronic, St Jude Medical Companies |
| **Comments** | **Causative organism**<br>The only procedure associated with a risk for IE due to viridans streptococci was scaling (n = 9/50 in the cases; n = 2/50 in the controls, OR=5.25, p=0.025)<br>The only procedure associated with the subsequent occurrence of IE was surgery for staphylococcal IE (n = 4/27 in the cases; n = 0/27 in the controls, p=0.03)<br>In multivariate analysis, scaling was associated with a significant risk for IE due to viridans streptococci, independently of an infectious episode. Conversely, only infectious episodes contributed to the risk of staphylococcal infective endocarditis, the risk after skin wound and surgery being non-significant in this analysis<br><br>**Study limitations**<br>- Retrospective nature of study; reliant on subjects memory for interventional procedures undergone and antibiotic use<br>- Of the 171 cases, only 34% had definite infective endocarditis; 48% probable IE and 18% possible IE<br>- In the case of medical consultation or procedure, information cited was checked by the cited practitioner; unclear whether what proportion of subjects this was possible for. |

| | |
|---|---|
| **Bibliographic reference** | **Lacassin F, Hoen B, Leport C, Selton-Suty C, Delahaye F, Goulet V et al. Procedures associated with infective endocarditis in adults. A case control study. European heart journal 1995;16:1968-74.** |
| | - Power calculation not reported |

1 **Table 105**

| | |
|---|---|
| **Bibliographic reference** | **van der Meer JT, van Wijk W, Thompson J, Vandenbroucke JP, Valkenburg HA, Michel MF. Efficacy of antibiotic prophylaxis for prevention of native-valve endocarditis. Lancet 1992;339:135-9.** |
| **Study type** | Case control |
| **Aim** | To assess the protective effect of antibiotic prophylaxis in subjects with native valve and cardiovascular anomalies. |
| **Patient characteristics** | Cases included: those with known cardiac disease (native valve and cardiovascular anomalies) in whom endocarditis developed within 180days of a medical or dental procedure for which prophylaxis was indicated. The diagnostic criteria for endocarditis described by Von Reyn et al was used.<br><br>Cases excluded: those with prosthetic heart valves, those where a casual relation between the procedure and endocarditis was ruled out because it was unlikely that the agent isolated from the blood originated from the area of the procedure<br><br>Controls included: with a cardiac lesion and increased risk of endocarditis, if they were in the same 5-yr age category as a case and had undergone a medical or dental procedure with an indication for prophylaxis within 180days of the interview<br><br>Cases and potential controls were NS different in the number of procedures they had undergone in the previous 180 days, though there were more men among the cases (p=0.05).<br><br><u>Median age in years, range</u><br>Cases: 41 (5 to 78)<br>Controls: 40 (5 to 80)<br><br><u>Gender, number male/female</u><br>Cases: 33/15<br>Controls: 109/91 |
| **Number of Patients** | n = 48 cases, 200 controls<br><br>Sample size and calculations of power were based on the assumption that a clinically important reduction in risk due to prophylaxis would have to be at least 75% and that 40% of the population at risk for endocarditis would be given prophylaxis. Based on significance level of 0.05, 31 cases and 4 controls per case would be needed. |
| **Intervention** | Cases with known cardiac disease in whom endocarditis developed within 180 days of a medical or dental procedure for which prophylaxis was indicated. |

| Bibliographic reference | **van der Meer JT, van Wijk W, Thompson J, Vandenbroucke JP, Valkenburg HA, Michel MF. Efficacy of antibiotic prophylaxis for prevention of native-valve endocarditis. Lancet 1992;339:135-9.** |
|---|---|
| | Subjects were interviewed using a structured questionnaire about recent medical or dental procedures and the use of prophylaxis. Data about previous diagnoses of heart disease, physical examination and lab results were obtained |
| **Comparison** | Controls selected from outpatients of the cardiology department of the university hospital and 4 regional hospitals, with same cardiac status in whom endocarditis did not develop within 180 days of a similar procedure. |
| **Length of follow up** | 180 days |
| **Location** | Netherlands |
| **Outcomes measures and effect size** | Cases<br>Total number of procedures was n = 48; 44 dental and 4 other, prophylaxis was definitely indicated in 28 of the 48 procedures. For the other 20, the indication for prophylaxis was not certain, all involved the removal of tartar.<br>Antibiotics were given in n = 8/48 (17%) cases<br>Prophylaxis was given more often to those who had previous IE than those who had not (n = 3/9 vs. n = 5/39)<br><br>Controls<br>n = 181/200 procedures were dental, prophylaxis was indicated in n = 96, for n = 104 the indication was possible because dental scaling had been done and it was unclear whether subgingival calculus had been removed.<br>n = 26/200 (13%) of controls with a definite indication had received prophylaxis before a procedure, including 1/104 (1%) of those undergoing a procedure with a possible indication.<br><br>First time epispdes<br>OR (90%CI) for for first time episodes for procedures within 180 days of onset of symptoms: 1.04 (0.36 to 2.99) |
| **Source of funding** | Netherlands Heart foundation |
| **Comments** | **Study limitations**<br>- Retrospective nature; data collected via structured questionnaire which although checked with medical and dental specialists, was highly reliant on patient's memory and reliability of medical records<br>- Cases who were very ill or who died were included in the analysis via the use of proxy responders, however this did not occur for the 53/889 controls who died<br>- Cases and controls did not undergo entirely the 'same' procedure however % undergoing dental procedures in both groups was comparable (92% and 91% cases and controls) |

1

# G.7 Review question 7a

**Table 106**

| | |
|---|---|
| **Bibliographic reference** | **Maharaj, B., Coovadia, Y., Vayej, AC. (2012). A comparative study of amoxicillin, clindamycin and chlorhexidine in the prevention of post-extraction bacteraemia. Cardiovascular journal of Africa. 23 (9): 491-494** |
| **Study type** | Randomised controlled trial |
| **Aim** | To assess and compare the effectiveness of amoxicillin, clindamycin, and the oral antiseptic chlorhexidine in eliminating post-extraction bacteraemia in black patients. |
| **Patient characteristics** | **Inclusion criteria**<br>- Adult black patients attending the dental clinic<br>- Healthy<br>- No history of cardiovascular disease<br>- Had not received antibiotics in the previous 2 weeks<br>- Not allergic to penicillin<br><br>**Exclusion criteria**<br>- Any patient found to have a dental abscess or who required the extraction of more than one tooth<br><br>**Other characteristics**<br>Males, n/N (%): amoxicillin – 14/40 (35%), clindamycin – 16/40 (40%), control – 12/40 (30%)<br>Females, n/N (%): amoxicillin – 26/40 (65%), clindamycin – 24/40 (60%), control – 28/40 (70%)<br>Age in years, mean (range): amoxicillin – 29.9 (18 to 56), clindamycin – 28.1 (18 to 66), control – 32.1 (18 to 60) |
| **Number of Patients** | 160 randomised to 4 groups (no therapy, chlorhexidine, amoxicillin or clindamycin) of 40 subjects each. |
| **Intervention** | Subjects were given 3g amoxicillin or 600mg clindamycin orally. Treatment was given one hour prior to dental extraction*.<br><br>*dental extraction: only one tooth was extracted per patient. The same dental surgeon performed the procedure using dental forceps. No surgical procedures were used in any patient. |
| **Comparison** | No therapy prior to dental extraction |
| **Length of follow up** | Not reported, post-extraction bacteraemia assessed based on blood sample drawn 3 minutes after extraction. |
| **Location** | South Africa |
| **Outcomes measures and effect size** | **1.Bacteraemia levels/intensity:** not reported<br>**2. Duration of bacteraemia:** not reported<br>**3. Incidence of positive blood culture after* dental extraction, n (%)**<br>Amoxicillin group: 3 (7.5) |

| Bibliographic reference | **Maharaj, B., Coovadia, Y., Vayej, AC. (2012). A comparative study of amoxicillin, clindamycin and chlorhexidine in the prevention of post-extraction bacteraemia. Cardiovascular journal of Africa. 23 (9): 491-494** |
|---|---|
| | Clindamycin group: 8 (20)<br>Control group: 14 (35)<br>*before data not reported, difference between amoxicillin and control group was statistically significant, p=0.003<br>(Adverse events not reported) |
| **Source of funding** | Not reported |
| **Comments** | **Statistical analysis**<br>- Results in each group were arranged in a contingency table an analysed using Fisher's exact test<br>- To analyse difference between control vs antibiotic groups and between antiseptic vs antibiotic group, the Chi Square test was used, employing Yates correction for continuity<br>- Power calculation not reported<br><br>**Assessment of bacteraemia**<br>- The skin at the site of the venepuncture was prepared using 0.5% chlorhexidine in 70% alcohol<br>- 8-10ml of blood was drawn 3 minutes after the extraction in each patient<br>- 3 to 5ml blood was injected into BACTEC blood culture vials<br>- Blood culture bottles transported to Microbiology Department within 2 hours of collection<br>- The blood culture vials were tested on days 1, 3, 5 and 7 and positive vials were sub-cultured and Gram stained smears were prepared<br>- The aerobic vials were sub-cultured onto chocolate, blood and MacConkey agar plates which were inoculated for 48 hours in air plus 10% carbon dioxide.<br>- The anaerobic vials were sub-cultured onto 10% blood agar plates with and without amikacin and incubated for 48 to 72 hours in anaerobic gas pak.<br>- The organisms isolated were identified using conventional laboratory methods and the identity of streptococcal isolates was confirmed using the API Strep 20 system.<br><br>**Microbial identity**<br>A range of microbes were identified including Streptococcus mitis, Streptococcus sanguis, Streptococcus anginosus, Viridans Streptococci, Streptococcus pneumonia, Staphylococcus epidermis, Enterococcus faecalis, Neisseria species, Corynebacterium species, Gram negative bacilli, Moraxella species, Peptostreptococcus species, Prevotella melaninogenica, Eikenella corrodens, Gemella haemolysins and mixed growth.<br><br>**Study limitations: assessed using GRADE risk of bias checklist**<br>- Allocation concealment not described<br>- Blinding not described |

| | |
|---|---|
| **Bibliographic reference** | **Maharaj, B., Coovadia, Y., Vayej, AC. (2012). A comparative study of amoxicillin, clindamycin and chlorhexidine in the prevention of post-extraction bacteraemia. Cardiovascular journal of Africa. 23 (9): 491-494** |
| | - Number of positive blood cultures before prophylaxis not reported – unclear if subjects were tested for bacteraemia<br>- Power calculation not reported |

1 **Table 107**

| | |
|---|---|
| **Bibliographic reference** | **Duvall, NB., Fisher, TD., Hensley, D. (2013). The comparative efficacy of 0.12% chlorhexidine and amoxicillin to reduce the incidence and magnitude of bacteraemia during third molar extractions. Oral surgery, oral medicine and oral pathology. 115 (6): 752-763** |
| **Study type** | RCT |
| **Aim** | To compare the incidence and magnitude of bacteraemia of a 0.12% chlorhexidine pre-procedure rinse to the AHA and the ADA/AAOS recommended 2g amoxicillin antibiotic prophylaxis during third molar extractions. |
| **Patient characteristics** | **Inclusion criteria**<br>- Subjects presenting to the surgical centre, oral surgery clinic for third molar extractions under conscious sedation from June 2011 to December 2011<br>-ASA I or II: healthy, no systemic disease<br>- Diagnosed/planned extraction #1, 16, 17, 32 under conscious sedation<br>- #17 and 32 required a mucogingival flap for extraction<br>- 18 years of age or older<br>- Previously received penicillin and/or amoxicillin without a hypersensitivity or allergic reaction<br><br>**Exclusion criteria**<br>- ASA III or IV: poorly controlled systemic disease<br>- Known penicillin, amoxicillin or cephalosporin drug allergy<br>- Pregnant women<br>- Current immunosuppressed status<br>- Active viral disease<br>- Cardiac anomalies or another condition/situation requiring pre- or intra-operative use of antibiotics<br>- Antibiotic use within the previous two months<br>- Steroid therapy within the previous two months<br>- Chlorhexidine use or other oral antimicrobial rinses within the previous 2 months<br>- The routine use of an oral antiseptic at home<br>- Gingival tissue manipulation within 2 hours of the procedure<br><br>**Other characteristics** |

<table>
<tr><td>Bibliographic reference</td><td>Duvall, NB., Fisher, TD., Hensley, D. (2013). The comparative efficacy of 0.12% chlorhexidine and amoxicillin to reduce the incidence and magnitude of bacteraemia during third molar extractions. Oral surgery, oral medicine and oral pathology. 115 (6): 752-763</td></tr>
<tr><td></td><td>Age in years, mean (range)<br>21.8 (18 to 29)<br>No significant difference among treatment arms, p=0.473<br><br>Gender, n<br>Male – 23<br>Female – 7<br>No significant difference among treatment arms, p=0.475<br><br>Surgical procedure length in minutes, mean (range)<br>42 (11 to 78)<br>No significant difference among treatment arms, p=0.632</td></tr>
<tr><td>Number of Patients</td><td>N=30<br>10 subjects per placebo, chlorhexidine and amoxicillin groups</td></tr>
<tr><td>Intervention</td><td>2g amoxicillin capsule and a placebo rinse.<br><br>The amoxicillin capsule (packaged and obtained from the 59th Pharmacy Squadron) was administered with a small amount of water 1 hour prior to procedure.<br>The placebo rinse was administered immediately prior to conscious sedation medication administration. The subjects rinsed with 15ml of the placebo rinse for one minute and expectorated.</td></tr>
<tr><td>Comparison</td><td>Placebo rinse and a placebo capsule.<br>The placebo rinse (1000ml sterile water for irrigation, [USP, Baxter Healthcare], where blue dye and mint extract was added until a similar appearance, taste and smell was obtained compared to the 0.12% chlorhexidine rinse). This was also administered immediately prior to conscious sedation medication administration. The subjects rinsed with 15ml of the placebo rinse for one minute and expectorated.</td></tr>
<tr><td>Length of follow up</td><td>Not reported</td></tr>
<tr><td>Location</td><td>USA</td></tr>
<tr><td>Outcomes measures and effect size</td><td>1) Bacteraemia levels/intensity<br><br>
<table>
<tr><th colspan="3">Total mean magnitude of bacteraemia</th></tr>
<tr><td></td><td>Total bacteraemia in cfu/ml, mean (SD)</td><td>Total bacteraemia range</td></tr>
<tr><td>Placebo</td><td>3.61 (7.09)</td><td>0.0 to 18.20</td></tr>
</table>
</td></tr>
</table>

| | |
|---|---|
| **Bibliographic reference** | **Duvall, NB., Fisher, TD., Hensley, D. (2013). The comparative efficacy of 0.12% chlorhexidine and amoxicillin to reduce the incidence and magnitude of bacteraemia during third molar extractions. Oral surgery, oral medicine and oral pathology. 115 (6): 752-763** |

| | | |
|---|---|---|
| Amoxicillin | 0.63 (1.33) | 0.0 to 4.30 |

| **Mean magnitude of bacteraemia per blood draw** | | | | | |
|---|---|---|---|---|---|
| | Blood draw 1, mean (SD) | Blood draw 2, mean (SD) | Blood draw 3, mean (SD) | Blood draw 4, mean (SD) | P value |
| Placebo | 0 (0) | 1.26 (3.67) | 1.90 (5.36) | 0.45 (0.83) | 0.031 |
| Amoxicillin | 0.05 (0.16) | 0.02 (0.06) | 0.30 (0.73) | 0.26 (0.60) | 0.310 |

**2) Duration of bacteraemia: not reported**

**3) Incidence of bacteraemia: defined as at least one positive culture of the four blood draws per subject and reported as n/N (%)**

Placebo group: 5/10 (50)

Amoxicillin group: 4/10 (40)

*P value not reported for the above comparison but for the comparison between all 3 groups in the study (amoxicillin, placebo and chlorhexidine);0.670

| | |
|---|---|
| **Source of funding** | Funding provided by the 59th Clinical Research Training Division, Lackland, AFB, TX |
| **Comments** | **Statistical analyses**<br>Incidence of bacteraemia analysed via Chi-square tests<br>Magnitude of bacteraemia analysed using the non-parametric Kruskal-Wallis test and the Friedman test with Bonferroni correction applied as there were multiple comparisons between the groups<br><br>**Assessment of bacteraemia**<br>- Once the IV access line was established, the first blood draw was completed at baseline<br>- A second IV access line for the conscious sedation medications was obtained in the opposite arm in a similar manner after the blood draw IV access line was obtained, blood draw 1 was collected and the placebo or amoxicillin capsules were administered.<br>- The third molar extractions was completed in the order of #1, 32, 16 and 17.<br>- Blood draw 2 was completed 1.5 minutes following initiation of the mucogingival flap #32, blood draw 3 was completed 1.5 minutes following initiation of the mucogingival flap #17 and blood draw 4 was completed 10 minutes following initiation of the mucogingival flap #17<br>- The 4 blood samples per subject were transported to an on-site microbiology laboratory for immediate processing. All blood samples were processed within 4 hours of blood draw 1.<br>- The bacterial concentrate was removed with an Isostat concentrate pipet and distributed equally onto 3 different agar plates: |

| Bibliographic reference | Duvall, NB., Fisher, TD., Hensley, D. (2013). The comparative efficacy of 0.12% chlorhexidine and amoxicillin to reduce the incidence and magnitude of bacteraemia during third molar extractions. Oral surgery, oral medicine and oral pathology. 115 (6): 752-763 |
|---|---|
| | Trypticase soy agar with 5% sheep blood (incubated aerobically), chocolate agar (incubated aerobically) and Brucella blood agar (incubated anaerobically)<br>- Colonies were counted and grouped by colonial morphology. Haemolytic reaction was recorded for colony types growing on Trypticase soy agar.<br>- Following primary isolation, each colony type was subcultured to Trypticase soy agar or Brucella blood agar to obtain a pure culture and verify the required environmental growth conditions<br>- A gram stain was performed on each pure culture with bacterial isolate identification accomplished using the VITEK 2 Compact bacterial identification system or the Biolog Microsation System<br><br>**Microbial identity**<br>- 33 different bacterial species were isolated among the placebo, chlorhexidine and amoxicillin groups<br>- There were 24 different bacterial species isolated in the placebo group, 15 isolated in the chlorhexidine group and 10 isolated in the amoxicillin group<br>- Of the 33 different bacterial species, 7 (21%) were alpha-hemolytic and also belonged to the viridans group streptococci. In the placebo group, 5 bacterial species isolated were alpha-hemolytic/viridans group streptococci, two isolated in the chlorhexidine group and one isolated in the amoxicillin group.<br><br>**Study limitations: assessed using GRADE risk of bias checklist**<br>- Blinding not described, insufficient information to judge whether subjects and/or assessors were blind<br>- Incidence of positive blood cultures at baseline before prophylaxis not reported separately but together with incidence at any of the blood draws<br>- Power calculation not reported |

1 **Table 108**

| Bibliographic reference | Sanchez-Carrion, S., Prim, MP., De Diego, JI., Sastre, N., Pena-Garcia, P. (2006). Utility of prophylactic antibiotics in pediatric adenoidectomy. International journal of pediatric otorhinolaryngology. 70 (7): 1275 -1281 |
|---|---|
| Study type | RCT (double blind) |
| Aim | To determine the utility of prophylactic antibiotics in non-risk pediatric patients undergoing adenoidectomy |
| Patient characteristics | **Inclusion criteria**<br>- Subjects under 14 years of age scheduled for adenoidectomy (without tonsillectomy)<br>- Absence of immunosuppressive (medical and/or pharmacological) status<br>- No risk of bacterial endocarditis |

| Bibliographic reference | Sanchez-Carrion, S., Prim, MP., De Diego, JI., Sastre, N., Pena-Garcia, P. (2006). Utility of prophylactic antibiotics in pediatric adenoidectomy. International journal of pediatric otorhinolaryngology. 70 (7): 1275 -1281 |
|---|---|
| | - No antimicrobial therapy for at least 15 days prior to operation<br>- No fever 1 week before surgery<br><br>**Exclusion criteria**<br>Not reported<br><br>**Other characteristics**<br>Age in months, mean<br>With prophylaxis: 72.4<br>Without prophylaxis: 69.6<br>p=0.655<br><br>Gender, n (%)<br>With prophylaxis: male – 29 (56.9), female – 22 (43.1)<br>Without prophylaxis: male – 28 (56.0), female – 22 (44.0)<br>P=1.000<br><br>Procedure, n (%)<br>With prophylaxis: with ear tubes – 25 (49%), without ear tubes – 26 (51%)<br>Without prophylaxis: with ear tubes – 27 (54%), without ear tubes – 23 (46%)<br>p=0.692<br><br>Length of procedure in minutes, mean<br>With prophylaxis: 28.1<br>Without prophylaxis: 30.2<br>p=0.662 |
| **Number of Patients** | 101 were randomised to:<br>- prophylactic group n= 51<br>- no prophylaxis n=50 |
| **Intervention** | Cefazolin 30 to 40mg/kg i.v given at induction of anaesthesia. Antibiotic prophylaxis was administered by the anaesthesiologist or the nurse before the entrance of the otolaryngologist into the operating room without his/her knowledge.<br><br>Adenoidectomy was performed by curettage of the nasopharynx (suction diathermy was not used after adenoidectomy in any |

<table>
<tr><td>Bibliographic reference</td><td>Sanchez-Carrion, S., Prim, MP., De Diego, JI., Sastre, N., Pena-Garcia, P. (2006). Utility of prophylactic antibiotics in pediatric adenoidectomy. International journal of pediatric otorhinolaryngology. 70 (7): 1275 -1281</td></tr>
<tr><td></td><td>case)</td></tr>
<tr><td>Comparison</td><td>No prophylaxis</td></tr>
<tr><td>Length of follow up</td><td>Not reported, blood samples taken up to 20 minutes after procedure</td></tr>
<tr><td>Location</td><td>Spain</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Outcomes measures and effect size<br>1) Bacteraemia levels/intensity<br>Not reported<br>2) Duration of bacteraemia<br>See 3) for number bacteraemia at different time points<br>3) Incidence of bacteraemia, n/N (%)<br>At 30 seconds<br>With prophylaxis – 2/51 (3.9), Without prophylaxis – 16/50 (32.7); p<0.001<br>At 20 minutes<br>With prophylaxis – 2/51 (3.9), Without prophylaxis – 7/50 (14.3) p=0.089<br>*In 4 cases from the without prophylaxis group, both samples were positive in the same subject<br>4) Complications (unclear whether these are complications of the procedures of effect of antibiotics)<br><br>
<table>
<tr><td>Complication</td><td>With prophylaxis, n/N (%)</td><td>Without prophylaxis, n/N (%)</td><td>p value</td></tr>
<tr><td>Immediate bleeding</td><td>1/51 (2)</td><td>1/50 (2)</td><td>1.000</td></tr>
<tr><td>Airway compromise</td><td>0/51 (0)</td><td>0/50 (0)</td><td>Not analysed as cases =0</td></tr>
<tr><td>Fever in the inpatient</td><td>2/51 (3.9)</td><td>7/50 (14)</td><td>0.092</td></tr>
<tr><td>Delayed bleeding</td><td>0/51 (0)</td><td>0/50 (0)</td><td>Not analysed as cases =0</td></tr>
<tr><td>Fever during first week</td><td>3/51 (5.9)</td><td>7/50 (14)</td><td>0.200</td></tr>
<tr><td>Odinophagia</td><td>5/51 (9.8)</td><td>11/50 (22)</td><td>0.092</td></tr>
<tr><td>Acute otitis media</td><td>1/51 (2)</td><td>4/50 (8)</td><td>0.205</td></tr>
<tr><td>Otalgia</td><td>1/51 (2)</td><td>3/50 (6)</td><td>0.362</td></tr>
<tr><td>Velopalatine insufficiency</td><td>0/51 (0)</td><td>1/50 (2)</td><td>0.495</td></tr>
<tr><td>Torticollis</td><td>0/51 (0)</td><td>0/50 (0)</td><td>Not analysed as cases</td></tr>
</table>
</td></tr>
</table>

| | |
|---|---|
| **Bibliographic reference** | **Sanchez-Carrion, S., Prim, MP., De Diego, JI., Sastre, N., Pena-Garcia, P. (2006). Utility of prophylactic antibiotics in pediatric adenoidectomy. International journal of pediatric otorhinolaryngology. 70 (7): 1275 -1281** |
| | =0 |
| **Source of funding** | Not reported |
| **Comments** | **Statistical analyses**<br>- All data collected were processed by one of the authors using SPSS statistical package, chi square test was used to compare variables. All tests received the same level of significance of 0.05.<br><br>**Assessment of bacteraemia**<br>- Venous blood samples were obtained under aseptic conditions at 30 seconds and 20 minutes after the removal of the adenoidal tissue<br>- 10ml blood was taken from a peripheral vein district from the one used for intravenous anaesthetic induction<br>- All samples taken to the microbiology lab within half an hour<br>- Blood samples were treated in aerobic and anaerobic blood culture flasks and evaluated by means of a BacT/Alert blood culture system<br>- All positive bottles were Gram stained and subcultured<br>- Terminal subcultures were made 7 days after incubation<br>- Bacteria from positive blood cultures were identified by standard laboratory methods<br><br>**Microbial identity**<br>- Organisms isolated from blood cultures in patients with prophylaxis included Haemophilus influenzae (n=1), Streptococcus viridans (n=2), Coagulase staphylococci (n=1)<br>- Organisms isolated from blood cultures in patients without prophylaxis included Coagulase staphylococci (n=3), Neisseria flavescens (n=2), Neisseria subflava (n=3), Bacillus sp (n=1), Streptococcus salivarius (n=2), Neisseria cinerea (n=1), Streptococcus viridans (n=4), Streptococcus pneumoniae (n=1), Haemophilus influenzae (n=2), Neisseria eleongata (n=1), Neisseria sicca (n=1), Corynebacterium sp (n=1), Streptococcus agalactie (n=1)<br><br>**Study limitations: assessed using GRADE risk of bias checklist**<br>- Randomisation not described<br>- Allocation concealment not described<br>- Incidence of bacteraemia at baseline before prophylaxis not reported, subjects not tested<br>- Power calculation not reported |

1 **Table 109**

| | |
|---|---|
| **Bibliographic reference** | **Diz DP, Tomas C, Limeres PJ, et al. (2006) Comparative efficacies of amoxicillin, clindamycin, and moxifloxacin in prevention of bacteremia following dental extractions. Antimicrobial Agents & Chemotherapy 50: 2996–3002.** ***[included in CG64]*** |
| **Study type** | RCT |
| **Aim** | To investigate the efficacies of the prophylactic administration of amoxicillin, clindamycin and moxifloxacin for the prevention of bacteraemia following dental extractions |
| **Patient characteristics** | **Inclusion:** patients who for behavioural reasons (autism, learning disabilities, phobias, etc) underwent dental extractions under general anaesthesia.<br><br>**Exclusion:** under 18yrs, antibiotics in the previous 3mths, routine use of oral antiseptics, history of allergy or intolerance to amoxicillin, clindamycin or moxifloxacin, any type of congenital or acquired immunodeficiency, any known risk factor for BE<br><br>**Other characteristics**<br>Age in years, mean (SD)<br>Control group: 26.1 (7.3)<br>Amoxicillin group: 23.8 (5.7)<br>Clindamycin group: 24 (5.9)<br>Moxifloxacin group: 22.4 (4.3)<br>Gender, n (%)<br>Control group: males – 29 (55), females – 24 (45)<br>Amoxicillin group: males – 34 (61), females – 22 (39)<br>Clindamycin group: males – 34 (63), females – 20 (37)<br>Moxifloxacin group: males – 29 (50), females – 29 (50)<br><br>There was NS difference in age, sex, oral health grade and number of dental extractions between the four groups |
| **Number of Patients** | N = 221 randomised<br><br>Power calculation: calculated by comparing the prevalence of bacteraemia at 30 seconds after the dental extractions between a preliminary control group and antibiotic groups. Prevalence of bacteraemia in control group was 93%, amoxicillin group 58% (power 0.6, sample size 21), clindamycin group 87% (statistical power 0.08; sample size 392) and moxifloxacin group 42% (power 0.8, sample size 11) |
| **Intervention** | Amoxicillin group: 2g amoxicillin (Clamoxyl; Smith Kline Beecham) orally 1 to 2 hours before anaesthesia induction (n=56)<br><br>Clindamycin group: 600 mg clindamycin (Dalacin) orally 1 to 2 hours before anaesthesia induction (n=54) |

| | |
|---|---|
| **Bibliographic reference** | **Diz DP, Tomas C, Limeres PJ, et al. (2006) Comparative efficacies of amoxicillin, clindamycin, and moxifloxacin in prevention of bacteremia following dental extractions. Antimicrobial Agents & Chemotherapy 50: 2996–3002.** ***[included in CG64]*** |
| | Moxifloxacin group: 400 mg moxifloxacin (Actira) orally 1 to 2 hours before anaesthesia induction (n=58) |
| **Comparison** | No prophylaxis (n = 53) |
| **Length of follow up** | Study dates January 2003 to December 2004, blood samples up to an hour after extraction |
| **Location** | Spain |
| **Outcomes measures and effect size** | **1) Bacteraemia levels/intensity**: not reported<br>**2) Duration of bacteraemia:** not reported<br>**3) Incidence of bacteraemia**<br><br>At baseline before dental manipulation but after nasotracheal intubation; control group (9.4%), amoxicillin (5%), clindamycin (12.5%), moxifloxacin (7.5%); n=40 in each group at baseline culture<br><br>At 30sec; control group (96.2%) vs. amoxicillin (46.4%), p<0.001, vs. moxifloxacin (56.9%), p<0.001, vs. clindamycin (85.1%), NS. Amoxicillin vs. clindamycin (p<0.001) moxifloxacin vs. clindamycin (p≤0.001); n=50, 54 and 56 patients in control, amoxicillin and moxifloxacin groups respectively (due to technical reasons)<br><br>At 15min; control group (64.2%) vs. amoxicillin (10.7%), p<0.001, vs. moxifloxacin (24.1%), p<0.001, vs. clindamycin (70.4%), NS. Amoxicillin vs. clindamycin (p<0.001) moxifloxacin vs. clindamycin (p<0.001); n=50, 54 and 56 patients in control, amoxicillin and moxifloxacin groups respectively (due to technical reasons)<br><br>At 1hr; control group (20%) vs. amoxicillin (3.7%), p≤0.01, vs. moxifloxacin (7.1%), p<0.05, vs. clindamycin (22.2%), NS. Amoxicillin vs. clindamycin (p<0.01) moxifloxacin vs. clindamycin (p<0.05); n=50, 54 and 56 patients in control, amoxicillin and moxifloxacin groups respectively (due to technical reasons)<br><br>Overall there were significant differences in the percentages of positive blood cultures between the control group (47.8%) vs. amoxicillin (17.5%) and vs. moxifloxacin (25.5%), p<0.001, but not vs. clindamycin (50%) |
| **Source of funding** | Xunta de Galicia of Spain |
| **Comments** | **Statistical analyses**<br>- Results analysed using SPSS. Fisher's exact test used to compare the prevalence of bacteraemia at the different time points and the frequency of polymicrobial blood cultures between the study groups. P<0.05 was considered statistically significant. Power calculation reported in study.<br><br>**Assessment of bacteraemia** |

| Bibliographic reference | **Diz DP, Tomas C, Limeres PJ, et al. (2006) Comparative efficacies of amoxicillin, clindamycin, and moxifloxacin in prevention of bacteremia following dental extractions. Antimicrobial Agents & Chemotherapy 50: 2996–3002.** ***[included in CG64]*** |
|---|---|
| | Venous blood samples taken from subjcts at baseline, 30 seconds, 15 minutes and 1 hour after dental extraction and immediately transported to laboratory. 829 pairs of blood cultures were processed in a BACTEC 9240 instrument, a gram stain was performed on each positive blood culture, the positive blood cultures in the aerobic media were subcultured on blood agar and chocolate agar and on MacConkey agar, in the anaerobic media subcultured on Schaedler agar.<br><br>**Microbial identity**<br>There was a significant difference in the proportion of polymicrobial blood cultures in the control group (29%) vs. amoxicillin (0%) p<0.001, vs. moxifloxacin (14.8%) p<0.05, NS vs. clindamycin (31.7%).<br>Most frequent in the positive blood cultures was streptococcus (63.1%), followed by staphylococcus (11.3%) and neisseria (7.5%).<br><br>**Study limitations: assessed using GRADE risk of bias checklist**<br>- Allocation concealment not described<br>- 'Double blind'; details not described<br>- Baseline blood samples only obtained from 40 subjects in each group (reason not given)<br>- For postextraction blood cultures, n=50, 54 and 56 patients in control, amoxicillin and moxifloxacin groups respectively (due to technical reasons). However, these numbers don't fully match the percentages reported in study therefore missing data possible.<br>- Unclear if the same subjects were bacteraemic at the different time points<br>- Incidence of bacteraemia at baseline not comparable between groups |

**Table 110**

| Bibliographic reference | **Hall G, Hedstrom SA, Heimdahl A, Nord CE. Prophylactic administration of penicillins for endocarditis does not reduce the incidence of postextraction bacteremia.[see comment]. Clinical Infectious Diseases 1993;17:188-94** ***[included in CG64]*** |
|---|---|
| **Study type** | RCT |
| **Aim** | To investigate with the use of a lysis filtration technique, the effects of prophylaxis with penicillin V and amoxicillin on the incidence, type and magnitude of bacteraemia in patients undergoing dental extraction. |
| **Patient characteristics** | **Inclusion:** otherwise healthy patients referred to the department of oral surgery for dental extraction, n = 42 male, mean age 47yrs (range 23 to 74yrs)<br><br>**Exclusion:** allergy to penicillins, cardiovascular, renal, hepatic or GI diseases, pregnant women |

| | |
|---|---|
| **Bibliographic reference** | **Hall G, Hedstrom SA, Heimdahl A, Nord CE. Prophylactic administration of penicillins for endocarditis does not reduce the incidence of postextraction bacteremia.[see comment]. Clinical Infectious Diseases 1993;17:188-94** ***[included in CG64]*** |
| | **Other characteristics**<br>Age in years, mean (range)<br>47 (23 to 74 years)<br><br>Gender, n<br>Men – 42<br>Female – 18<br><br>None of the patients were receiving any medication except analgesics |
| **Number of Patients** | N = 60 |
| **Intervention** | Penicillin V group: two 1g penicillin V tablets plus 4 tablets of amoxicillin placebo (n=20)<br>Amoxicillin group: four 750mg amoxicillin tablets plus two tablets of penicllin V placebo (n=20)<br><br>All interventions given orally 1hr before dental extraction*<br>*Single tooth extraction all by the same surgeon because of dental caries or chronic periradicular osteitis. |
| **Comparison** | Placebo group: 2 tablets of penicillin V placebo and 4 tablets of amoxicillin placebo 1 hour before dental extraction (n=20) |
| **Length of follow up** | Blood samples taken up to 10 minutes after extraction |
| **Location** | Sweden |
| **Outcomes measures and effect size** | **1) Bacteraemia levels/intensity, reported as median cfu/ml in positive samples**<br>Placebo: bacteraemia during surgery – 0.84, 10 minutes after surgery – 0.36<br>Penicillin V, 2g: bacteraemia during surgery – 0.66, 10 minutes after surgery – 0.36<br>Amoxicillin, 3g: bacteraemia during surgery – 1.08, 10 minutes after surgery – 0.24<br><br>**2) Duration of bacteraemia: not reported**<br><br>**3) Incidence of bacteraemia (N=20 in each group)**<br>No microorganisms were observed in any pre-treatment blood samples<br>During dental extraction; placebo (90%), penicillin V (90%), amoxicillin (85%)<br>10mins after surgery; placebo (80%), penicillin V (70%), amoxicillin (60%)<br><br>NS difference in the incidence or magnitude of bacteraemia, of bacteraemia due to viridans streptococci, or of bacteraemia due to anaerobic bacteria among the three patient groups at any of the sampling times |

| | |
|---|---|
| **Bibliographic reference** | **Hall G, Hedstrom SA, Heimdahl A, Nord CE. Prophylactic administration of penicillins for endocarditis does not reduce the incidence of postextraction bacteremia.[see comment]. Clinical Infectious Diseases 1993;17:188-94** ***[included in CG64]*** |
| | 10mins after dental extraction, the number of microorganisms had decreased in similar ways in all three patient groups from that found during extraction ($p<0.01$) |
| **Source of funding** | Supported by the Swedish National Association against Heart and Chest Diseases and the Swedish Dental Society |
| **Comments** | **Statistical analyses**<br>Differences in the incidence of bacteraemia among the 3 patient groups were analysed with the use of Fisher's exact test.<br><br>**Assessment of bacteraemia**<br>- Blood samples were drawn before, during and 10 minutes after dental extraction and samples immediately processed to the laboratory.<br>- The blood samples were injected into bottles with 0.193L of a lysin solution and vacuum filtration was performed.<br>- Aerobic and anaerobic microorganisms were identified using the methods described in the Manual of Clinical Microbiology. Quantitative counts were estimated from the numbers of colonies visible on the filters.<br>- Lysis filtration under anaerobic conditions Blood samples: before, during and 10mins after dental extraction.<br><br>**Microbial identity**<br>- Streptococcus intermedius was the most common species isolated and was also found to have the highest number of organisms per ml of blood in all 3 samples.<br>- Other frequently isolated viridans streptococci were Streptococcus mitior, Streptococcus mutans and Streptococcus sanguis.<br>- Aerobic species other than viridans streptococci were isolated in small numbers.<br><br>**Study limitations assessed using GRADE risk of bias checklist**<br>- Randomisation, allocation concealment and blinding not described<br>- Unclear if subjects bacteraemic 10 minutes after surgery were those who were also bacteraemic during surgery<br>- Power calculation not reported |

1 **Table 111**

| | |
|---|---|
| **Bibliographic reference** | **Roberts GJ, Radford P, Holt R. Prophylaxis of dental bacteraemia with oral amoxycillin in children. British Dental Journal 1987;162:179-82.** ***[included in CG64]*** |
| **Study type** | RCT |
| **Aim** | To determine the incidence of bacteraemia from dental extractions, the levels of circulating amoxicillin following one dose equivalent to 3g in an adult, the feasibility of using this dose prior to a general anaesthetic and the efficacy of amoxicillin in |

| Bibliographic reference | **Roberts GJ, Radford P, Holt R. Prophylaxis of dental bacteraemia with oral amoxycillin in children. British Dental Journal 1987;162:179-82. *[included in CG64]*** |
|---|---|
| | eliminating dental bacteraemia |
| **Patient characteristics** | **Inclusion:** under 16yrs and required admission for extensive conservative dental work as well as the extraction of at least one tooth. The presence of a peripheral vein suitable for cannulation was necessary.<br><br>**Exclusion:** allergy to one of the penicillin group of drugs or a significant medical disorder<br><br>**Other characteristics**<br>Age, mean (SD)<br>Controls: 9 years, 11 months (4 years, 1 month)<br>Oral amoxicillin: 8 years, 4 months (2 years, 11 months)<br>Gender, number female/male<br>Controls: 19/28<br>Oral amoxicillin: 22/25<br><br>The randomised groups were comparable in age and sex |
| **Number of Patients** | n = 108 (47 control arm, 47 oral amoxicillin, 6 additional refusers and 8 additional cardiac patients) |
| **Intervention** | Oral amoxicillin 50mgs/kg 2hrs before the scheduled time for surgery (mean dose 50.4mg/kg)<br>(n=47) |
| **Comparison** | No prophylaxis (n=47) |
| **Length of follow up** | Blood samples taken up to 5 minutes after extraction |
| **Location** | UK |
| **Outcomes measures and effect size** | **1) Bacteraemia levels/intensity: not reported**<br>**2) Duration of bacteraemia: not reported**<br>**3) Incidence of bacteraemia**<br>- All samples taken at the pre-intubation sampling time were negative<br>- 2mins after intubation n = 3/47 in the control group and n = 2/6 in the refusers had positive blood cultures (these were typical of those commonly colonising the upper respiratory tract). All other groups (amoxicillin and cardiac patients) were negative.<br>- The post extraction samples (2 minutes post-extraction); n = 18/47 positive in the control group, n = 1/47 in the amoxicillin group and n = 2/6 in the refusers group, control vs. amoxicillin, p<0.001 (the organisms isolated were typical of those normally found in bacterial dental plaque)<br>- All cardiac patients had sterile blood cultures pre and post extraction. |
| **Source of funding** | Not stated |
| **Comments** | **Statistical analyses** |

| Bibliographic reference | **Roberts GJ, Radford P, Holt R. Prophylaxis of dental bacteraemia with oral amoxycillin in children. British Dental Journal 1987;162:179-82. *[included in CG64]*** |
|---|---|
| | Statistical tests used were the Chi Square and Student's t –test<br><br>**Assessment of bacteraemia**<br>- 4x1ml blood samples processed using differing broths, plates were incubated and positive results recorded as cfu, bacteria grown were identified by a described procedure (a broad spectrum penicillinase was added to all samples from those who had received amoxicillin, a pilot study confirmed that the addition did not alter culture results)<br>- Blood samples: prior to nasotracheal intubation, 2mins after nasotracheal intubation, extensive conservative dental work was carried out before extraction; 2mins after extraction of the first tooth samples were taken. (supplementary studies; one had additional samples taken at 45secs post extraction, another 5mins post extraction)<br><br>**Microbial identity**<br>The organisms isolated were typical of those normally found in bacterial dental plaque.<br><br>**Study limitations: assessed using GRADE risk of bias checklist**<br>- Randomisation not described ('at random'), allocation concealment not described, blinding not described.<br>- Patients 'satisfactorily' consume the oral amoxicillin<br>- Unclear whether those positive post extraction were those positive post intubation<br>- Power calculation not reported |

1 **Table 112**

| Bibliographic reference | **Hall G, Heimdahl A, Nord CE. Effects of prophylactic administration of cefaclor on transient bacteremia after dental extraction. European journal of clinical microbiology & infectious diseases 1996; 15: 646–49 *[included in CG64]*** |
|---|---|
| **Study type** | RCT (Double-blind) |
| **Aim** | To investigate the effects of prophylaxis with ceflacor on the incidence, type and magnitude of bacteraemia in patients undergoing dental extraction |
| **Patient characteristics** | **Inclusion:** those undergoing dental extraction<br><br>**Exclusion:** not reported<br><br>**Other characteristics**<br>Age in years, mean (range)<br>Cefaclor group: 43 (26 to 66)<br>Placebo group: 46 (21 to 61) |

| Bibliographic reference | **Hall G, Heimdahl A, Nord CE. Effects of prophylactic administration of cefaclor on transient bacteremia after dental extraction. European journal of clinical microbiology & infectious diseases 1996; 15: 646–49 *[included in CG64]*** |
|---|---|
| | Gender, n<br>Cefaclor group: 10 males, 10 females<br>Placebo group: 10 males, 9 females |
| **Number of Patients** | N = 39 randomised |
| **Intervention** | Two 0.5g Cefaclor tablets (Eli Lilly, UK) 1g, 1 hr prior to dental extraction<br>(n = 19) |
| **Comparison** | Two tablets of placebo 1 hr prior to dental extraction<br>(n=20) |
| **Length of follow up** | Not reported, blood samples taken up to 10 mins following extraction |
| **Location** | Sweden |
| **Outcomes measures and effect size** | 1) Bacteraemia levels/intensity<br>The magnitude of bacteraemia (counts of cfu's) was reduced by 75% in the 10 minute blood sample in both patient groups (average in each group not reported)<br>2) Duration of bacteraemia<br>Not reported<br>3) Incidence of bacteraemia<br>- None of the patients were bacteraemic prior to dental extraction<br>- During dental extraction positive blood cultures; 79% cefaclor group; 85% placebo group<br>- 10mins after extraction positive blood cultures; 53% cefaclor group; 47% placebo group |
| **Source of funding** | Swedish Medical Research Council |
| **Comments** | **Statistical analyses**<br>Difference in the incidence of bacteraemia between the 2 groups were analysed by use of a two sided chi-square test. The Wilcoxon rank sum test was used to compare the groups with respect to the counts of microorganisms isolated.<br><br>**Assessment of bacteraemia**<br>- 8.3ml blood samples were taken before, during and 10 minutes after dental extraction<br>- The blood samples were processed immediately by lysis filtration<br>- Aerobic and anaerobic microorganisms were identified using standard methods |

| Bibliographic reference | **Hall G, Heimdahl A, Nord CE. Effects of prophylactic administration of cefaclor on transient bacteremia after dental extraction. European journal of clinical microbiology & infectious diseases 1996; 15: 646–49 *[included in CG64]*** |
|---|---|
| | **Microbial identity**<br>Post-extraction bacteraemia had a dominance of gram-positive strains (>90%) in both groups<br>Viridans streptococci during extraction; 79% cefaclor; 50% placebo group<br>Viridans streptococci 10mins after extraction; 26% cefaclor; 30% placebo group<br>Strains of streptococcus intermedius most frequently isolated, followed by streptococcus sanguis and streptococcus mitis in both patient groups<br>Anaerobic bacteraemia during extraction; 74% cefaclor; 75% placebo group<br>Anaerobic bacteraemia 10 minutes after extraction; 47% cefaclor; 35% placebo group<br>Actinomyces spp. were most commonly identified strains (Veilloneela and Prevotella isolated from single patients)<br><br>**Study limitations: assessed using GRADE risk of bias checklist**<br>- Randomisation, concealment not described<br>- 'Double blind', details not described<br>- Unclear if those positive after extraction are those positive during extraction<br>- Unclear if one subject lost from control group at 10 minutes<br>- Power calculation not reported |

1 **Table 113**

| Bibliographic reference | **Shanson DC, Akash S, Harris M, Tadayon M. Erythromycin stearate, 1.5 g, for the oral prophylaxis of streptococcal bacteraemia in patients undergoing dental extraction: efficacy and tolerance. Journal of Antimicrobial Chemotherapy 1985;15:83-90 *[included in CG64]*** |
|---|---|
| **Study type** | RCT |
| **Aim** | To determine the efficacy of 1.5g oral loading dose of erythromycin stearate given 1 hour before extraction for the prophylaxis of post-extraction streptococcal bacteraemia and to compare the incidence of gastrointestinal side effects associated with this dose of erythromycin with that of a placebo administered to a control group of dental patients. |
| **Patient characteristics** | **Inclusion**<br>- Side effects study: adult patients aged 18 to 78 undergoing dental extractions in the out-patient department<br>- Dental bacteraemia study: healthy non-fasting adults aged between 18 to 71 attending the outpatient department<br><br>**Exclusion:** not reported<br><br>**Other characteristics**<br>Side effects study: age 18 to 78 years, male:female ratio 3:1 |

| | |
|---|---|
| **Bibliographic reference** | **Shanson DC, Akash S, Harris M, Tadayon M. Erythromycin stearate, 1.5 g, for the oral prophylaxis of streptococcal bacteraemia in patients undergoing dental extraction: efficacy and tolerance. Journal of Antimicrobial Chemotherapy 1985;15:83-90 *[included in CG64]*** |
| | Dental bacteraemia study: aged 18 to 71 years |
| **Number of Patients** | n = 109 side effects study n = 82 dental bacteraemia study |
| **Intervention** | 1.5g erythromycin stearate orally 1hr before dental extraction (n=56 for side effects study, n=40 for dental bacteraemia study) |
| **Comparison** | Matched placebo (n=53 for side effects study and n= 42 for dental bacteraemia study) |
| **Length of follow up** | 7days |
| **Location** | London |
| **Outcomes measures and effect size** | **1) Bacteraemia levels/intensity: not reported**<br>**2) Duration of bacteraemia: not reported**<br>**3) Incidence of bacteraemia**<br><br><u>Streptococcal bacteraemia post extraction</u><br>Streptococci were isolated from the nutrient broth cultures in n = 18/42 (43%) in the control group compared with n = 6/40 (15%) erythromycin group, p=0.01<br><br>**4) Side-effects**<br>n = 29/56 (52%) receiving erythromycin reported GI side-effects compared with n = 10/53 (19%) placebo group. Side effects included mild or transient nausea, abdominal discomfort or flatulence usually occurring within a few hours of dental extraction. No patients vomited. |
| **Source of funding** | Abbott Laboratories |
| **Comments** | **Statistical analyses**<br>Chi square test<br><br>**Assessment of bacteraemia**<br>- Blood samples were collected from patients 1 to 2 minutes after the dental procedure<br>- Each blood sample was cultured by 3 different methods designed to reduce anti-streptococcal activity due to erythromycin using high dilution techniques after different time intervals (immediate 1 in 250 dilution blood culture broths, 6h 1 in 20 dilution blood culture broths and 24h 1 in 250 dilution blood culture broths)<br>- All 1 litre blood culture bottles were subcultured after 24 hours, 48 hours and 5 days incubation. The plates were incubated aerobically for 48 hours in carbon dioxide incubator.<br>-The identification of viridans streptococci was carried out using optochin tests and AP strep 20 tests.<br><br>**Microbial identity** |

| | |
|---|---|
| **Bibliographic reference** | **Shanson DC, Akash S, Harris M, Tadayon M. Erythromycin stearate, 1.5 g, for the oral prophylaxis of streptococcal bacteraemia in patients undergoing dental extraction: efficacy and tolerance. Journal of Antimicrobial Chemotherapy 1985;15:83-90 *[included in CG64]*** |
| | - Study specifically examined streptococci prevalence as summarised above<br><br>**Study limitations: assessed using GRADE risk of bias checklist**<br>- Number bacteraemic at baseline not reported (unclear if subjects were tested)<br>- Power calculation not reported |

1 **Table 114**

| | |
|---|---|
| **Bibliographic reference** | **Wahlmann U, Al Nawas B, Jutte M, Wagner W. Clinical and microbiological efficacy of single dose cefuroxime prophylaxis for dental surgical procedures. International Journal of Antimicrobial Agents 1999;12:253-6 *[included in CG64]*** |
| **Study type** | RCT |
| **Aim** | To study the effect of a single dose of cefuroxime before multiple tooth extractions on the clinical findings and occurrence of bacteraemia |
| **Patient characteristics** | **Inclusion:** patients with multiple tooth extraction in preparation for radiotherapy of oral cancer,<br>**Exclusion:** those with allergy to cephalosporins, had received antibiotics in the past 3wks, those with an absolute indication for perioperative chemoprophylaxis<br>**Other characteristics**<br>Gender, n/N<br>Male – 54/59<br>Age in years, mean (range)<br>48 (31 to 81) |
| **Number of Patients** | n = 59 |
| **Intervention** | 1.5g IV cefuroxime 10mins before multiple tooth extractions* (n=30)<br>***** A mean of 8.8 teeth were extracted in each patient |
| **Comparison** | Placebo - 0.9% NaCl (n=29) |
| **Length of follow up** | Not reported, blood drawn at upto 40 minutes after drug administration in intervention group, and upto 30 minutes after procedure in control group |
| **Location** | Germany |
| **Outcomes measures and effect size** | **1) Bacteraemia levels/intensity: not reported**<br>**2) Duration of bacteraemia: not reported**<br>**3) Incidence of bacteraemia**<br>A significantly lower rate of bacteraemia was identified after cefuroxime administration at 10min (cefuroxime n = 7/30, 23% vs. |

| | |
|---|---|
| **Bibliographic reference** | **Wahlmann U, Al Nawas B, Jutte M, Wagner W. Clinical and microbiological efficacy of single dose cefuroxime prophylaxis for dental surgical procedures. International Journal of Antimicrobial Agents 1999;12:253-6 *[included in CG64]*** |
| | control n = 23/29, 79%) and 30min (cefuroxime n = 6/30, 20% vs. control n = 20/29, 69%) after the start of surgery. This was also significant for 10 or 30min (n = 10/30, 33% vs. n = 25/30, 86%) |
| **Source of funding** | Not stated |
| **Comments** | **Statistical analyses**<br>- Statistical analysis was performed using SAS<br>- Fisher's exact test was used to test categorical variables for significant differences<br><br>**Assessment of bacteraemia**<br>- Blood cultures were drawn at the start of the surgical procedure and 30 minutes later.<br>- Blood was inoculated into a Signal system and processed according to the manufacturer's recommendations<br>- Susceptibility testing was carried out using he standard agar diffusion technique<br><br>**Microbial identity**<br>Gram positive cocci mostly streptococci were the predominant organisms followed by Gram negative rods; growth mainly anaerobic<br><br>**Study limitations: assessed using GRADE risk of bias checklist**<br>- Randomisation, concealment and blinding not described<br>- Number bacteraemic at baseline not reported (unclear if subjects tested)<br>- Unclear whether subjects bacteraemic at 30 minutes were same subjects bacteraemic at 10 minutes<br>- Power calculation not reported |

1 **Table 115**

| | |
|---|---|
| **Bibliographic reference** | **Allan WR, Kumar A (1985) Prophylactic mezlocillin for transurethral prostatectomy. British Journal of Urology 57: 46–49. *[included in CG64]*** |
| **Study type** | RCT |
| **Aim** | To test the efficiency of prophylactic mezlocillin in a prospective clinical trial |
| **Patient characteristics** | **Inclusion:** undergoing transurethral prostatectomy<br><br>**Exclusion:** allergy to penicillin, known UTI, had received antibiotics in the week before surgery<br><br>**Other characteristics** |

| Bibliographic reference | **Allan WR, Kumar A (1985) Prophylactic mezlocillin for transurethral prostatectomy. British Journal of Urology 57: 46–49. *[included in CG64]*** |
|---|---|
| | Age in years, mean<br>Mezlocillin group: 68.78<br>Control group: 70.72<br><br>There was NS difference between the groups in terms of age, presence of malignant prostate, time taken for operation. |
| **Number of Patients** | N = 100 |
| **Intervention** | 2g intravenous mezlocillin about the time of induction of anaesthesia (n=50) |
| **Comparison** | No prophylaxis (n=50) |
| **Length of follow up** | Not reported |
| **Location** | UK |
| **Outcomes measures and effect size** | **1) Bacteraemia levels/intensity: not reported**<br>**2) Duration of bacteraemia: not reported**<br>**3) Incidence of bacteraemia**<br>After completion of operation n = 2 (4%) in mezlocillin group; n = 16 (32*%) in control group; p<0.001<br>First day post-op and after removal of catheter NS difference between the groups<br><br>*Calculated by reviewer based on assumption that subjects were not lost |
| **Source of funding** | Bayer Company |
| **Comments** | **Statistical analyses**<br>Not reported<br><br>**Assessment of bacteraemia**<br>Immediately after the operation blood was obtained for culture and further blood culture was carried out on the first post-operative day and again when the catheter was removed. Further details of microbiological analysis not reported.<br><br>**Microbial identity**<br>Mezlocillin group; blood (Escherichia coli, Bacteroides fragilis), urine (E. coli, proteus, enterococci, Staphylococcus aureus, Staphylococcus albus)<br>Control group; blood (E. coli, proteus, enterococci, S. aureus, S. albus, Streptococcus faecalis), urine (E. coli, proteus, Pseudomonas spp, enterococci, S. aureus, S. albus, S. faecalis)<br><br>**Study limitations: assessed using GRADE risk of bias checklist**<br>- Unclear if subjects lost from control group as percentages reported in study do not match up with number randomised to |

| Bibliographic reference | **Allan WR, Kumar A (1985) Prophylactic mezlocillin for transurethral prostatectomy. British Journal of Urology 57: 46–49. *[included in CG64]*** |
|---|---|
| | control arm<br>- Blood culture methods not reported<br>- Number bacteraemic at baseline not reported<br>- Power calculation not reported |

1 **Table 116**

| Bibliographic reference | **Bhattacharya S, Parkin DE, Reid TM et al. (1995) A prospective randomised study of the effects of prophylactic antibiotics on the incidence of bacteraemia following hysteroscopic surgery. European Journal of Obstetrics, Gynecology & Reproductive Biology 63: 37–40 *[included in CG64]*** |
|---|---|
| **Study type** | RCT |
| **Aim** | To examine the incidence of bacteraemia in women undergoing endometrial ablation with and without antibiotic prophylaxis |
| **Patient characteristics** | **Inclusion:** women with menorrhagia undergoing either transcervical resection (TCRE) or laser ablation of the endometrium (ELA)<br><br>**Exclusion:** not reported<br><br>**Other characteristics**<br>Age, etc not reported |
| **Number of Patients** | N = 116<br><br>Power calculation: 80% power to detect a difference of 15% from 1% to 16% at the 5% significance level (based on review of data from first 100 cases) |
| **Intervention** | 1.2 g augmentin IV at the induction of anaesthesia<br>(n = 55) |
| **Comparison** | No antibiotic<br>(n = 61) |
| **Length of follow up** | Discharged same or following day, given a diary to record events over the next 2 wks |
| **Location** | UK |
| **Outcomes measures and effect size** | **1) Bacteraemia levels/intensity: not reported**<br>**2) Duration of bacteraemia: not reported**<br>**3) Incidence of bacteraemia**<br>n = 10 (16%) positive blood cultures in the no antibiotic group compared with n = 1 (2%) in the antibiotic group, p<0.02, |

| | |
|---|---|
| **Bibliographic reference** | **Bhattacharya S, Parkin DE, Reid TM et al. (1995) A prospective randomised study of the effects of prophylactic antibiotics on the incidence of bacteraemia following hysteroscopic surgery. European Journal of Obstetrics, Gynecology & Reproductive Biology 63: 37–40 *[included in CG64]*** |
| | 95%CI: 5 to 25.<br><br>Infectious morbidity: post-operative outcome within 2 weeks of endometrial ablation<br>No antibiotic; pain (n = 26, 43%); offensive discharge (n = 14, 23%); fever (n = 4, 7%); visit to GP (n = 11, 18%); antibiotics prescribed by GP (n = 7, 11.4%)<br>Antibiotic; pain (n = 29, 53%); offensive discharge (n = 14, 26%); fever (n = 9, 16%); visit to GP (n = 11, 20%); antibiotics prescribed by GP (n = 5, 9%)<br><br>None of the participants, regardless of their blood culture status, became seriously ill. |
| **Source of funding** | Chief Scientists Office of the Scottish Office |
| **Comments** | **Statistical analyses**<br>Analysis by intention to treat. The chi square test was used for significance.<br><br>**Assessment of bacteraemia**<br>20ml blood samples obtained immediately after the routine TCRE or ELA<br>Sample divided equally between 2 culture bottles, one aerobic and one anaerobic.<br>Blood culture bottles incubated in a non-radiometric Bactec 860 analyser at 37˚C for 5 days<br>Any bottles giving a reading above the detection threshold were subcultured on to plates containing blood agar, MacConkey agar and incubated. Endocervical swabs were cultured on blood and MacConkey agar and chocolate agar.<br><br>**Microbial identity**<br>Organisms isolated from the endocervix were mixed anaerobes, Group B haemolytic Streptococcus and E.coli.<br><br>**Study limitations: assessed using GRADE risk of bias checklist**<br>- Incidence of bacteraemia at baseline not reported, unclear if subjects tested<br>- Baseline characteristics not reported |

1 **Table 117**

| | |
|---|---|
| **Bibliographic reference** | **Selby WS, Norton ID, Pokorny CS et al. (1994) Bacteremia and bacterascites after endoscopic sclerotherapy for bleeding esophageal varices and prevention by intravenous cefotaxime: a randomized trial. Gastrointestinal Endoscopy 40: 680-4 *[included in CG64]*** |
| **Study type** | RCT |

| | |
|---|---|
| **Bibliographic reference** | **Selby WS, Norton ID, Pokorny CS et al. (1994) Bacteremia and bacterascites after endoscopic sclerotherapy for bleeding esophageal varices and prevention by intravenous cefotaxime: a randomized trial. Gastrointestinal Endoscopy 40: 680-4 *[included in CG64]*** |
| **Aim** | To examine the effect of prophylactic cefotaxime on the frequency of bacteraemia and bacterascites occurring after endoscopic injection of bleeding esophageal varices and its effect on clinical infection, in particular bacterial peritonitis. |
| **Patient characteristics** | **Inclusion:** all patients presenting with bleeding esophageal varices and who underwent emergency endoscopic sclerotherapy, defined as performed within 48hrs of bleeding<br>**Exclusion:** antibiotics within 72hrs, antibiotics required for other indications, patients who met the criteria for spontaneous bacterial peritonitis*, allergy to penicillin or cephalosporins, refused entry to study or whose relative or attending physician declined.<br>*Previous episodes of spontaneous bacterial peritonitis were not a reason for exclusion.<br><br>**Other characteristics**<br>Age in years, mean (SD)<br>Antibiotic group: 58.9 (14.2)<br>Control group: 49.5 (10.7)<br><br>Gender, number male: number female<br>Antibiotic group: 15:4<br>Control group: 13:7<br><br>There was no difference between the groups in cause of liver disease, use of ET tubes, need for vasopressin or balloon tamponade. |
| **Number of Patients** | n = 31 (39 episodes of bleeding) |
| **Intervention** | 1g cefotaxime IV immediately before endoscopic sclerotherapy<br>(n = 19) |
| **Comparison** | No antibiotic<br>(n = 20) |
| **Length of follow up** | Study between August 1989 to December 1991 |
| **Location** | Australia |
| **Outcomes measures and effect size** | **1) Bacteraemia levels/intensity: not reported**<br>**2) Duration of bacteraemia: not reported**<br>**3) Incidence of bacteraemia** |

| | |
|---|---|
| **Bibliographic reference** | **Selby WS, Norton ID, Pokorny CS et al. (1994) Bacteremia and bacterascites after endoscopic sclerotherapy for bleeding esophageal varices and prevention by intravenous cefotaxime: a randomized trial. Gastrointestinal Endoscopy 40: 680-4 *[included in CG64]*** |
| | Antibiotic group: 1/19 (5.3%) positive at 5mins with cefotaxime, none positive at 4 hours or 24 hours.<br>Control group*: 6/19 (31.6%) positive cultures at 5mins, 1 (out of the 6 positive at 5 mins) was positive at 4 hours, no patient was bacteraemic at 24 hours<br>P at 5 minutes=0.04<br><br>*1 subjects was positive before procedure and therefore not considered in analysis<br><br><u>Mortality</u><br>2/19 in antibiotics group vs 5/19 in control group. |
| **Source of funding** | Not stated |
| **Comments** | **Statistical analyses**<br>Fisher's exact test<br><br>**Assessment of bacteraemia**<br>- Blood samples before endoscopy, 5mins, 4hrs and 24hrs after sclerotherapy<br>- Cultures were performed using standard aerobic and anaerobic techniques at 37C, organisms were identified using conventional means<br><br>**Microbial identity**<br>Antibiotic group: organism identified was an alpha-haemolytic streptococcus<br>Control group: organism identified included alpha-haemolytic streptococcus, Veillonella sp, Streptococcus milleri, Streptococcus salivarius, Neisseria sp.<br><br>**Study limitations assessed using GRADE risk of bias checklist**<br>- Blinding not described<br>- Power calculation not reported |

1 **Table 118**

| | |
|---|---|
| **Bibliographic reference** | **Lockhart PB, Brennan MT, Kent ML, Norton HJ, Weinrib DA. Impact of amoxicillin prophylaxis on the incidence, nature, and duration of bacteraemia in children after intubation and dental procedures. Circulation 2004;109:2878-84. *[included in CG64]*** |
| **Study type** | RCT |

| | |
|---|---|
| **Bibliographic reference** | **Lockhart PB, Brennan MT, Kent ML, Norton HJ, Weinrib DA. Impact of amoxicillin prophylaxis on the incidence, nature, and duration of bacteraemia in children after intubation and dental procedures. Circulation 2004;109:2878-84. *[included in CG64]*** |
| **Aim** | To determine the impact of amoxicillin prophylaxis on the incidence, nature and duration of bacteremia from nasotracheal intubation and dental procedures in children. |
| **Patient characteristics** | **Inclusion:** children who required dental treatment (extraction) in the operating room setting because of behaviour, young age and/or the scope of treatment needs<br><br>**Exclusion:** poorly controlled systemic illness, physical status level III or IV, medical conditions requiring antibiotic prophylaxis, allergy to penicillin-type drugs, weight <12kg, exposure to systemic antibiotics within the past 2wks<br><br>**Other characteristics**<br>Age in years, mean (SD)<br>Amoxicillin group: 3.4 (1.3)<br>Placebo group: 3.5 (1.5)<br><br>Male, n (%)<br>Amoxicillin group: 30 (61)<br>Placebo group: 26 (51)<br><br>There was NS difference in the baseline characteristics for all subjects, stratified by treatment group |
| **Number of Patients** | n = 100<br><br>Power calculation: based on proportion of subjects who had a development of bacteraemia. To detect a 30% difference in incidence with a power of 80%, 100 subjects would be required. |
| **Intervention** | Amoxicillin elixir 50mg/kg one hour before the anticipated time of intubation<br>(n = 49) |
| **Comparison** | Placebo<br>(n = 51) |
| **Length of follow up** | |
| **Location** | USA |
| **Outcomes measures and effect size** | **1) Bacteraemia levels/intensity: not reported**<br>**2) Duration of bacteraemia:**<br>Not reported as continuous outcome<br>**3) Incidence bacteraemia** |

| Bibliographic reference | **Lockhart PB, Brennan MT, Kent ML, Norton HJ, Weinrib DA. Impact of amoxicillin prophylaxis on the incidence, nature, and duration of bacteraemia in children after intubation and dental procedures. Circulation 2004;109:2878-84.** ***[included in CG64]*** |
|---|---|
| | The overall incidence from all 8 draws was greater in the placebo group than the amoxicillin group (n = 43, 84% vs. n = 16, 33%), p<0.0001<br>Highest incidence at a single time point occurred at 1.5mins (fifth draw) after extraction, placebo vs. amoxicillin (n = 34, 76% vs. n = 6, 15%), p<0.0001<br>Incidence at baseline after intubation (D1) 18% placebo vs. 4% amoxicillin , p=0.05<br>Incidence restorative and cleaning procedures (D2) 20% placebo vs. 6% amoxicillin, NS<br>Bacteraemia incidence in the placebo group; 15mins (n = 7, 18%); 30mins (n = 6, 16%); 45mins (n = 5, 14%)<br>Bacteraemia incidence in the amoxicillin group; n = 1 at 15mins, none positive at other time points<br><br>Statistically significant decrease in the incidence of bacteraemia from amoxicillin at all but one draw (D2); D1 (p=0.05), D3 (p=0.03), D4 (p=0.0001), D5 (p=0.0001), D6 (p=0.04), D7 (p=0.01), D8 (p=0.03)<br><br>No subject had a positive culture at D6,7 or 8 who did not have a positive extraction blood draw |
| **Source of funding** | Health Services Foundation Inc, Carolinas HealthCare System, Charlotte, NC |
| **Comments** | **Statistical analyses**<br>Chi square and Fisher's exact test for nominal data.<br><br>**Assessment of bacteraemia**<br>Blood samples: 2mins after the initiation of intubation; dental restorations, pulp therapy and cleaning were then completed and a second sample drawn; 10mins later a third sample for a baseline culture before dental extraction, 90secs after the initiation of the first extraction a fourth draw was taken, the remaining teeth were extracted and a fifth blood draw 90secs after the final extraction. Further draws at 15, 30 and 45mins after the end of extraction<br><br>Aerobic and anaerobic were processed according to standard methods, cultures with bacterial growth were gram stained and subcultured onto appropriate media; blood cultures were continued monitored for growth with the use of an automated Microscan (Baxter) system and standard biochemical tests were done manually to complete the identity; blood cultures were incubated for up to 14days before considered no growth to avoid missing more slow-growing oral pathogens<br><br>**Microbial identity**<br>There was a >5-fold difference in the number of positive blood cultures with placebo vs. amoxicillin, n = 128 vs. n = 24. Streptococci made up 45% (n = 57) of the total bacteria in the placebo group vs. 33% (n = 8) of the amoxicillin group<br><br>**Study limitations assessed using GRADE risk of bias checklist**<br>- Unclear if same subjects bacteraemic at different time points |

| | |
|---|---|
| **Bibliographic reference** | **Lockhart PB, Brennan MT, Kent ML, Norton HJ, Weinrib DA. Impact of amoxicillin prophylaxis on the incidence, nature, and duration of bacteraemia in children after intubation and dental procedures. Circulation 2004;109:2878-84. *[included in CG64]*** |
| | - Some subjects lost at 15 minutes; unclear how many from each group |

1 **Table 119**

| | |
|---|---|
| **Bibliographic reference** | **Qiang W, Jianchen W, MacDonald R et al. (2005) Antibiotic prophylaxis for transurethral prostatic resection in men with preoperative urine containing less than 100,000 bacteria per ml: a systematic review. [Review] [40 refs]. Journal of Urology 173: 1175-81 *[included in CG64]*** |
| **Study type** | Systematic review |
| **Aim** | To determine whether antibiotic prophylaxis can reduce the risk of postoperative infective complications in men undergoing transurethral resection of the prostate who have preoperative urine with less than 100,000 bacteria per ml. |
| **Patient characteristics** | **Inclusion:** electronic databases searched; MEDLINE 1966 to 2003, EMBASE from 1980 to 2002, Cochrane Library for RCTs and quasi-RCTs comparing antibiotic prophylaxis and placebo/or controls in men undergoing TURP.<br><br>RCTs or quasi-RCT were included if they met the criteria of comparing antibiotic prophylaxis with placebo or no treatment control patients undergoing TURP, no local or systemic signs of urinary infection, sterile preoperative urine specimen, reports of at least 1 of postoperative bacteriuria, fever, bacteraemia, septicaemia, additional antibiotic treatment, urethral stricture, catheterisation or hospitalisation duration, and were published in English<br><br>**Exclusion:** studies were excluded from analysis if patients had a preoperative temperature greater than 38C, a preoperative indwelling catheter, kidney dysfunction, bladder tumour, hypersensitivity to antibiotics, preoperative UTI and antibiotic treatment within a week before TURP<br><br>Missing or additional information was sought from authors and sponsors<br><br>**Other characteristics**<br>n = 28 trials, n = 4694 patients, mean age 69yrs, n = 10 trials placebo controlled n = 18 no treatment control<br>n = 23 compared a single type of antibiotic with placebo or no treatment, n = 5 compared 2 different antibiotic groups with placebo or no treatment |
| **Number of Patients** | 10 trials of relevance to this review question (n=1394) |
| **Intervention** | Antibiotic prophylaxis |
| **Comparison** | Placebo or no prophylaxis |
| **Length of follow up** | Various |
| **Location** | Various |

| | |
|---|---|
| **Bibliographic reference** | **Qiang W, Jianchen W, MacDonald R et al. (2005) Antibiotic prophylaxis for transurethral prostatic resection in men with preoperative urine containing less than 100,000 bacteria per ml: a systematic review. [Review] [40 refs]. Journal of Urology 173: 1175-81 *[included in CG64]*** |
| **Outcomes measures and effect size** | Incidence of bacteraemia after transurethral resection of the prostate<br>Risk difference (95%CI): -0.02 (-0.04 to 0.00) |
| **Source of funding** | Not stated |
| **Comments** | |

| Study | Antibiotic agent/class | Dosing | Inclusion criteria |
|---|---|---|---|
| Charlton et al., 1987 | Netilmicin 150mg/aminoglycoside | 1 dose intramuscularly 1 hour before surgery | French men (100), mean age, 68 years, undergoing TURP for prostatic anomaly |
| Nielsen et al., 1981 | Cefoxitin 1g/cephalosporin | 1 dose IM 2 to 4 hours before surgery + 3 times/day after surgery as long as indwelling catheter remained | American men (10), 60 to 71 years old (mean 62), undergoing TURP |
| Qvist et al., 1984 | Cefotaxime 2g/cephalosporin | 1 dose iv 1 hour before surgery | Danish men (88), mean age 68 years |
| Botto et al., 1984 | Cefotaxime 1g/cephalosporin | 1 dose IV before surgery + 2 doses after surgery | French men (167), mean 69 years, undergoing TURP |
| Charlton et al., 1984 | Mezlocillin 2g/penicillin | 1 dose IV 1 hour before surgery | French men (100), 48-86 years, undergoing TURP |
| Morris et al., 1976 | Kanamycin 1g/aminoglycoside, co-trimoxazole x2/co-trimoxazole | Kanamycin 1 dose IM before surgery, co-trimoxazole orally 2 times/day for 3 weeks after surgery | Australia men (101), mean age 71 years, undergoing TURP for prostatic obstruction |
| Stricker et al., 1988 | Gentamicin 80mg/aminoglycoside + ampicillin 1g/penicillin | 1 dose IV before surgery | Australian men (100) undergoing TURP |
| Taylor et al., 1988 | Temocillin 1g/penicillin | 1 dose IV before surgery + 2 doses after surgery | British men (308), 38-90 years undergoing TURP |
| Viitanen et al., 1993 | Ceftriaxone 2g/cephalosporin (3rd generation), | Ceftriazone 1 dose IV before surgery, sulfamethoxazole- | Finnish men (599), 45-89 years, undergoing TURP |

| Bibliographic reference | **Qiang W, Jianchen W, MacDonald R et al. (2005) Antibiotic prophylaxis for transurethral prostatic resection in men with preoperative urine containing less than 100,000 bacteria per ml: a systematic review. [Review] [40 refs]. Journal of Urology 173: 1175-81 *[included in CG64]*** |
|---|---|

| | | | |
|---|---|---|---|
| | sulfamethoxazole-trimethoprim 800/160mg/co-trimoxazole | trimethoprim 1 dose IV before surgery | |
| Weiss et al., 1983 | Nitrofurantoin 50mg x 4/nitrofurantoin | Group 1 orally 4 times/day for 5 days after surgery, group 2 orally 4 times/day for 10 days after surgery | American men (223) undergoing TURP |

**Study limitations assessed using systematic review checklist in NICE guidelines manual 2012**

Random effects model but unclear how heterogeneity was assessed; I squared or similar value not reported

1 **Table 120**

| Bibliographic reference | **Morozumi T, Kubota T, Abe D, Shimizu T. (2010) Effects of irrigation with an antiseptic and oral administration of azithromycin on bacteraemia caused by scaling and root planning. Journal of Periodontology 81 (11): 1555-1563 *[included in CG64]*** |
|---|---|
| **Study type** | Randomised controlled trial |
| **Aim** | To investigate the prevalence of bacteremia caused by scaling and root planning and to evaluate the efficacies of 2 prophylactic methods of bacteremia secondary to scaling and root planning |
| **Patient characteristics** | **Inclusion criteria**<br>- systemically healthy subjects who possessed a minimum of 20 teeth and had generalised moderate to severe chronic periodontitis which was defined as having ≥3 teeth with probing depth ≥5mm in each quadrant<br><br>**Exclusion criteria**<br>- congenital valve defects or any other risk situation for infectious endocarditis<br>- low levels of haematocrit or haemoglobin<br>- high risk of cardiovascular disease and diabetes<br>- allergy to macrolides<br>- patients who had taken systemic antibiotics, anti-inflammatory drugs or immunosuppressive drugs within 3 months before the experiment<br>- subjects receiving periodontal treatment within the previous 6 months<br>- regularly used an oral irrigation device or mouthrinse |

| Bibliographic reference | **Morozumi T, Kubota T, Abe D, Shimizu T. (2010) Effects of irrigation with an antiseptic and oral administration of azithromycin on bacteraemia caused by scaling and root planning. Journal of Periodontology 81 (11): 1555-1563** ***[included in CG64]*** |
|---|---|
| | - had an incompatible dentition (orthodontic bands, partial dentures, teeth unsuitable for extensive ultrasonic scaling<br><br>**Other characteristics**<br>Age in years, mean (SD)<br>Control group: 55.4 (9.3)<br>Azithromycin group: 56.9 (9.9)<br><br>Gender, number male/female<br>Control group: 8/2<br>Azithromycin group: 6/4 |
| **Number of Patients** | N=30<br>Randomised to control, essential-oil containing antiseptic and oral azithromycin (10 subjects each) |
| **Intervention** | Azithromycin 500mg once a day 3 days before quadrant scaling and root planning was performed<br>(n=10)<br><br>The quadrant scaling and root planning was completed within 40 minutes. All clinical procedures were performed by one dentist. Subjects were requested not to brush their teeth and to consume only liquids for ≥2 hours before sampling to avoid the possibility of any toothbrushing or chewing-induced bacteraemia. |
| **Comparison** | No prophylaxis<br>n=10 |
| **Length of follow up** | 1 week |
| **Location** | Japan |
| **Outcomes measures and effect size** | **1) Bacteremia levels/intensity: not reported**<br>**2) Duration of bacteraemia: not reported**<br>**3) Incidence of bacteraemia:**<br>Baseline: control – 0/10, azithromycin – 0/10<br>After SRP: control – 9/10, azithromycin – 2/10 |
| **Source of funding** | Grant in aid for young scientists from the Ministry of Education, Culture, Sports, Science and Technology |
| **Comments** | **Statistical analyses**<br>Chi square/Fisher's exact tests<br>**Assessment of bacteraemia**<br>Blood was collected at baseline and 6 minutes after the initiation of scaling and root planning. |

| Bibliographic reference | **Morozumi T, Kubota T, Abe D, Shimizu T. (2010) Effects of irrigation with an antiseptic and oral administration of azithromycin on bacteraemia caused by scaling and root planning. Journal of Periodontology 81 (11): 1555-1563** ***[included in CG64]*** |
|---|---|
| | Blood samples were inoculated into an anaerobic culture bottle that could both anaerobic and aerobic bacteria and immediately transported to the laboratory. Bottles were incubated and monitored over 6 days, any bottles signalled negative were discarded.<br>Bottles that signalled positive were Gram stained and subcultured onto an appropriate plate. All plates were incubated up to 14 days and examined daily. Biochemical tests were performed.<br><br>**Microbial identity**<br>All isolates were facultative or obligate anaerobes. Organisms identified included alpha streptococcus, bete-streptococcus, streptococcus constellatus, streptococcus mutans, parvimonas micra, Peptostreptococcus anaerobius, Eubacterium spp, Eggerthella lenta, Fusobacterium nucleatum, Propionibacterium acnes and Actinomyces spp.<br><br>**Study limitations assessed using GRADE risk of bias checklist**<br>- Randomisation, blinding and concealment not described<br>- Power calculation not reported |

1 **Table 121**

| Bibliographic reference | **Lockhart, PB., Brennan, MT., Sasser, HC., Fox, PC., Paster, BJ., Bahrani-Mougeot, FK. (2008). Bacteremia associated with toothbrushing and dental extraction. Circulation. 117: 3118-3125** |
|---|---|
| **Study type** | Double blind randomised controlled trial |
| **Aim** | To compare the incidence, duration, nature and magnitude of endocarditis-related bacteremia from single-tooth extraction and toothbrushing and to determine the impact of amoxicillin prophylaxis on single tooth extraction |
| **Patient characteristics** | **Inclusion criteria**<br>- Patients presenting to urgent care service with the need for extraction of at least 1 erupted tooth<br>**Exclusion criteria**<br>- Fewer than 10 teeth<br>- Use of systemic antibiotics within the previous 2 weeks<br>- Need for antibiotic prophylaxis based on current practice guidelines<br>- Active viral disease<br>- Immunocompromised<br>- Poorly controlled systemic disease<br>- History of penicillin allergy<br>- Temperature >100.5F<br>- Facial cellulitis |

| Bibliographic reference | Lockhart, PB., Brennan, MT., Sasser, HC., Fox, PC., Paster, BJ., Bahrani-Mougeot, FK. (2008). Bacteremia associated with toothbrushing and dental extraction. Circulation. 117: 3118-3125 |
|---|---|
| | - Manipulation of the gingival tissues (eg: chewing, toothbrushing) within one hour before the study<br><br>**Other characteristics**<br>1. Age in years, mean (SD)<br>Extraction-amoxicillin group: 39.7 (10.5)<br>Extraction-placebo group: 40.5 (10.9)<br><br>2. Male, n (%)<br>Extraction-amoxicillin group: 61 (64)<br>Extraction-placebo group: 51 (53)<br><br>3. Ethnicity, n (%)<br>Extraction-amoxicillin group: white – 18 (19), black – 73 (76), Hispanic – 3 (3), Other – 2(2)<br>Extraction-placebo group: white – 23 (24), black- 73 (76), Hispanic – 1 (1), Other – 0 (0)<br><br>4. Diabetes, n (%)<br>Extraction-amoxicillin group: 9 (9)<br>Extraction-placebo group: 8 (8)<br><br>5. Surgery type, n (%)<br>Extraction-amoxicillin group: simple – 83 (87), complex – 9 (9), missing – 4 (4)<br>Extraction-placebo group: simple – 70 (73), complex – 18 (19), missing – 8 (8) |
| **Number of Patients** | N=290<br>Subjects randomised to the following groups:<br>1. Toothbrushing n=98<br>2. Single tooth extraction with amoxicillin prophylaxis n=96<br>3. Single tooth extraction with an identical placebo (placebo not defined) n=96<br><br>Power calculation: assuming a significance level of 0.05, 80 subjects per study arm would yield power of 90% to detect a difference in cumulative incidences of at least 20% (prior work suggested that the incidence of bacteraemia from single tooth extraction would range between 70% and 100%. No consenus available on incidence after toothbrushing). |
| **Intervention** | Amoxicillin prophylaxis according to AHA recommendations 1 hour before extraction |

| | |
|---|---|
| **Bibliographic reference** | **Lockhart, PB., Brennan, MT., Sasser, HC., Fox, PC., Paster, BJ., Bahrani-Mougeot, FK. (2008). Bacteremia associated with toothbrushing and dental extraction. Circulation. 117: 3118-3125** |
| **Comparison** | Identical placebo |
| **Length of follow up** | 60 minutes after completion of brushing or extraction |
| **Location** | USA |
| **Outcomes measures and effect size** | **1) Bacteraemia levels/intensity: all analysed samples were below the detection threshold of 104 CFU per millilitre of blood**<br>**2) Duration of bacteraemia: not reported as continuous outcome**<br>**3) Incidence of bacteraemia**<br><u>Overall incidence</u><br>The overall incidence of bacteraemia at any of the 6 draws was 56% and 80% for the amoxicillin and placebo groups respectively*<br>The highest incidence occurred at the time of the procedures; 79% (66/84) in placebo group and 56% (50/89) in amoxicillin group*<br>*p value reported in study not for this specific comparison<br>All baseline cultures negative apart from 3 – unclear which group<br><br><u>Incidence from endocarditis related species</u><br>All baseline samples in amoxicillin and placebo groups negative<br>The cumulative incidence from all 6 draws was 33% and 60% in the amoxicillin and placebo groups<br>The highest incidence of positive cultures occurred in the first 5 minutes; 33% (29/89) and 58% (49/84) for amoxicillin and placebo groups.<br>The extraction placebo group had a greater incidence of positive cultures at 20 minutes; 10% (8/83) vs 1% (1/88) in the amoxicillin group.<br>Pattern persisted to 40 minutes |
| **Source of funding** | Supported by National Institute of Dental and Craniofacial Research/National Institutes of Health grant |
| **Comments** | **Statistical analyses**<br>- For analysis of incidence, each patient was assessed at each blood draw and coded as positive for any bacterium that was common to the list of 275 bacterial species reported to cause IE. Comparison by study arm at each blood draw and a summary comparison by study arm that combined all draws were made with Chi square tests.<br>- Duration of bacteraemia was defined as the number of blood draws at which any target organism was cultured.<br>- Intercurrent negative findings were rare (n=2), were judged to be spurious and were considered positive for analysis.<br>- Duration of specific intervals by study arm was compared with x2 tests.<br>- Statistical significance of 0.05 was used in all cases.<br><br>**Assessment of bacteraemia** |

| Bibliographic reference | Lockhart, PB., Brennan, MT., Sasser, HC., Fox, PC., Paster, BJ., Bahrani-Mougeot, FK. (2008). Bacteremia associated with toothbrushing and dental extraction. Circulation. 117: 3118-3125 |
|---|---|
| | - Baseline blood samples before prophjylaxis drawn (20ml) and 7 to 8ml inoculated directly into both aerobic and anaerobic BACTEC bottles for bacterial culturing<br>- Extraction began one hour after ingestion of amoxicillin or placebo<br>- Brushing arm subjects brushed all surfaces of the teeth adjacent to the gingiva with a new toothbrush without toothpaste for 2 minutes, timed as 30 seconds for each of the maxillary and mandibular quadrants of teeth.<br>- Subsequent blood draws of 20ml were taken at 1.5 minutes and at 5 minutes after the initiation of surgery or brushing.<br>- Additional blood samples (20ml) were drawn at 20, 40 and 60 minutes after the end of the procedure. 2mls of blood was drawn into a new syringe and discarded before each of the 6 blood draws and the catheter was flushed with 2ml of saline from a new syringe after each blood draw.<br>- Blood samples were cultured in BACTEC Plus Aerobic/F and LYTIC/10 Anaerobic/F. All false-positive bottles were further incubated for a total of 2 weeks.<br>- Bottles with positive cultures were kept for 2 weeks and subcultured periodically to ensure recover of additional species.<br>- The 16S ribosomal RNA sequencing method was used for bacterial identification.<br>- Bacterial lysates were used as templates in PCR with 16S rRNA universal primers according to standard protocols.<br>- Identification of strains was based on comparisons of the first 500 bases with Database Project and GenBank by BLAST.<br>- For those strains that were potentially new species, full 1500-base pair sequences were obtained.<br>- Investigators involved in bacterial culturing and identification were blinded as to subject randomisation.<br>- Sensitive, real time quantitative PCR was used to quantify bacteria<br>- Bacterial DNA was isolated from patient blood draws and from blood seeded with known quantities of several common oral pathogens.<br>- For real time quantitative PCR, TaqMan technology and probes and universal 16S rRNA primers conserved among oral pathogens were used with the Smart Cycler system. Standard curves were established for the seeded pathogens and calculated the levels of bacteria in subject blood cultures.<br>- The sensitivity of the method was 25 CFU per PCR, which corresponds to 103 to 104 CFU per millilitre of blood.<br><br>**Microbial identity of organisms identified in study**<br>a) overall nature of bacteraemia<br>98 different bacterial species, the most common which belonged to Streptococcus (49%), Prevotella (9%), Actinomyces (5%) and Fusobacterium (5%)<br><br>b) nature of bacteraemia from endocarditis related bacterial species<br>10 (31%) of the 32 IE associated oral bacterial species were viridans streptococci. 13 (48%) of 27 positive cultures in the brushing group were viridans streptococci compared with 23 (49%) of 47 in the extraction-amoxicillin group and 106 (70%) of 151 in the extraction-placebo group. With the exception of one subject in the placebo group, polymicrobial blood cultures occurred within the first 5 minutes of the procedure – 2%, 6% and 29% in the brushing, extraction-amoxicillin and extraction- |

| Bibliographic reference | Lockhart, PB., Brennan, MT., Sasser, HC., Fox, PC., Paster, BJ., Bahrani-Mougeot, FK. (2008). Bacteremia associated with toothbrushing and dental extraction. Circulation. 117: 3118-3125 |
|---|---|
| | placebo group respectively.<br><br>**Study limitations: assessed using GRADE risk of bias checklist**<br>- Although the incidence and duration of bacteraemia at various other time points are reported, this is in graphical form without accompanying numbers and therefore could not be extracted<br>- Numbers bacteraemic at each time point not explicitly reported<br>- Unclear whether same subjects bacteraemic at different time points |

1 **Table 122**

| Bibliographic reference | Harris A, Chan AC, Torres-Viera C et al. (1999) Meta-analysis of antibiotic prophylaxis in endoscopic retrograde cholangiopancreatography (ERCP). Endoscopy 31: 718-24 |
|---|---|
| **Study type** | Meta-analysis |
| **Aim** | To synthesise the data from all published clinical trials of antibiotic prophylaxis in ERCP in order to determine whether antibiotic prophylaxis reduces the rate of occurrence of bacteraemia and cholangitis among patients undergoing ERCP |
| **Patient characteristics** | Clinical trials were identified Medline using “ERCP”, “antibiotic”, “antibiotic prophylaxis” as subject words and text words; bibliography reviews of relevant articles, and contacts with experts in the fields of gastroenterology and infectious disease, the search was not limited to the English language. A similar search was completed in Pubmed.<br><br>**Inclusion:** RCTs, placebo controlled studies of the efficacy of antibiotic prophylaxis in ERCP using oral or intravenous antibiotics. All studies included adult patients who underwent diagnostic or therapeutic ERCP and had a variety of underlying pathologies.<br><br>**Exclusion:** studies in which patients had received other antibiotics in addition to prophylaxis, were diagnosed with sepsis or cholangitis prior to ERCP |
| **Number of Patients** | 4 RCTs of relevance to this review question (n=478) |
| **Intervention** | Antibiotic prophylaxis for ERCP |
| **Comparison** | Placebo |
| **Length of follow up** | Various |
| **Location** | Various |
| **Outcomes measures and effect size** | Bacteraemia<br>4 studies reported bacteraemia, the RR in those receiving antibiotics compared with those receiving the placebo was NS; RR: 0.39 (0.12 to 1.29); p=0.12; Q test: 4.3 (p=0.23)<br>Q test for heterogeneity was 4.3 with P 0.23; ‘little heterogeneity’ |

| | |
|---|---|
| **Bibliographic reference** | **Harris A, Chan AC, Torres-Viera C et al. (1999) Meta-analysis of antibiotic prophylaxis in endoscopic retrograde cholangiopancreatography (ERCP). Endoscopy 31: 718-24** |
| **Source of funding** | Not reported |
| **Comments** | **Study characteristics** |

| Study | Study design | Treatment | Inclusion criteria | Exclusion criteria |
|---|---|---|---|---|
| Sauter et al., 1990 | RCT (n=100) | Cefotaxime 2g i.v. 15 mins before ERCP | Unselected | History of endocarditis or valvular heart disease, history of allergy to antibiotics, antibiotic therapy less than a week before ERCP, outpatient ERCP |
| Niederau et al., 1994 | RCT (n=100) | Cefotaxime 2g i.v. 15 mins before ERCP | Any patient having an ERCP | History of endocarditis or valvular heart disease, allergy to antibiotics, antibiotic less than 48 hours before ERCP, patient with signs of cholangitis, refusal to participate |
| Finkelstein et al., 1996 | RCT (n=179) | Cefonicid 1g i.v. 1 hour before ERCP | Age > 18 years, written consent | Allergies to beta-lactams, sepsis, ascending cholangitis a week before ERCP or antibiotic therapy 72 hours before ERCP |
| Lorenz et al., 1996 | RCT (n=99) | Cefuroxime 1.5g i.v. 30 mins before ERCP | Any patient having an ERCP or percutaneous transhepatic cholangiography | Not indicated |

**Statistical analyses**

| Bibliographic reference | Harris A, Chan AC, Torres-Viera C et al. (1999) Meta-analysis of antibiotic prophylaxis in endoscopic retrograde cholangiopancreatography (ERCP). Endoscopy 31: 718-24 |
|---|---|
| | Relative risks and 95%Cis for bacteraemia were calculated based on raw data reported in studies. Using the DerSimonian and Laird random effects model, summary estimates of the risk ratios were calculated. A statistical test of homogeneity was done using the method of DerSimonian and Laird which produced a Q statistic.<br><br>**Study limitations assessed using checklist from NICE guidelines manual 2012**<br>Overall quality of individual studies assessed but not reported<br>Unclear whether any subjects were bacteraemic before procedure in the individual studies |

1 **Table 123**

| Bibliographic reference | Rolando N, Gimson A, Philpott-Howard J et al. (1993) Infectious sequelae after endoscopic sclerotherapy of oesophageal varices: role of antibiotic prophylaxis. Journal of Hepatology 18: 290-4 |
|---|---|
| **Study type** | RCT |
| **Aim** | To determine the incidence of infection following sclerotherapy and the role of antimicrobial prophylaxis |
| **Patient characteristics** | **Inclusion:** patients admitted for sclerotherapy for bleeding oesophageal varicies<br><br>**Exclusion:** <18yrs, pregnant women, antimicrobials within the preceding 72hrs, history of allergy to imipenem/cilastatin<br><br>**Other characteristics**<br>Age in years, median (range)<br>Antibiotic group: 54 (20 to 76)<br>Control group: 46 (18 to 84)<br><br>Gender, number male/female<br>Antibiotic group: 30/17<br>Control group: 24/26<br><br>Groups were comparable for age, sex, encephalopathy grade, ascites and biochemical parameters |
| **Number of Patients** | n = 97 (n = 115 emergency endoscopy/sclerotherapy sessions and 80 routine endoscopy/sclerotherapy sessions) |
| **Intervention** | IV imipenem/cilastatin over 20min<br>n = 47 |

| Bibliographic reference | **Rolando N, Gimson A, Philpott-Howard J et al. (1993) Infectious sequelae after endoscopic sclerotherapy of oesophageal varices: role of antibiotic prophylaxis. Journal of Hepatology 18: 290-4** |
|---|---|
| **Comparison** | Control IV dextrose-saline<br>n = 50 |
| **Length of follow up** | Blood cultures taken up to 30 minutes post procedure |
| **Location** | London |
| **Outcomes measures and effect size** | **1) Bacteraemia levels/intensity: not reported**<br>**2) Duration of bacteraemia: not reported**<br>**3) Incidence of bacteraemia**<br><br>n = 2/97 bacteraemia in the pre-endoscopy samples (excluded in the analysis for efficacy of prophylaxis)<br><br>Early bacteraemia (isolation of any pathogen from cultures taken 30-min post-sclerotherapy without clinical signs of infection and with a negative blood culture taken before sclerotherapy); n = 1/57 (1.8%) sessions imipenem/cilastatin group; n = 5/58 (8.6%) sessions control group, NS difference (organisms; Staphylococcus aureus, Eschericha coli, Enterobacter cloacae, Xanthomonas maltophilia)<br><br>Clinical bacteraemia (isolation of any pathogen from blood cultures with clinical signs of infection) was detected in n = 8 patients in the first 4days after sclerotherapy and occurred in equal numbers in both groups (organisms; Staphylococcus aureus, Staphylococcus epidermis, Escherichia coli, Kledsiella pneumoniae) – denominator unclear<br><br>There were no adverse reactions to the antibiotic in the 50 patients that received any dose of this. |
| **Source of funding** | Merck, Sharpe & Dohme Ltd |
| **Comments** | **Statistical analyses**<br>Chi square tests were performed with appropriate corrections for small numbers.<br><br>**Assessment of bacteraemia**<br>Blood samples were taken before and immediately after each endoscopic procedure and inoculated into aerobic and anaerobic blood culture bottles. Blood culture bottles examined twice a day for the first 2days and daily for a further 5days; analysed using conventional microbiological techniques.<br><br>**Microbial identity**<br>See results section<br><br>**Study limitations assessed using GRADE risk of bias checklist**<br>- Concealment and blinding not described |

| Bibliographic reference | Rolando N, Gimson A, Philpott-Howard J et al. (1993) Infectious sequelae after endoscopic sclerotherapy of oesophageal varices: role of antibiotic prophylaxis. Journal of Hepatology 18: 290-4 |
|---|---|
| | - Denominator unclear for clinical bacteraemia cases<br>- Power calculation not reported |

# G.8 Review question 7b

**Table 124**

| Bibliographic reference | Maharaj, B., Coovadia, Y., Vayej, AC. (2012). A comparative study of amoxicillin, clindamycin and chlorhexidine in the prevention of post-extraction bacteraemia. Cardiovascular journal of Africa. 23 (9): 491-494 |
|---|---|
| Study type | Randomised controlled trial |
| Aim | To assess and compare the effectiveness of amoxicillin, clindamycin, and the oral antiseptic chlorhexidine in eliminating post-extraction bacteraemia in black patients. |
| Patient characteristics | **Inclusion criteria**<br>- Adult black patients attending the dental clinic<br>- Healthy<br>- No history of cardiovascular disease<br>- Had not received antibiotics in the previous 2 weeks<br>- Not allergic to penicillin<br><br>**Exclusion criteria**<br>- Any patient found to have a dental abscess or who required the extraction of more than one tooth<br><br>**Other characteristics**<br>Males, n/N (%): chlorhexidine – 8/40 (20%), control – 12/40 (30%)<br>Females, n/N (%): chlorhexidine – 32/40 (80%), control – 28/40 (70%)<br>Age in years, mean (range): chlorhexidine – 28 (18 to 55), control – 32.1 (18 to 60) |
| Number of Patients | 160 randomised to 4 groups (no therapy, chlorhexidine, amoxicillin or clindamycin) of 40 subjects each. |
| Intervention | Subjects rinsed their mouths vigorously with 10ml of 0.2% chlorhexidine for one minute and expectorated. Procedure repeated one minute later. Treatment was given one hour prior to dental extraction*.<br><br>*dental extraction: only one tooth was extracted per patient. The same dental surgeon performed the procedure using dental forceps. No surgical procedures were used in any patient. |

| Bibliographic reference | **Maharaj, B., Coovadia, Y., Vayej, AC. (2012). A comparative study of amoxicillin, clindamycin and chlorhexidine in the prevention of post-extraction bacteraemia. Cardiovascular journal of Africa. 23 (9): 491-494** |
|---|---|
| | |
| **Comparison** | No chlorhexidine prophylaxis: no therapy prior to dental extraction |
| **Length of follow up** | Not reported, post-extraction bacteraemia assessed based on blood sample drawn 3 minutes after extraction. |
| **Location** | South Africa |
| **Outcomes measures and effect size** | **1.Bacteraemia levels/intensity:** not reported<br>**2. Duration of bacteraemia:** not reported<br>**3. Incidence of positive blood culture after* dental extraction, n (%)**<br>0.2% chlorhexidine group: 16 (40)<br>Control group: 14 (35)<br>*blood drawn 3 minutes post extraction, before extraction data not reported |
| **Source of funding** | Not reported |
| **Comments** | **Statistical analysis**<br>- Results in each group were arranged in a contingency table an analysed using Fisher's exact test<br>- To analyse difference between control vs antibiotic groups and between antiseptic vs antibiotic group, the Chi Square test was used, employing Yates correction for continuity<br>- Power calculation not reported<br><br>**Assessment of bacteraemia**<br>- The skin at the site of the venepuncture was prepared using 0.5% chlorhexidine in 70% alcohol<br>- 8-10ml of blood was drawn 3 minutes after the extraction in each patient<br>- 3 to 5ml blood was injected into BACTEC blood culture vials<br>- Blood culture bottles transported to Microbiology Department within 2 hours of collection<br>- The blood culture vials were tested on days 1, 3, 5 and 7 and positive vials were sub-cultured and Gram stained smears were prepared<br>- The aerobic vials were sub-cultured onto chocolate, blood and MacConkey agar plates which were inoculated for 48 hours in air plus 10% carbon dioxide.<br>- The anaerobic vials were sub-cultured onto 10% blood agar plates with and without amikacin and incubated for 48 to 72 hours in anaerobic gas pak.<br>- The organisms isolated were identified using conventional laboratory methods and the identity of streptococcal isolates was confirmed using the API Strep 20 system.<br><br>**Microbial identity**<br>A range of microbes were identified including Streptococcus mitis, Streptococcus sanguis, Streptococcus anginosus, Viridans |

| Bibliographic reference | **Maharaj, B., Coovadia, Y., Vayej, AC. (2012). A comparative study of amoxicillin, clindamycin and chlorhexidine in the prevention of post-extraction bacteraemia. Cardiovascular journal of Africa. 23 (9): 491-494** |
|---|---|
| | Streptococci, Streptococcus pneumonia, Staphylococcus epidermis, Enterococcus faecalis, Neisseria species, Corynebacterium species, Gram negative bacilli, Moraxella species, Peptostreptococcus species, Prevotella melaninogenica, Eikenella corrodens, Gemella haemolysins and mixed growth.<br><br>**Study limitations: assessed using GRADE risk of bias checklist**<br>- Allocation concealment not described<br>- Blinding not described<br>- Number of positive blood cultures before extraction not reported – unclear if subjects were tested for bacteraemia<br>- Power calculation not reported |

1 **Table 125**

| Bibliographic reference | **Pineiro, A., Tomas, I., Blanco, J., Alvarez, M. (2010). Bacteraemia following dental implants' placement. Clinical oral implants research. 21: 913-918** |
|---|---|
| **Study type** | Randomised controlled trial |
| **Aim** | To investigate the prevalence, duration and aetiology of bacteraemias following the placement of dental implants as well as the prophylactic efficacy of a chlorhexidine digluconate mouth rinse |
| **Patient characteristics** | **Inclusion criteria**<br>- Patients suitable for oral rehabilitation using osseointegrated implants<br><br>**Exclusion criteria**<br>- Patients <18 years<br>- Use of antibiotics in the previous 3 months<br>- Routine use of oral antiseptics<br>- Immunodeficiency<br>- Any other disease that could predispose them to infections or bleeding complications<br><br>**Other characteristics**<br>Gender, n (%)<br>Chlorhexidine group: male – 11 (55), female – 9 (45)<br>Control group: male – 8 (26.7), female – 22 (73.3)<br><br>Age in years, mean (SD)<br>Chlorhexidine group: 56.9 (12.5) |

| Bibliographic reference | **Pineiro, A., Tomas, I., Blanco, J., Alvarez, M. (2010). Bacteraemia following dental implants' placement. Clinical oral implants research. 21: 913-918** |
|---|---|
| | Control group: 55 (13.5)<br><br><u>Duration of surgical procedure, n (%)</u><br><60 minutes: chlorhexidine group – 3 (15), control group – 12 (40)<br>60 to 120 minutes: chlorhexidine group – 17 (85), control group – 18 (60)<br>p=0.069 |
| **Number of Patients** | N=50<br>0.2% chlorhexidine mouth rinse: n=20<br>Control group: n=30 |
| **Intervention** | 0.2% chlorhexidine (10ml for 1 min, Oraldine Perio, Johnson and Johnson) mouth rinse before surgery* and before the injection of local anaesthesia<br><br>*all patients received intravenous sedation with midazolam and propofol , together with infiltrative local anaesthesia by injection of 2% lidocaine with epinephrine. A supracrestal mucosal incision was made and a full-thickness mucoperiosteal flap was lifted to expose the bone surface. All treatments performed by the same dental surgeon. |
| **Comparison** | No prophylactic intervention before surgery |
| **Length of follow up** | Not reported, measurements up to 15 minutes following procedure |
| **Location** | Spain |
| **Outcomes measures and effect size** | **1.Bacteraemia levels/intensity:** not reported<br>**2. Duration of bacteraemia:** not reported<br>**3. Incidence of positive blood culture before and after implant placement:** see data at different time points in table below |

| Bibliographic reference | **Pineiro, A., Tomas, I., Blanco, J., Alvarez, M. (2010). Bacteraemia following dental implants' placement. Clinical oral implants research. 21: 913-918** |
|---|---|

| | Chlorhexidine group, n(%) | Controls, n(%) |
|---|---|---|
| Bacteraemia at baseline | 0 (0) | 1 (3.3) *Streptococcus viridans (anginosus group)* |
| Bacteraemia at 30 seconds following implant placement | 0 (0) | 2 (6.7) *Streptococcus viridans (mitis group), Neisseria cinerea* |
| Bacteraemia at 15 minutes following implant placement | 0 (0) | 1** (3.3) *Streptococcus viridans (mitis group)* |
| *'the differences between the control and chlorhexidine group were not statistically significant'<br>**same subject who also had bacteraemia at 30 seconds | | |

| | |
|---|---|
| **Source of funding** | Supported by the Xunta de Galicia and Research Intensification |
| **Comments** | **Statistical analyses**<br>Fisher's exact test or the Chi Square test was used to compare nominal qualitative variables eg: gender. Fisher's exact test was also used to compare prevalence of bacteraemia at 30 seconds and 15 minutes after the implant procedure between the control group and the chlorhexidine group. P<0.05 was considered significant.<br><br>**Assessment of bacteraemia**<br>- After disinfection with alcohol and poidone iodine, an intravenous catheter was inserted into the antecubital fossa or on the dorsum of the hand using an angiocath.<br>- A peripheral venous blood sample (10ml) was collected from each patient before the start of the procedure to determine the prevalence of bacteraemia before the intervention (baseline)<br>- Further peripheral blood samples (10ml) were taken 30 seconds and 15 minutes after the procedure to determine the prevalence and duration of bacteraemia secondary to the implant placement<br>The venous canula was flushed with 3ml of saline after each blood collection and the first 2ml of blood drawn was discarded<br>- Each sample was inoculated into containers with aerobic and anaerobic culture media and immediately transported to the laboratory<br>- Blood samples processed using Bactec 9240<br>- Gram stain performed on each positive blood culture<br>- Positive aerobic blood cultures were subcultured on blood agar, chocolate agar and MacConkey agar in an aerobic atmosphere<br>- The same protocol was used for positive anaerobic blood cultures including subculture on Schaedler agar incubated in an anaerobic atmosphere |

| Bibliographic reference | Pineiro, A., Tomas, I., Blanco, J., Alvarez, M. (2010). Bacteraemia following dental implants' placement. Clinical oral implants research. 21: 913-918 |
|---|---|
| | - The bacteria isolated were identified using biochemical tests provided by the Vitek system<br><br>**Microbial identity**<br>See table under 'outcomes measure and effect size' section<br><br>**Study limitations: assessed using GRADE risk of bias checklist**<br>- Randomisation not described<br>- Allocation concealment not described<br>- Blinding not described<br>- Power calculation not reported |

1 **Table 126**

| Bibliographic reference | Duvall, NB., Fisher, TD., Hensley, D. (2013). The comparative efficacy of 0.12% chlorhexidine and amoxicillin to reduce the incidence and magnitude of bacteraemia during third molar extractions. Oral surgery, oral medicine and oral pathology. 115 (6): 752-763 |
|---|---|
| **Study type** | Randomised controlled trial |
| **Aim** | To compare the incidence and magnitude of bacteraemia of a 0.12% chlorhexidine pre-procedure rinse to the AHA and the ADA/AAOS recommended 2g amoxicillin antibiotic prophylaxis during third molar extractions. |
| **Patient characteristics** | **Inclusion criteria**<br>- Subjects presenting to the surgical centre, oral surgery clinic for third molar extractions under conscious sedation from June 2011 to December 2011<br>-ASA I or II: healthy, no systemic disease<br>- Diagnosed/planned extraction #1, 16, 17, 32 under conscious sedation<br>- #17 and 32 required a mucogingival flap for extraction<br>- 18 years of age or older<br>- Previously received penicillin and/or amoxicillin without a hypersensitivity or allergic reaction<br><br>**Exclusion criteria**<br>- ASA III or IV: poorly controlled systemic disease<br>- Known penicillin, amoxicillin or cephalosporin drug allergy<br>- Pregnant women<br>- Current immunosuppressed status<br>- Active viral disease |

| Bibliographic reference | **Duvall, NB., Fisher, TD., Hensley, D. (2013). The comparative efficacy of 0.12% chlorhexidine and amoxicillin to reduce the incidence and magnitude of bacteraemia during third molar extractions. Oral surgery, oral medicine and oral pathology. 115 (6): 752-763** |
|---|---|
| | - Cardiac anomalies or another condition/situation requiring pre- or intra-operative use of antibiotics<br>- Antibiotic use within the previous two months<br>- Steroid therapy within the previous two months<br>- Chlorhexidine use or other oral antimicrobial rinses within the previous 2 months<br>- The routine use of an oral antiseptic at home<br>- Gingival tissue manipulation within 2 hours of the procedure<br>- 7 of the original 37 eligible subjects were excluded due to technical reasons (complications during blood draws and/or unavailable microbiological lab support)<br><br>**Other characteristics**<br>Age in years, mean (range)<br>21.8 (18 to 29)<br>No significant difference among treatment arms, p=0.473<br><br>Gender, n<br>Male – 23<br>Female – 7<br>No significant difference among treatment arms, p=0.475<br><br>Surgical procedure length in minutes, mean (range)<br>42 (11 to 78)<br>No significant difference among treatment arms, p=0.632 |
| **Number of Patients** | N=30<br>10 subjects per placebo chlorhexidine and amoxicillin groups |
| **Intervention** | 0.12% chlorhexidine rinse and a placebo capsule.<br>The 0.12% chlorhexidine rinse (PerioGuard Oral Rinse, Colgate Oral Pharmaceuticals) was administered immediately prior to conscious sedation medication administration. The subjects rinsed with with 15ml of the chlorhexidine rinse for one minute and expectorated.<br>The placebo capsule for both the intervention and control groups were administered with a small amount of water 1 hour prior to the procedure. |
| **Comparison** | Placebo rinse and a placebo capsule.<br>The placebo rinse (1000ml sterile water for irrigation, [USP, Baxter Healthcare], where blue dye and mint extract was added until a similar appearance, taste and smell was obtained compared to the 0.12% chlorhexidine rinse). This was also |

<table>
<tr><td>Bibliographic reference</td><td>Duvall, NB., Fisher, TD., Hensley, D. (2013). The comparative efficacy of 0.12% chlorhexidine and amoxicillin to reduce the incidence and magnitude of bacteraemia during third molar extractions. Oral surgery, oral medicine and oral pathology. 115 (6): 752-763</td></tr>
<tr><td></td><td>administered immediately prior to conscious sedation medication administration. The subjects rinsed with 15ml of the placebo rinse for one minute and expectorated.</td></tr>
<tr><td>Length of follow up</td><td>Not reported</td></tr>
<tr><td>Location</td><td>USA</td></tr>
<tr><td>Outcomes measures and effect size</td><td>1) Bacteraemia levels/intensity<br><br>
<table>
<tr><th colspan="3">Total mean magnitude of bacteraemia</th></tr>
<tr><td></td><td>Total bacteraemia in cfu/ml, mean (SD)</td><td>Total bacteraemia range</td></tr>
<tr><td>Placebo (n=10)</td><td>3.61 (7.09)</td><td>0.0 to 18.20</td></tr>
<tr><td>Chlorhexidine (n=10)</td><td>2.76 (4.28)</td><td>0.0 to 11.10</td></tr>
</table>
<br>
<table>
<tr><th colspan="6">Mean magnitude of bacteraemia per blood draw</th></tr>
<tr><td></td><td>Blood draw 1, mean (SD)</td><td>Blood draw 2, mean (SD)</td><td>Blood draw 3, mean (SD)</td><td>Blood draw 4, mean (SD)</td><td>P value</td></tr>
<tr><td>Placebo (n=10)</td><td>0 (0)</td><td>1.26 (3.67)</td><td>1.90 (5.36)</td><td>0.45 (0.83)</td><td>0.031</td></tr>
<tr><td>Chlorhexidine (n=10)</td><td>0.04 (0.13)</td><td>0.18 (0.29)</td><td>2.37 (4.11)</td><td>0.17 (0.24)</td><td>0.062</td></tr>
</table>
<br>2) Duration of bacteraemia: not reported<br>3) Incidence of bacteraemia: defined as at least one positive culture of the four blood draws per subject and reported as n/N (%)<br>Placebo group: 5/10 (50)<br>Chlorhexidine group: 6/10 (60)<br>*P value not reported for the above comparison but for the comparison between all 3 groups in the study (amoxicillin, placebo and chlorhexidine) was 0.670</td></tr>
<tr><td>Source of funding</td><td>Funding provided by the 59th Clinical Research Training Division, Lackland, AFB, TX</td></tr>
<tr><td>Comments</td><td>Statistical analyses<br>Incidence of bacteraemia analysed via Chi-square tests<br>Magnitude of bacteraemia analysed using the non-parametric Kruskal-Wallis test and the Friedman test with Bonferroni correction applied as there were multiple comparisons between the groups<br><br>Assessment of bacteraemia</td></tr>
</table>

| Bibliographic reference | Duvall, NB., Fisher, TD., Hensley, D. (2013). The comparative efficacy of 0.12% chlorhexidine and amoxicillin to reduce the incidence and magnitude of bacteraemia during third molar extractions. Oral surgery, oral medicine and oral pathology. 115 (6): 752-763 |
|---|---|
| | - Once the IV access line was established, the first blood draw was completed at baseline<br>- A second IV access line for the conscious sedation medications was obtained in the opposite arm in a similar manner after the blood draw IV access line was obtained, blood draw 1 was collected and the placebo or amoxicillin capsules were administered.<br>- The third molar extractions was completed in the order of #1, 32, 16 and 17.<br>- Blood draw 2 was completed 1.5 minutes following initiation of the mucogingival flap #32, blood draw 3 was completed 1.5 minutes following initiation of the mucogingival flap #17 and blood draw 4 was completed 10 minutes following initiation of the mucogingival flap #17<br>- The 4 blood samples per subject were transported to an on-site microbiology laboratory for immediate processing. All blood samples were processed within 4 hours of blood draw 1.<br>- The bacterial concentrate was removed with an Isostat concentrate pipet and distributed equally onto 3 different agar plates: Trypticase soy agar with 5% sheep blood (incubated aerobically), chocolate agar (incubated aerobically) and Brucella blood agar (incubated anaerobically)<br>- Colonies were counted and grouped by colonial morphology. Haemolytic reaction was recorded for colony types growing on Trypticase soy agar.<br>- Following primary isolation, each colony type was subcultured to Trypticase soy agar or Brucella blood agar to obtain a pure culture and verify the required environmental growth conditions<br>- A gram stain was performed on each pure culture with bacterial isolate identification accomplished using the VITEK 2 Compact bacterial identification system or the Biolog Microsation System<br><br>**Microbial identity**<br>- 33 different bacterial species were isolated among the placebo, chlorhexidine and amoxicillin groups<br>- There were 24 different bacterial species isolated in the placebo group, 15 isolated in the chlorhexidine group and 10 isolated in the amoxicillin group<br>- Of the 33 different bacterial species, 7 (21%) were alpha-hemolytic and also belonged to the viridans group streptococci. In the placebo group, 5 bacterial species isolated were alpha-hemolytic/viridans group streptococci, two isolated in the chlorhexidine group and one isolated in the amoxicillin group.<br>**Study limitations: assessed using GRADE risk of bias checklist**<br>- Blinding not described, insufficient information to judge whether subjects and/or assessors were blind<br>- Incidence of positive blood cultures at baseline not reported separately but together with incidence at any of the blood draws<br>- Power calculation not reported |

1 **Table 127**

| | |
|---|---|
| **Bibliographic reference** | **Tuna, A., Delilbasi, C., Arslan, A., Gurol, Y., Tekkanat, ZT. (2012). Do antibacterial mouthrinses affect bacteraemia in third molar surgery? A pilot study. Australian dental journal. 57: 435-439** |
| **Study type** | Randomised controlled trial |
| **Aim** | To evaluate the effects of mouthrinses containing 0.2% chlorhexidine and 7.5% povidone iodine on bacteraemia following impacted third molar surgery |
| **Patient characteristics** | **Inclusion criteria**<br>- Patients who underwent surgical removal of impacted mandibular third molar under local anaesthesia<br>- Aged over 18 years<br>- Requiring surgical removal of a third molar<br>- Neither any systemic disorder nor any signs or symptoms of pericoronitis at the time of surgery nor during the previous month<br>- No known risk factor for bacterial endocarditis<br>- Received no antibiotic treatment during the previous 30 days<br>- Was not using routine oral antiseptic mouthrinse nor suffering any type of congenital or acquired immunodeficiency<br>- No other disease or condition which could predispose to infections or bleeding<br><br>**Exclusion criteria**<br>- Patients with an oral hygiene index and gingival bleeding index higher than 10%<br>- Those with the presence of bacteraemia in preoperative blood culture<br><br>**Other characteristics**<br>Gender, n female; n male<br>Chlorhexidine: 8;4<br>Controls: 5;5<br>p=0.451 (including povidone-iodine group data as well)<br><br>Age in years, mean (SD)<br>Chlorhexidine: 27.7 (10.01)<br>Controls: 27.0 (8.30)<br>p=0.971 (including povidone-iodine group data as well)<br><br>Operation time in minutes, mean (SD)<br>Chlorhexidine: 23.1 (9.05)<br>Controls: 20.0 (13.30) |

<table>
<tr><td>Bibliographic reference</td><td>Tuna, A., Delilbasi, C., Arslan, A., Gurol, Y., Tekkanat, ZT. (2012). Do antibacterial mouthrinses affect bacteraemia in third molar surgery? A pilot study. Australian dental journal. 57: 435-439</td></tr>
<tr><td></td><td>p=0.670 (including povidone-iodine group)</td></tr>
<tr><td>Number of Patients</td><td>N=38* randomised to the following groups:<br>1. Chlorhexidine group: n= 12<br>2. Povidone iodine group: n=12<br>3. Control group (NaCl sterile saline): 10<br>*4 (from 38 randomised) excluded (2 subjects from the control group due to injury of the venous pathway during the insertion of the angiocath and further 2 subjects from the chlorhexidine group due to presence of bacteraemia in the preoperative blood culture).</td></tr>
<tr><td>Intervention</td><td>Subjects were asked to rinse the mouth with 15ml 0.2% chlorhexidine mouthrinse for one minute following blood collection, before the surgical procedure*. Patients were supervised during mouthrinsing to ensure they were using the mouthrinse appropriately.<br><br>* surgical removal of impacted mandibular third molar under local anaesthesia (the indications for extractions were pericoronitis reported by the patient and/or the dentist (excluding patients who had experienced some episode in the month prior to enrolment) and extractions for non-infective reasons</td></tr>
<tr><td>Comparison</td><td>Subjects were asked to rinse the mouth with 0.9% NaCl (sterile saline) solution.</td></tr>
<tr><td>Length of follow up</td><td>Not reported, blood samples up to 15 minutes post-extraction</td></tr>
<tr><td>Location</td><td>Turkey</td></tr>
<tr><td>Outcomes measures and effect size</td><td>1) Bacteraemia levels/intensity: not reported<br>2) Duration of bacteraemia: not reported<br>3) Incidence of bacteraemia
<table>
<tr><td></td><td>Chlorhexidine group, n (%)</td><td>Control group, n(%)</td></tr>
<tr><td>Bacteraemia present overall</td><td>4 (33)</td><td>5 (50)</td></tr>
<tr><td>Bacteraemia at 1st minute</td><td>3 (25)</td><td>4 (40)</td></tr>
<tr><td>Bacteraemia at 15th minute</td><td>2 (17)</td><td>3 (30)</td></tr>
<tr><td>McNemar’s p value</td><td>0.250</td><td>0.810</td></tr>
</table>
* A further p value is reported in the study for the comparison of all treatment groups (povidone-iodine, chlorhexidine and control group) as opposed to the comparison we are interested in for this question and has therefore not been extracted.<br>**Those with bacteraemia in preoperative blood culture were excluded (n=2 from chlorhexidine group)</td></tr>
</table>

| Bibliographic reference | **Tuna, A., Delilbasi, C., Arslan, A., Gurol, Y., Tekkanat, ZT. (2012). Do antibacterial mouthrinses affect bacteraemia in third molar surgery? A pilot study. Australian dental journal. 57: 435-439** |
|---|---|
| **Source of funding** | Not reported |
| **Comments** | **Statistical analyses**<br>- Descriptive statistics (mean, SD) are presented and the Kruskal-Wallis test was used to compare multiple groups<br>- For two sample comparisons, the Mann-Whitney U test was used and for comparisons of qualitative data, the chi-square test and McNemar's test were used. Significance was set at p ≤0.05.<br><br>**Microbial identity**<br>The positive blood cultures displayed 58% anaerobic bacteria and 42% aerobic bacteria. 92% were Streptococcus bacteria. Among them, Streptococcus viridans was most frequently observed; 38% of the 24 bacteria were S.anginosus, 13% were S.salivarius and 13% S.mitis.<br>Statistical analyses<br>Descriptive statistics are presented and the Kruskal-Wallis test was used to compare multiple groups. For two sample comparisons, the Chi Square test and McNemar's test were used. Statistical significance was set at p ≤0.05.<br>Method of bacteraemia assessment<br>- Peripheral venous blood samples were collected from each patient at baseline (before injection of local anaesthesia), 1 minute and 15 minutes after completion of the extraction<br>- Every blood sample comprised 20ml of blood which was divided into 2 bottles with anaerobic culture medium (10ml) and aerobic culture medium (10ml)<br>- Altogether, 60ml of blood was obtained from each patient by a researcher blind to the details of the study<br>- After each sample was drawn, the angiocath needle and the line were flushed with 3ml of saline. The bottles were transported immediately to the microbiology laboratory.<br>- All blood cultures were processed in the BACTEC 9120 system. At the 7th day of incubation, samples which showed no production were subcultured on 5% sheep blood agar and chocolate agar; those which did not show any production were designated negative. Positive samples were subcultured on 5% sheep blood agar and chocolate agar. At the end of 24 hours of incubation, these samples were further subjected to further biochemical tests using the mini API kit in line with the recommendations of the American Society for Microbiology and bacteria were isolated.<br>- Samples identified as positive by BACTEC 9120 but no microorganism detected with the Gram stain were accepted as false positives.<br><br>**Study limitations: assessed using GRADE risk of bias checklist**<br>- Allocation concealment not described<br>- Blinded not described in detail: 'blinded researcher', unclear if subjects were blinded too<br>- Unclear whether it's the same subjects bacteraemic at different time points (possible double counting of subjects)<br>- Power calculation not reported |

1 **Table 128**

| | |
|---|---|
| **Bibliographic reference** | **Brown AR, Papasian CJ, Shultz P, et al (1998) Bacteremia and intraoral suture removal: can an antimicrobial rinse help? Journal of the American Dental Association 129: 1455–61. *[included in CG64]*** |
| **Study type** | Randomised controlled trial |
| **Aim** | To determine whether a relationship exists between the incidence of bacteraemia and suture removal especially in patients who experience bleeding at the surgical site and to quantify the inoculum. Also, to determine whether a 0.12% chlorhexidine rinse, performed before the removal of sutures, could reduce or eliminate bacteraemia. |
| **Patient characteristics** | **Inclusion**<br>- Healthy patients requiring the removal of a third molar which would require at least 8 sutures,<br><br>**Exclusion**<br>- Patients with systemic disease<br>- Taking steroids<br>- Had used systemic antibiotics or oral rinses within the previous 4wks<br>- Moderate-to-severe periodontitis or residual pericoronitis<br>- Required preoperative prophylactic antibiotics<br>- Patients were dropped from the study if they required antibiotic therapy during the postoperative week<br>- Extraction sites developing alveolar osteitis after surgery were selectively dropped from recovered data but the patient and his or her remaining uninvolved sites were retained<br><br>**Other characteristics**<br>Gender, n<br>Female – 37<br>Male – 24<br><br>Age in years, range<br>15 to 35 |
| **Number of Patients** | - 71 randomised<br>- 10 lost to follow-up (2 from experimental and 8 from control)<br>- 6 additional subjects eliminated because of contaminated cultures<br>- Therefore, 55 subjects analysed; 31 in experimental arm and 24 in control arm |
| **Intervention** | 30 cubic centimetres of 0.12% chlorhexidine preprocedural rinse (Peridex) for 1 min (n=31)<br><br>Interventional procedure: The third molars were removed by one of the 3 board-certified oral surgeons. All used similar flap designs and 3–0 black silk suture placement, used no medication in the sockets, nor did they use preoperative irrigation or |

| Bibliographic reference | **Brown AR, Papasian CJ, Shultz P, et al (1998) Bacteremia and intraoral suture removal: can an antimicrobial rinse help? Journal of the American Dental Association 129: 1455–61. *[included in CG64]*** |
|---|---|
| | rinses. Subjects returned for suture removal seven days after the extraction and were randomly assigned to one of two groups. |
| **Comparison** | No-treatment control (n=24) |
| **Length of follow up** | All plates examined daily for 7 days |
| **Location** | USA |
| **Outcomes measures and effect size** | **1) Bacteraemia levels/intensity**: not reported<br>**2) Duration of bacteraemia**: not reported<br>**3) Incidence of bacteraemia**<br>Pre-treatment blood samples were all negative<br>Post-treatment*: 4/31 in chlorhexidine group and 2/24 in control group had positive cultures, total incidence 10.9%<br>There was NS difference in the proportion of bacteraemia with experimental vs. control groups; P>0.05 (Fisher's exact test)<br>*Blood drawn 90 seconds after suture removal |
| **Source of funding** | Not stated |
| **Comments** | **Statistical analyses**<br>- Fisher's exact test for comparison of proportion of bacteraemia between experimental and control groups<br>- 90% power at p=0.05, n=55 was determined from results obtained from an initial pilot study<br><br>**Assessment of bacteraemia**<br>- The first 10ml of blood withdrawn for the pre-and postprocedural specimens was discarded<br>- 90 seconds after suture removal, a second 10ml blood sample was obtained for culturing<br>- All specimens were placed in an aerobic/anaerobic culture medium and immediately transported to the laboratory<br>- Specimens were promptly transferred to a lysis centrifugation collection tube and centrifuged for 30 minutes<br>- Supernatant fluid was discarded and the entire pellet was used to inoculate chocolate agar, blood agar and LKV agar<br>- All plates were examined daily for 7 days before negative results were reported<br>- Organisms were identified using morphologic criteria and routine bacteriologic methods<br><br>**Microbial identity**<br>Facultative organisms, predominantly Streptococcus were present in all specimens. Two samples yielded anaerobic growth of either Prevotella or Peptostreptococcus.<br><br>**Study limitations: assessed using GRADE risk of bias checklist**<br>- Randomisation and allocation concealment not described |

| Bibliographic reference | **Brown AR, Papasian CJ, Shultz P, et al (1998) Bacteremia and intraoral suture removal: can an antimicrobial rinse help? Journal of the American Dental Association 129: 1455–61. *[included in CG64]*** |
|---|---|
| | - Blinding not described: the doctor performing suture removal was unaware of whether or not a patient had used a rinse. Unclear whether subjects were blinded.<br>- (Missing data but sufficient reasons given)<br>- Power calculation not reported |

1 **Table 129**

| Bibliographic reference | **Jokinen MA. Prevention of postextraction bacteremia by local prophylaxis. International Journal of Oral Surgery 1978;7:450-2. *[included in CG64]*** |
|---|---|
| **Study type** | RCT |
| **Aim** | To investigate the effect of various local preventative methods for postextraction bacteraemia |
| **Patient characteristics** | **Inclusion:** patients from various departments of the hospital for a cleaning of the mouth or because of acute symptoms in the teeth or periodontal tissues indicating dental extraction<br><br>**Exclusion:** those who had systemic chemotherapeutic medication during the 10 previous days<br><br>**Other characteristics:**<br>Gender, male: 74%<br>Age in years: 16 to 75<br>There were no significant differences among the 4 groups in regard to sex or age of the patients |
| **Number of Patients** | n = 152, 38 subjects in each treatment arm |
| **Intervention** | Operative field isolation and disinfection with 0.5% chlorhexidine gluconate solution (n=38)<br><br>(The other 2 treatment arms in this study [1% iodine solution and operative field isolation and disinfection with 10% iodine solution] are not of interest to this review question).<br><br>Interventional procedure: dental extraction performed under local anaesthesia. Operating time was 1 to 2 hours postprandially. |
| **Comparison** | Operative field isolation with sterile cotton rolls and saliva ejector (n=38) – saliva from gingival crevices, the surfaces of the teeth and from the surrounding gum was dried with an air syringe. During and about 10 minutes after extraction, the saliva ejector and cotton rolls were kept in place. |
| **Length of follow up** | Not reported |
| **Location** | Finland |

| | |
|---|---|
| **Bibliographic reference** | **Jokinen MA. Prevention of postextraction bacteremia by local prophylaxis. International Journal of Oral Surgery 1978;7:450-2. *[included in CG64]*** |
| **Outcomes measures and effect size** | **1) Bacteraemia levels/intensity:** not reported<br>**2) Duration of bacteraemia:** not reported<br>**3) Incidence of bacteraemia post extraction**<br><br>Positive cultures; operative field in isolation n = 13/38, operative field isolation and disinfection with chlorhexidine n = 5/38, 13% |
| **Source of funding** | Not stated |
| **Comments** | **Statistical analyses**<br>The chi-square method<br><br>**Assessment of bacteraemia**<br>- Immediately after extraction, the vein was punctured and blood began to flow into the first anaerobic bottle 30 to 60 seconds after the termination of the extraction<br>- The bacteriologic determinations were made in the laboratory without the investigator having any knowledge of the nature of the individual samples (Jokinen 1970 referred to for further details of methods)<br><br>**Microbial identity**<br>78% of the bacterial strains isolated from the positive cultures in the prophylactic groups were streptococci of the viridans type<br><br>The strains isolated were most sensitive to chloramphenicol, ampicillin, erythromycin and penicillin<br><br>**Study limitations: assessed using GRADE risk of bias checklist**<br>- Study design difficult to judge based on description given<br>- Randomisation not described<br>- Allocation concealment not described<br>- Blinding of subjects not described<br>- Blinding of subjects not described<br>- Insufficient information to permit judgment of selective reporting (outcomes not pre-specified)<br>- Incidence of bacteraemia before extraction not reported<br>- Power calculation not reported |

**Table 130**

| | |
|---|---|
| **Bibliographic reference** | **Lockhart PB. An analysis of bacteremias during dental extractions. A double-blind, placebo-controlled study of chlorhexidine. Archives of Internal Medicine 1996;156:513-20 *[included in CG64]*** |
| **Study type** | RCT, double blind |
| **Aim** | To determine the incidence and nature of bacteraemia during single tooth extraction in adults |
| **Patient characteristics** | **Inclusion:** study patients were selected consecutively from a large pool of outpatients who underwent dental extractions; >18yrs, no valvular heart disease, not pregnant, no infectious disease, no poorly controlled systemic disease or facial cellulitis or if the patient's risk classification was more than II based on the American Society of Anesthesiologists' criteria<br><br>**Exclusion:** use of steroids or chlorhexidine during the previous 2mths, use of antibiotics during the previous 2wks, any manipulation of the gingiva (eg: brushing, eating) within 1hr of the extraction<br><br>**Other characteristics**<br>Gender, n<br>37 male, 37 women<br><br>Age in years, mean (range)<br>37 (21 to 72)<br><br>There was an equal distribution between maxillary and mandibular teeth |
| **Number of Patients** | 82 eligible, 12 dropped out (technical reasons), therefore a total of 70 subjects<br><br>Power calculation: based on previous studies; a need of 70 patients to ensure statistical significance. Sample size of 35 per group would be sufficient for detecting a decrease in positive culture rate from 60% in the placebo group to 25% in chlorhexidine group, with 80% power at significance of 0.05. |
| **Intervention** | 10ml 0.2% chlorhexidine hydrochloride (peridex) rinse for 30sec and expectorated, rinsing was repeated 1min later (n=37)<br><br>Interventional procedure: dental extraction, all extractions were performed by one of three general practice dental residents with essentially equal skills. |
| **Comparison** | 10ml placebo rinse(identical to chlorhexidine without active ingredient) for 30sec, rinsing was repeated 1min later (n=33) |
| **Length of follow up** | Not reported, measurements up to 3 minutes following extraction |
| **Location** | USA |
| **Outcomes measures and effect size** | **1) Bacteraemia levels/intensity:** not reported<br>**2) Duration of bacteraemia**<br>Not reported |

| | |
|---|---|
| **Bibliographic reference** | **Lockhart PB. An analysis of bacteremias during dental extractions. A double-blind, placebo-controlled study of chlorhexidine. Archives of Internal Medicine 1996;156:513-20 *[included in CG64]*** |
| | **3) Incidence of bacteraemia**<br>There was NS difference between the 1 and 3min samples in either the incidence of blood cultures or between the chlorhexidine and the placebo groups; placebo group positive cultures in n = 31/33 (94%); chlorhexidine group n = 31/37 (84%); p=0.27 |
| **Source of funding** | Not stated |
| **Comments** | **Statistical analyses**<br>A chi-square or Fisher's exact test was performed on the data<br><br>**Assessment of bacteraemia**<br>- The first blood draw of 20ml began at 1 minute following initiation of surgery<br>- A second drawing of 20ml was begun at the 3 minute mark<br>- A blood specimen was drawn into a separate syringe continuously between the two 20ml drawings and discarded<br>- Any additional extractions were performed after the completion of the 2nd blood drawing<br>- Blood specimens were processed and tested on a blood culture system – BACTEC 660 for 5 days until yields were positive<br>- Blood culture bottles that were flagged as positive were gram stained<br>- If microorganisms were found in the aerobic bottle, the mixture was subcultured onto separate plates<br>- Identification of gram positive organisms was performed using conventional and chromogenic tests<br>- Gram negative organisms were identified using biochemical tests<br><br>**Microbial identity**<br>The majority of organisms at the 1 and 3min samples were gram-positive cocci, with a predominance of Streptococci viridans and α-haemolytic pyogenic streptococci<br><br>**Study limitations: assessed using GRADE risk of bias checklist**<br>- Numbers in each group not explicitly stated, calculated by reviewer based on %'s reported in study<br>- Incidence of bacteraemia at baseline not reported, subjects not tested |

1 **Table 131**

| | |
|---|---|
| **Bibliographic reference** | **MacFarlane TW, Ferguson MM, Mulgrew CJ. Post-extraction bacteremia : role of antiseptics and antibiotics. Br Dent J 1984;156:179-81. *[included in CG64]*** |

<table>
<tr><td>Bibliographic reference</td><td>MacFarlane TW, Ferguson MM, Mulgrew CJ. Post-extraction bacteremia : role of antiseptics and antibiotics. Br Dent J 1984;156:179-81. [included in CG64]</td></tr>
<tr><td>Study type</td><td>RCT</td></tr>
<tr><td>Aim</td><td>To test the effect of two different topical antiseptics, chlorhexidine and povidone-iodine on reducing bacteraemia consequent to tooth extraction. In addition, the antibiotic sensitivity of the microorganisms isolated from the bacteremia was tested against 8 antibiotics.</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion: patients attending the department of oral surgery for tooth extraction, 16 to 70 years of age, had normal medical history and required an uncomplicated extraction of a single premolar or first or second molar tooth under local anaesthetic, extractions were confined to lower teeth in order to reduce variability<br><br>Exclusion: cases of gross decay, advanced periodontal disease, or dental abscess with facial swelling, a history of antibiotic therapy during the previous 3mths<br><br>Other characteristics<br>The groups were matched for age and sex, and the ratios of premolar to molar teeth in each group were similar</td></tr>
<tr><td>Number of Patients</td><td>n = 60</td></tr>
<tr><td>Intervention</td><td>n = 20, 10mls 1% chlorhexidine solution<br><br>n = 20, 10mls 1% povidine-iodine (not of interest to this review question)<br><br>Solutions irrigated the gingival crevice through a blunted needle, the patient was asked to retain the solution in the mouth for 2mins before rinsing out</td></tr>
<tr><td>Comparison</td><td>n = 20, 10mls normal saline</td></tr>
<tr><td>Length of follow up</td><td>Not reported, cultures subcultured up to 8 days after initial collection</td></tr>
<tr><td>Location</td><td>Glasgow</td></tr>
<tr><td>Outcomes measures and effect size</td><td>1) Bacteraemia levels/intensity: not reported<br>2) Duration of bacteraemia: not reported<br>3) Incidence of bacteremia (positive cultures) pre- and post-extraction
<table>
<tr><th>Irrigant</th><th>Pre extraction, number positive</th><th>30 seconds post extraction, number positive</th></tr>
<tr><td>Saline</td><td>0/20</td><td>16/20</td></tr>
<tr><td>Chlorhexidine</td><td>0/20</td><td>5/20</td></tr>
<tr><td></td><td></td><td>chlorhexidine vs controls p<0.001</td></tr>
</table></td></tr>
<tr><td>Source of funding</td><td>Not stated</td></tr>
</table>

| Bibliographic reference | **MacFarlane TW, Ferguson MM, Mulgrew CJ. Post-extraction bacteremia : role of antiseptics and antibiotics. Br Dent J 1984;156:179-81. *[included in CG64]*** |
|---|---|
| **Comments** | **Statistical analyses**<br>Chi square test<br>**Assessment of bacteraemia**<br>- Venous blood (10ml) was removed via an indwelling intravenous cannula immediately before and 30 seconds after tooth extraction<br>- Part of the culture was incubated into a diphasic culture medium for aerobic growth and the other half inoculated into thioglycollate broth<br>- The samples were immediately sent to the laboratory for incubation and subcultured on days 1, 4 and 8 after initial collection<br>- Pure cultures of all bacteria were prepared and identified using standard techniques after which the antibiotic sensitivity of each isolate was assessed according to the Stokes method<br><br>**Microbial identity**<br>46 isolates; anaerobic streptococci (n = 11), Streptococcus sanguis (n = 8), Streptococcus mitior (n = 5), Streptococcus mutans (n = 6), Diptheroids (n = 3), other n = 2 or less<br><br>**Study limitations: assessed using GRADE risk of bias checklist**<br>- Study design not described in detail, assumption is that it is an RCT<br>- Randomisation, allocation concealment and blinding not described<br>- Power calculation not reported |

1 **Table 132**

| Bibliographic reference | **Rahn R, Schneider S, Diehl O, Schafer V, Shah PM. Preventing post-treatment bacteremia: comparing topical povidone-iodine and chlorhexidine.[see comment]. Journal of the American Dental Association 1995;126:1145-9 *[included in CG64]*** |
|---|---|
| **Study type** | RCT Single-blind |
| **Aim** | To determine whether irrigation of the gingival sulcus with one of two antiseptic solutions would affect the incidence and type of bacteraemia after dental treatment |
| **Patient characteristics** | **Inclusion:** those who were scheduled for dental treatment involving either intraligamental injection (n = 60), or elective extraction of a molar (n = 60)<br><br>**Exclusion:** those receiving antibiotics or immunosuppressive therapy or who had a history of bacterial endocarditis, rheumatic fever or congenital heart disease |

| Bibliographic reference | **Rahn R, Schneider S, Diehl O, Schafer V, Shah PM. Preventing post-treatment bacteremia: comparing topical povidone-iodine and chlorhexidine.[see comment]. Journal of the American Dental Association 1995;126:1145-9** ***[included in CG64]*** |
|---|---|
| | **Other characteristics**<br>Gender<br>n = 28 female, 92 male<br><br>Age in years, mean (range)<br>33.6 (22 to 77)<br><br>The mean oral hygiene scores and periodontal scores (plaque index, gingival index, sulcus bleeding index, clinical pocket depth) were similar among the patients of all three groups |
| **Number of Patients** | n = 120, 40 in each of the three arms (chlorhexidine, povidone-iodine and control) |
| **Intervention** | 0.2% chlorhexidine solution [Corsodyl Losung] (n=40)<br><br>The above solution was delivered Into the sulcus of the affected tooth with an endodontic syringe, the solution was left in place for 2 minutes |
| **Comparison** | n = 40 control sterile water |
| **Length of follow up** | Not reported, blood samples drawn up to 6 minutes after procedure |
| **Location** | Germany |
| **Outcomes measures and effect size** | **1) Bacteraemia level/intensity:** not reported<br>**2) Duration of bacteraemia:** not reported<br>**3) Incidence of bacteraemia**<br>- The blood samples obtained before the dental procedure were completely negative for bacteraemia in all groups<br>- Post-procedure bacteraemia; control (n = 21/40, 52.5%), chlorhexidine (n = 18/40, 45.0%); NS difference chlorhexidine vs control |
| **Source of funding** | Mundipharma/Limburg |
| **Comments** | **Statistical analyses**<br>The chi-square test<br><br>**Assessment of bacteraemia**<br>- Four 10ml blood samples were drawn from each patient by the physician before the dentist administered the antiseptic, and at 2, 4 and 6 minutes after the dental procedure was finished<br>- The blood samples were inoculated into blood culture bottles (BACTEC 6A and 7A, Becton-Dickinson) and the bottles |

| Bibliographic reference | **Rahn R, Schneider S, Diehl O, Schafer V, Shah PM. Preventing post-treatment bacteremia: comparing topical povidone-iodine and chlorhexidine.[see comment]. Journal of the American Dental Association 1995;126:1145-9** ***[included in CG64]*** |
|---|---|
| | were processed as recommended by the American Society for Microbiology.<br>- All microorganisms were identified by standard identification procedures<br><br>**Microbial identity**<br>- A total of 206 organisms; 87 in the control group, 42 in the iodine group and 77 in the chlorhexidine group<br>- Viridans streptococci was detected in 13 cultures of the control group and 14 of the chlorhexidine group<br><br>**Study limitations: assessed using GRADE risk of bias checklist**<br>- Randomisation not described<br>- Allocation concealment not described<br>- Single blind only, details not described<br>- Unclear whether the same subjects were bacteraemia at the 2, 4 and 6 minute cultures as data presented together<br>- Power calculation not reported |

1 **Table 133**

| Bibliographic reference | **Tomas I, Alvarez M, Limeres J, Tomas M, Medina J, Otero JL et al. Effect of a chlorhexidine mouthwash on the risk of postextraction bacteremia. Infection Control & Hospital Epidemiology 2007;28:577-82** ***[included in CG64]*** |
|---|---|
| **Study type** | RCT |
| **Aim** | To investigate the prevalence, duration and etiology of bacteraemia following dental extractions performed after a single administration of chlorhexidine mouthwash |
| **Patient characteristics** | **Inclusion:** patients with mental and behavioural disabilities who underwent dental extractions under general anaesthesia.<br><br>**Exclusion:** use of antibiotics in the previous 3mths, use of oral antiseptics, any type of congenital or acquired immunodeficiency , disease that predisposes the patient to infections or bleeding<br><br>**Other characteristics**<br>Age in years, mean (SD)<br>Chlorhexidine: 25.5 (10.3)<br>Control: 26.1 (12.3)<br><br>Gender, n (%)<br>Chlorhexidine: Male – 23 (43), Female – 30 (57) |

| Bibliographic reference | **Tomas I, Alvarez M, Limeres J, Tomas M, Medina J, Otero JL et al. Effect of a chlorhexidine mouthwash on the risk of postextraction bacteremia. Infection Control & Hospital Epidemiology 2007;28:577-82 *[included in CG64]*** |
|---|---|
| | Control: Male – 29 (55), Female – 24 (45)<br><br>Number of dental extractions, mean (SD)<br>Chlorhexidine: 5.4 (4.3)<br>Control: 5.7 (4.7)<br><br>There were NS differences between the groups with regard to age, sex, oral health status, or number of teeth extracted |
| **Number of Patients** | 106 randomised to:<br>- Chlorhexidine: n=53<br>- Control: n=53 |
| **Intervention** | Endotracheal intubation and oesophageal packing and then had their mouths filled with 0.2% chlorhexidine digluconate solution (Oraldine Perio;Pfizer) for 30 seconds before dental manipulation was performed |
| **Comparison** | No chlorhexidine prophylaxis before dental manipulation |
| **Length of follow up** | Blood samples obtained up to 1 hour after procedure |
| **Location** | Spain |
| **Outcomes measures and effect size** | **1) Bacteraemia levels/intensity:** not reported<br>**2) Duration of bacteraemia:** not reported<br>**3) Incidence of bacteraemia**<br>Positive blood cultures at baseline; 9% chlorhexidine, 8% control, p=ns (n=53 in each group)<br>Bacteraemia 30sec; chlorhexidine 79% vs. control 96%, p=0.008 (n=53 in each group)<br>Bacteraemia 15min; chlorhexidine 30% vs. control 64%, p<0.001 (n=53 in each group)<br>Bacteraemia 1hr; chlorhexidine 2% vs. control 20%, p=0.005 (n=50 in each group, numbers lost to due technical reasons)<br><br>The risk of bacteraemia after dental extraction at 30sec was x1.21 (1.04 to 1.40, 95%CI) higher in the control group; x2.12 (1.34 to 3.35, 95%CI) higher at 15mins; x10 (1.32 to 75.22, 95%CI) higher at 1hr<br><br>Percentage blood cultures with positive results 48% chlorhexidine vs. 30% control, p<0.001<br>Incidence of polymicrobial culture results 29% vs. 11%, p=0.005 |
| **Source of funding** | Xunta de Galicia, Spain |
| **Comments** | **Statistical analyses**<br>- The Fisher's exact test was used to compare the prevalence of bacteraemia at baseline, 30 seconds, 15 minutes and 1 |

| Bibliographic reference | Tomas I, Alvarez M, Limeres J, Tomas M, Medina J, Otero JL et al. Effect of a chlorhexidine mouthwash on the risk of postextraction bacteremia. Infection Control & Hospital Epidemiology 2007;28:577-82 *[included in CG64]* |
|---|---|
| | hour after dental extractions; the percentage of blood cultures with positive results and the frequency of polymicrobial culture finding. P<0.05 was used.<br>- The relative risk was calculated to estimate the risk of bacteraemia after dental extraction and significance was evaluated using 95%CIs<br><br>**Assessment of bacteraemia**<br>- A peripheral venous blood sample (10ml) was collected at baseline, 30 seconds after the final dental extraction, and at 15 minutes and 1 hour after finishing the surgical procedure<br>- Each blood sample was divided into 2 bottles, one aerobic culture media and one anaerobic culture media; they were immediately transported to the laboratory and processed using Bactec 9240<br>- Gram staining was performed on each blood culture that showed microbial growth<br>- The bacteria isolated were identified using the battery of biochemical tests provided by the Vitek system<br>- Facklam's criteria was used to identify unusual Streptococcus species and other gram positive cocci in chains<br><br>**Microbial identity**<br>The most frequently identified were Streptococcus species (64% control, 68% chlorhexidine), then Staphylococcus species (11% control, 8% chlorhexidine), Neisseria species (8% control, 5% chlorhexidine)<br><br>**Study limitations: assessed using GRADE risk of bias checklist**<br>- Allocation concealment and blinding not described<br>- Unclear whether it's the same subjects bacteraemic at different time points (possible double counting of subjects)<br>- Power calculation not reported |

1

# Appendix H: GRADE profiles/Result summary tables

## H.1 Review question 1a and 1b

**Table 134: Congenital Heart Disease (where available, abnormality specified)**

| | | | | Effect Estimate | | Quality comment |
|---|---|---|---|---|---|---|
| Study ID | N | N IE cases (%) | Controls Number (%) | Unadjusted Rate Ratio (RR) (95% CI) | Multivariate analysis Adjusted Rate Ratio (aRR) (95% CI) P-value | |
| **Outcome: IE (Cyanotic CHD)** | | | | | | |
| Rushani et al. | 3885 | 62/185 | 348/3700 | 6.38 (4.02-10.13) P=NR | 6.44 (3.95-10.5) P=NR | Low risk bias |
| **Outcome: IE (Endocardial cushion)** | | | | | | |
| Rushani et al. | 3885 | 18/185 | 154/3700 | 4.37 (2.35-8.15) P=NR | 5.47 (2.89-10.36) P=NR | Low risk bias |
| **Outcome: IE (Left-sided lesions)** | | | | | | |
| Rushani et al. | 3885 | 18/185 | 414/3700 | 1.57 (0.86-2.88) P=NR | 1.88 (1.01-3.49) P=NR | Low risk bias |
| **Outcome: IE (R sided lesions)** | | | | | | |
| Rushani et al. | 3885 | 7/185 (4) | 216/3700 (6) | 1.12 (0.49-2.59) P=NR | 1.22 (0.52-2.86) P=NR | Low risk bias |
| **Outcome: IE (Patent ductus arteriosus)** | | | | | | |
| Rushani et al. | 3885 | 6/185 (3) | 161/3700 (4) | 1.33 (0.54-3.27) P=NR | 1.25 (0.50-3.13) P=NR | Low risk bias |
| **Outcome: IE (Ventricular septal defect)** | | | | | | |
| Rushani et al. | 3885 | 27/185 (15) | 988/3700 (27) | 0.95 (0.56-1.62) P=NR | 0.97 (0.56-1.66) P=NR | Low risk bias |
| **Outcome: IE (Atrial septal defect)** | | | | | | |
| Rushani et al. | 3885 | 29/185 (16) (156) | 1004/3700 (27) | 0.449 (0.33-0.75)* P= NR | NR | Low risk bias |

* Calculated by reviewer, NR = not reported

| | | | | Effect Estimate | | Quality comment |
|---|---|---|---|---|---|---|
| **Study ID** | **N** | **N IE cases (%)** | **Controls Number (%)** | **Univariate analysis OR (95% CI) P-Value** | **Multivariate analysis Adjusted OR (aOR) (95% CI) P-Value** | |
| **Outcome: IE** | | | | | | |
| Strom et al (CG64) | 546 | 26/273 (9.5) | 7/273 (2.6) | NR | 6.7 (2.3-19.4) P=NR | Low risk bias |
| **Outcome: IE** | | | | | | |
| Ammar et al | 350 | 15/350 (8.6) | 12/350 (6.9) | 1.26 (0.58-2.73)* P=NR | NR. P=NR - NS only | High risk bias |
| **Outcome: Single episode IE vs >1 episode** | | | | | | |
| Alagna et al | 1874 | 165/1783 (9.2) (Single cases) | 8/91 (8.7) (repeat cases) | 1.06 (0.50-2.22)* P=NR | NR. P=1.00 | High risk bias |

1 * Calculated by reviewer, NR = not reported, NS = non significant

2 **Table 135: Rheumatic Heart Disease**

| | | | | Effect Estimate | | Quality comment |
|---|---|---|---|---|---|---|
| **Study ID** | **N** | **N IE cases (%)** | **Controls Number (%)** | **Univariate analysis OR (95% CI) P-Value** | **Multivariate analysis Adjusted OR (aOR) (95% CI) P-Value** | |
| **Outcome: IE** | | | | | | |
| Strom (CG64)[1] | 546 | 32/273 (11.7) | 10/273 (3.7) | NR | 13.4 (4.5-39.5) P=NR | Low risk bias |

3 [1] Rheumatic heart fever with heart involvement, NR = not reporte

4 **Table 136: Known Structural Heart Disease**

| | | | | Effect Estimate | | Quality comment |
|---|---|---|---|---|---|---|

| Study ID | N | N IE cases (%) | Controls Number (%) | Univariate Analysis OddsRatio(OR) 95% CI P-Value | Multivariate analysis Adjusted OR (aOR) (95% CI) P-Value | |
|---|---|---|---|---|---|---|
| **Outcome: IE** | | | | | | |
| Ammar et al | 350 | 117/175 (66.9) | 111/175 (63.4) | 1.16 (0.74-1.80)* P=NR | NR. NS | High risk bias |

1 *Calculated by reviewer, NR = not reported, NS = non significant

2 **Table 137: Valvular Heart Disease**

| | | | | Effect Estimate | | Quality comment |
|---|---|---|---|---|---|---|
| **Study ID** | **N** | **N IE cases (%)** | **Controls Number (%)** | **Univariate Analysis OddsRatio(OR) 95% CI P-Value** | **Multivariate analysis Adjusted OR (aOR) (95% CI) P-Value** | |
| **Outcome: IE** | | | | | | |
| Ammar et al | 350 | 53/175 (30.3) | 54/175 (30.9) | 0.97 (0.62-1.53)* P=NR | NR. NS. | High risk bias |
| **Outcome: IE** | | | | | | |
| Strom (CG64) | 546 | 104/273 (38.1) | 17/273 (6.2) | NR. NR. | 16.7 (7.4-37.4) P=NR | Low risk bias |

3 *Calculated by reviewer, NR = not reported, NS = non significant

4 **Table 138: Mitral Valve Prolapse**

| | | | | Effect Estimate | | Quality comment |
|---|---|---|---|---|---|---|
| **Study ID** | **N** | **N IE cases (%)** | **Controls Number (%)** | **Matched OR (95% CI) P-Value** | **Multivariate analysis OR (95% CI) P-Value** | |
| **Outcome: IE** | | | | | | |
| Clemens et al | 204 | 13/51 (25) | 10/153 (7) | 4.7 (1.1-19.5) | NR. NR. | Low risk bias |

| | | | | Effect Estimate | | Quality comment |
|---|---|---|---|---|---|---|
| Study ID | N | N IE cases (%) | Controls Number (%) | Matched OR (95% CI) P-Value | Multivariate analysis OR (95% CI) P-Value | |
| (CG64) | | | | P=NR | | |
| Hickey et al (CG64) | 224 | 11/56 (20) | 7/168 (4) | 6.8 (2.1-22.0) P=NR | NR. NR. | High risk bias |
| Strom et al (CG64) | 546 | 52/273 (19) | 6/273 (2.2) | 19.4 (6.4-58.4) P=NR | NR. NR. | Low risk bias |

1 NR = not reported, NS = non significant

2 **Table 139: Prosthetic Heart Valve**

| | | | | Effect Estimate | | Quality comment |
|---|---|---|---|---|---|---|
| Study ID | N | N IE cases (%) | Controls Number (%) | Univariate Analysis OddsRatio(OR) 95% CI P-Value | Multivariate analysis Adjusted Rate Ratio (aRR) (95% CI) P-value | |
| **Outcome: IE - Single episode IE vs >1 episode** | | | | | | |
| Alagna et al | 1874 | 431/1783 (24) (Single episode) | 16/91 (18) (repeat episode) | 1.49 (0.86-2.59)* P=0.17 | NR. | High risk bias |
| **Outcome: IE** | | | | | | |
| Ammar et al | 350 | 49/175 (28.0) | 45/175 (25.7) | 1.12 (0.70-1.80)* P=NR | NR. NS | High risk bias |

3 *calculated by reviewer, NR = not reported, NS = non significant

4 **Table 140: Cardiac Surgery A**

| | | | | Effect Estimate | | Quality comment |
|---|---|---|---|---|---|---|
| Study ID | N | N IE cases (%) | Controls Number (%) | Unadjusted Rate Ratio (RR) (95% CI) P Value | Multivariate analysis Adjusted Rate Ratio (aRR) (95% CI) P-value | |

| | | | | Effect Estimate | | Quality comment |
|---|---|---|---|---|---|---|
| Study ID | N | N IE cases (%) | Controls Number (%) | Unadjusted Rate Ratio (RR) (95% CI) P Value | Multivariate analysis Adjusted Rate Ratio (aRR) (95% CI) P-value | |
| **Outcome: IE** | | | | | | |
| Rushani et al[1] | 3885 | 17/185 (9) | 25/3700 (1) | 15.52 (8.08-29.80) P=NR | 5.34 (2.49-11.43) P=NR | Low risk bias |

1 [1]Cardiac valvular surgery, NR = not reported, NS = non significant

2 **Table 141: Cardiac Surgery B**

| | | | | Effect Estimate | | Quality comment |
|---|---|---|---|---|---|---|
| Study ID | N | N IE cases (%) | Controls Number (%) | Univariate Analysis OddsRatio(OR) 95% CI P-Value | Multivariate analysis OR (95% CI) P Value | |
| **Outcome: IE** | | | | | | |
| Strom (CG64)[2] | 546 | 37/273 (13.6) | 2/273 (0.7) | NR. NR. | 74.6 (12.5-447) P=NR | Low risk bias |

3 [2] In previous 6 months, NR = not reported, NS = non significant

4 **Table 142: Previous IE**

| | | | | Effect Estimate | | Quality comment |
|---|---|---|---|---|---|---|
| Study ID | N | N (%) IE cases | N (%) controls | Univariate Analysis OddsRatio(OR) 95% CI P-Value | Multivariate analysis OR (95% CI) P Value | |
| **Outcome: IE (Single episode IE vs >1 episode)** | | | | | | |
| Alagna et al | 1874 | 135/1783 (7.4) (Single cases) | 17 (19) (Repeat cases) | NR. NR. | 2.81 (1.5-5.1) P=0.001 | High risk bias |
| **Outcome: IE** | | | | | | |
| Ammar et al | 350 | 9/175 (5.1) | 2/175 (1.1) | 4.69 (0.998-22.03) | 5.841 (1.2-28.4) P=0.029 | High risk bias |

| | | | | Effect Estimate | | Quality comment |
|---|---|---|---|---|---|---|
| Study ID | N | N (%) IE cases | N (%) controls | Univariate Analysis OddsRatio(OR) 95% CI P-Value | Multivariate analysis OR (95% CI) P Value | |
| Strom (CG64) | 546 | 17/273 (6.2) | 1/273 (0.4) | NR. NR. | 37.2 (4.4-317) NR | Low risk bias |

1 NR = not reported, NS = non significant

2 **Table 143: Composite risk factors - Prior valve damage (Prosthetic heart valves, pacemaker or congenital heart disease)**

| | | | | Effect Estimate | | Quality comment |
|---|---|---|---|---|---|---|
| Study ID | N | N (%) with valvular heart damage | N (%) without | Univariate Analysis OddsRatio(OR) 95% CI P-Value | Multivariate analysis OR (95% CI) P Value | |
| **Outcome: IE** | | | | | | |
| Richet et al | | 1152/1939 (59.4) | 787/1939 (41.6) | NR. NR. | 8.2 (5-13.3) P<0.00001 | Low risk bias |

3 NR = not reported, NS = non significant

# H.24 Review question 2

5 **Table 144: Congenital Heart Disease and IE**

| | | | | | | Effect Estimate | | Quality comment |
|---|---|---|---|---|---|---|---|---|
| Study ID | N with risk factor/ total | N with RF with outcome | N without RF with outcome | N With RF without outcome | N without RF Without outcome | Univariate Analysis OddsRatio(OR) 95% CI P-Value | Multivariate analysis OR (95% CI) P Value | |
| **Outcome: Mortality (in hospital)** | | | | | | | | |
| Erbay et al | 7/107 | 2 | 29 | 5 | 78 | 1.08 (0.20-5.86)* p=0.613 | NR. NS. | Low risk bias |
| Lin et al | 31/48 | 6 | 7 | 25 | 41 | 1.41 (0.42-4.66)* P=NR | NA. NA. | High risk bias |

| | | | | | | Effect Estimate | | Quality comment |
|---|---|---|---|---|---|---|---|---|
| **Study ID** | **N with risk factor/ total** | **N with RF with outcome** | **N without RF with outcome** | **N With RF without outcome** | **N without RF Without outcome** | **Univariate Analysis OddsRatio(OR) 95% CI P-Value** | **Multivariate analysis OR (95% CI) P Value** | |
| Murdoch et al | 311/2656 | NR | NR | NR | NR | NR. NR. | 1.22 (0.74-2.02) p=0.44 | Low risk bias |
| Yoshinaga et al[1] | 40/137 | 9 | 40 | 31 | 123 | 5.34 (1.66-17.2) p=0.005 | NR. NS. | High risk bias |
| **Outcome: Mortality (5 year)** | | | | | | | | |
| Aksoy et al | 36/333 | 10 | 162 | 26 | 171 | 0.41 (0.19-0.87)* p = 0.008 | NA. NA. | Low risk bias |
| **Outcome: Cardiac Surgery** | | | | | | | | |
| Lin et al | 31/48 | 9 | 17 | 22 | 31 | 0.75 (0.28-1.98)* P=NR | NR. NR. | High risk bias |
| Lin et al[2] | 31/48 | 3 | 11 | 28 | 37 | 0.36 (0.09-1.42)* P=NR | NR. NR. | High risk bias |
| Murakami et al | 61/239 | 49 | 216 | 12 | 23 | 0.27 (0.11-0.65) P=0.0044 | NR. NS. | Low risk bias |
| **Outcome: Recurrence** | | | | | | | | |
| Alagna et al | 173/1874 | 8 | 91 | 165 | 1783 | 0.95 (0.45-1.99)* P=NR | NR. P=1.00 | High risk bias |

1 *calculated by reviewer [1] Cyanotic congenital heart disease only. [2] Lin – Valve replacement surgery specifically. NR = not reported, NS = non significant, NA= not available

2 **Table 145: Composite risk factors – predisposing cardiac diseases and IE**

| | | | | | | Effect Estimate | | Quality comment |
|---|---|---|---|---|---|---|---|---|
| **Study ID** | **N with risk factor/ total** | **N with RF with outcome** | **N without RF with outcome** | **N With RF without outcome** | **N without RF Without outcome** | **Univariate Analysis OddsRatio(OR) 95% CI P-Value** | **Multivariate analysis OR (95% CI) P Value** | |
| **Outcome: Mortality (in-hospital)** | | | | | | | | |
| Erbay et al1 | 87/107 | 25 | 29 | 62 | 78 | 1.09 (0.58-2.04)* p=0.312 | NIIM NA | Low risk bias |

| | | | | | | Effect Estimate | | Quality comment |
|---|---|---|---|---|---|---|---|---|
| **Study ID** | **N with risk factor/ total** | **N with RF with outcome** | **N without RF with outcome** | **N With RF without outcome** | **N without RF Without outcome** | **Univariate Analysis OddsRatio(OR) 95% CI P-Value** | **Multivariate analysis OR (95% CI) P Value** | |
| **Outcome: Mortality (after recovery from acute phase of IE, median follow-up 2.2 years)** | | | | | | | | |
| Thuny et al (2012)[2] | 206/328 | 30 | 55 | 176 | 273 | 0.85 (0.52-1.37)* p = 0.16 | EHR – NR. NR. | Low risk bias |
| **Outcome: Stroke (Cerebrovascular complications, silent embolism, ischaemic stroke, TIA, primary ICH)** | | | | | | | | |
| Thuny (2007) et al [3] | 275/496 | 59 | 109 | 216 | 387 | 0.97 (0.68-1.39)* p = 0.75 | NA. NA. | Low risk bias |

*calculated by reviewer. EHR = extended hazard ratio, NR = not reported, NS = non significant, NA= not available, NIIM = not entered in model*
*1 Pre-existing heart disease not specified*
*2 Underlying heart disease (not defined)*
*3Underlying heart disease included RHD, non-rheumatic valve disease, congenital heart disease and degenerative cardiac disease.*

**Table 146: Rheumatic Heart Disease and IE**

| | | | | | | Effect Estimate | | Quality comment |
|---|---|---|---|---|---|---|---|---|
| **Study ID** | **N with risk factor/ total** | **N with RF with outcome** | **N without RF with outcome** | **N With RF without outcome** | **N without RF Without outcome** | **Univariate Analysis OddsRatio(OR) 95% CI P-Value** | **Multivariate analysis OR (95% CI) P Value** | |
| **Outcome: Mortality** | | | | | | | | |
| Da Costa et al | 45/186 | 9 | 49 | 36 | 137 | 0.70 (0.31-1.56)* p = 0.365 | NR. NS(no value) | Low risk bias |
| Delahaye et al | 13/559 | NR | NR | NR | NR | NR. P=0.01 | NR. NS(no value) | High risk bias |
| Erbay et al | 11/107 | 5 | 29 | 6 | 78 | 2.24 (0.64-7.91)* p = 0.148 | NIIM. NA. | Low risk bias |
| **Outcome: Recurrence** | | | | | | | | |
| Wong et al | 9/47 | 1 | 8 | 8 | 39 | 0.61 (0.07-5.58)* p=1.00 | NA. NA. | Low risk bias |
| **Outcome: Events (Death OR Surgery)** | | | | | | | | |

| | | | | | | Effect Estimate | | Quality comment |
|---|---|---|---|---|---|---|---|---|
| **Study ID** | **N with risk factor/ total** | **N with RF with outcome** | **N without RF with outcome** | **N With RF without outcome** | **N without RF Without outcome** | **Univariate Analysis OddsRatio(OR) 95% CI P-Value** | **Multivariate analysis OR (95% CI) P Value** | |
| San Roman et al | 32/317 | 17 | 187 | 15 | 130 | 0.79 (0.38-1.63)* p = 0.47 | NIIM. NA. | Low risk bias |

1 *calculated by reviewer, NR = not reported, NS = non significant, NA= not available, NIIM = not entered in model

2 **Table 147: Degenerative Heart Disease and IE**

| | | | | | | Effect Estimate | | Quality comment |
|---|---|---|---|---|---|---|---|---|
| **Study ID** | **N with risk factor/ total** | **N with RF with outcome** | **N without RF with outcome** | **N With RF without outcome** | **N without RF Without outcome** | **Univariate Analysis OddsRatio(OR) 95% CI P-Value** | **Multivariate analysis OR (95% CI) P Value** | |
| **Outcome: Mortality** | | | | | | | | |
| Erbay et al | 15/107 | 4 | 29 | 11 | 78 | 0.98 (0.29-3.32)* p = 0.608 | NIIM NA | Low risk bias |
| **Outcome: Events (Death OR Surgery)** | | | | | | | | |
| San Roman et al | 29/317 | 16 | 187 | 13 | 130 | 0.86 (0.40-1.84)* p = 0.65 | NIIM. NA. | Low risk bias |

3 *calculated by reviewer, NR = not reported, NS = non significant, NA= not available, NIIM = not entered in model

4 **Table 148: Aortic Valve Disease/Disorder and IE**

| | | | | | | Effect Estimate | | |
|---|---|---|---|---|---|---|---|---|
| **Study ID** | **N with risk factor/ total** | **N with RF with outcome** | **N without RF with outcome** | **N With RF without outcome** | **N without RF Without outcome** | **Univariate Analysis OddsRatio(OR) 95% CI P-Value** | **Multivariate analysis OR (95% CI) P Value** | **Quality comment** |
| **Outcome: Mortality (in hospital)** | | | | | | | | |
| Erbay et al [1] | 3/107 | 2 | 29 | 1 | 78 | 5.38 (0.47-61.60)* p = 0.178 | NIIM. NA. | Low risk bias |

| | | | | | | Effect Estimate | | |
|---|---|---|---|---|---|---|---|---|
| **Study ID** | **N with risk factor/ total** | **N with RF with outcome** | **N without RF with outcome** | **N With RF without outcome** | **N without RF Without outcome** | **Univariate Analysis OddsRatio(OR) 95% CI P-Value** | **Multivariate analysis OR (95% CI) P Value** | **Quality comment** |
| **Outcome: Mortality (5 Year)** | | | | | | | | |
| Aksoy et al | 5/333 | 5 | 162 | 0 | 171 | 11.61 (0.64-211.63)* p = 0.003 | NA. NA. | Low risk bias |
| **Outcome: Recurrence** | | | | | | | | |
| Wong et al[2] | 4/47 | 2 | 8 | 2 | 39 | 4.88 (0.60-39.91)* p = 1.00 | NA. NA. | Low risk bias |

1 *calculated by reviewer 1 Bicuspid aortic valve. 2 Aortic stenosis specifically. NR = not reported, NS = non significant, NA= not available, NIIM = not entered in model

2 **Table 149: Mitral Valve Prolapse and IE**

| | | | | | | Effect Estimate | | Quality comment |
|---|---|---|---|---|---|---|---|---|
| **Study ID** | **N with risk factor/ total** | **N with RF with outcome** | **N without RF with outcome** | **N With RF without outcome** | **N without RF Without outcome** | **Univariate Analysis OddsRatio(OR) 95% CI P-Value** | **Multivariate analysis OR (95% CI) P Value** | |
| Outcome: Recurrence | | | | | | | | |
| Wong et al | 8/47 | 1 | 8 | 7 | 39 | 0.70 (0.08-6.47)* p = 1.00 | NA. NA. | Low risk bias |

3 *calculated by reviewer, NA= not available.

4 **Table 150: Previous valve replacement/Prosthetic valve and IE A**

| | | | | | | Effect Estimate | | Quality comment |
|---|---|---|---|---|---|---|---|---|
| **Study ID** | **N with risk factor/ total** | **N with RF with outcome** | **N without RF with outcome** | **N With RF without outcome** | **N without RF Without outcome** | **Univariate Analysis OddsRatio(OR) 95% CI P-Value** | **Multivariate analysis OR (95% CI) P Value** | |
| **Outcome: Mortality (in-hospital)** | | | | | | | | |
| Galvez-Acebal et al | 171/705 | 67 | 208 | 104 | 497 | 1.48 (1.17-1.87). P=0.001 | 1.99 (1.26-3.14) P=0.003 | Low risk bias |

| | | | | | | Effect Estimate | | Quality comment |
|---|---|---|---|---|---|---|---|---|
| **Study ID** | **N with risk factor/ total** | **N with RF with outcome** | **N without RF with outcome** | **N With RF without outcome** | **N without RF Without outcome** | **Univariate Analysis OddsRatio(OR) 95% CI P-Value** | **Multivariate analysis OR (95% CI) P Value** | |
| Yoshinaga et al | 4/137 | 0 | 14 | 4 | 123 | NR. P=0.99 | NR. NS | High risk bias |
| Murdoch et al | 563/2636 | NR | NR | NR | NR | NR. NR. | 1.47 (1.13-1.90) P=0.004 | Low risk bias |
| Da Costa et al | 55/186 | 20 | 49 | 137 | 186 | NR | 4.77 (1.44-15.76) P<0.01 | Low risk bias |
| Alonso-Valle et al | 133 | NR | NR | NR | NR | 0.9 (RR) (0.4-2.1). NR | NR. NS. | High risk bias |
| Delahaye et al | 95/559(17) | NR | NR | NR | NR | NR. P=0.04 | NR. NS. | High risk bias |
| Erbay et al | 47/107 | 10 | 29 | 37 | 78 | 0.73 (0.32-1.65)* p=0.230 | NIIM. NA. | Low risk bias |
| **Outcome: Mortality (in hospital and within 30 days of discharge)** | | | | | | | | |
| Fernandez-Guerrero et al 2007[1] | 17/44 | 2 | 17 | 15 | 27 | 0.21 (0.04-1.04)* P=NR | NIIM. NA. | High risk bias |
| Fernandez-Guerrero et al 2010[2] | 28/84 | 12 | 28 | 16 | 56 | 0.53 (0.21-1.37) NR (NS) | NA | High risk bias |
| **Outcome: Mortality (after recovery from acute phase of IE, median follow-up 2.2 years)** | | | | | | | | |
| Thuny et al (2012) | 206/328 | 30 | 55 | 176 | 273 | 0.85 (0.52-1.37)* P=0.16 | EHR 0.72 (0.35-1.50) P=0.39 | Low risk bias |
| **Outcome: Mortality (In hospital + 5 year)** | | | | | | | | |
| Bannay et al | 160/449 | NR | NR | NR | NR | HR 1.09 (0.72-1.67) 0.677 | Low risk bias | |
| **Outcome: Cardiac Surgery** | | | | | | | | |

| | | | | | | Effect Estimate | | Quality comment |
|---|---|---|---|---|---|---|---|---|
| **Study ID** | **N with risk factor/ total** | **N with RF with outcome** | **N without RF with outcome** | **N With RF without outcome** | **N without RF Without outcome** | **Univariate Analysis OddsRatio(OR) 95% CI P-Value** | **Multivariate analysis OR (95% CI) P Value** | |
| Bannay et al[1] | 71/449 | 37 | 240 | 34 | 209 | 0.95 (0.57-1.56)* P=NR | NR P=0.897 | Low risk bias |
| Bannay et al [2] | 257/449 | 142 | 240 | 115 | 209 | 1.08 (0.79-1.46)* P=NR | NR P=0.446 | Low risk bias |
| Fernandez-Guerrero et al 2007[3] | 17/44 | 6 | 17 | 11 | 27 | 0.87 (0.27-2.78)* P=NR | NIIM. NA | High risk bias |
| Fernandez-Guerrero et al 2010[4] | 28/84 | 20 | 41 | 8 | 43 | 0.24 (0.09-0.64) P=NR | NA. | High risk bias |
| **Outcome: Events (Death OR Surgery)** | | | | | | | | |
| San Roman et al | 124/317 | 72 | 187 | 52 | 130 | 0.96 (0.63-1.47)* p = 0.76 | NIIM. NA | Low risk bias |
| **Outcome: Recurrence** | | | | | | | | |
| Wong et al | 13/47 | 1 | 8 | 12 | 39 | 0.41 (0.05-3.58)* p = 0.41 | NA. | Low risk bias |
| Alagna et al | 447/1874 | 16 | 91 | 431 | 1783 | 0.73 (0.42-1.25)* p=1.00 | NR. | High risk bias |
| **Outcome: Stroke** | | | | | | | | |
| Fernandez-Guerrero et al 2007[3] | 9/44 | 4 | 17 | 5 | 27 | 1.27 (0.30-5.41)* P=NR | NIIM. NA | High risk bias |
| Fernandez-Guerrero et al 2010[4] | 28/84 | 10 | 26 | 18 | 58 | 0.72 (0.27-1.89) P=NR | NA | High risk bias |
| Thuny et al (2007)[5] | 110/496 | 24 | 109 | 86 | 387 | 0.99 (0.60-1.63)* p = 0.96 | NA | Low risk bias |

1 *calculated by reviewer, NR = not reported, NS = non significant, NA= not available, NIIM = not entered in model

1 1 Valvular prosthesis only. 2 Both native and prosthetic vavles. 3 Specifically IE caused by enterococci. OUTCOME = Brain emboli. 4 L-sided IE only caused by staphylococcus
2 aureus. OUTCOME = CNS complications including "brain bleeding". 5 Complications defined as silent cerebral embolism, ischaemic stroke, TIA, Primary ICH)

3 **Table 151: Prosthetic Valve Replacement/Prosthetic Valve and IE B**

| | | | | Effect Estimate | Quality comment |
|---|---|---|---|---|---|
| **Study ID** | **N with Risk Factor/ total** | **Number (%) observed deaths** | **Expected number of deaths** | **SMR 95% CI** | |
| **Outcome: Mortality (In hospital)** | | | | | |
| Ternhag et al | 890 | 154 (17.3) | 68 | 2.3 (1.9-2.7) P=NR | Low risk bias |

4 NR = not reported, NS = non significant, NA= not available, NIIM = not entered in model

5 **Table 152: Previous Valve Replacement (Mechanical prosthesis) and IE**

| | | | | | | Effect Estimate | | Quality comment |
|---|---|---|---|---|---|---|---|---|
| **Study ID** | **N with risk factor/ total** | **N with RF with outcome** | **N without RF with outcome** | **N With RF without outcome** | **N without RF Without outcome** | **Univariate Analysis OddsRatio(OR) 95% CI P-Value** | **Multivariate analysis OR (95% CI) P Value** | |
| **Outcome: Mortality (in-hospital)** | | | | | | | | |
| Alonso-Valle et al[1] | 64/133 | NR | NR | NR | NR | 1.1 (RR) 0.5-2.4. P= NR (NS) | NIIM NA | High risk bias |
| Smith et al | 22/87 | 2 | 10 | 20 | 77 | 0.77 (0.16-3.80)* p = 0.665 | NIIM NA | Low risk bias |

6 *calculated by reviewer using OR but p-value reported by authors related to their analysis which was RR. NR = not reported, NS = non significant, NA= not available, NIIM = not
7 entered in model
8 1 Population was people with prosthetic valves (compared mechanical valve with bio-prostheses for this outcome)

9 **Table 153: Previous cardiac surgery and IE**

| | | | | | | Effect Estimate | Quality comment |
|---|---|---|---|---|---|---|---|

| Study ID | N with risk factor/ total | N with RF with outcome | N without RF with outcome | N With RF without outcome | N without RF Without outcome | Univariate Analysis OddsRatio(OR) 95% CI P-Value | Multivariate analysis OR (95% CI) P Value | |
|---|---|---|---|---|---|---|---|---|
| **Outcome: Mortality** | | | | | | | | |
| Yoshinaga et al | 14/137 | 11 | 65 | 3 | 72 | 4.69 (1.25-17.6) p=0.02 | NR. NS | High risk bias |
| **Outcome: Surgery** | | | | | | | | |
| Murakami et al[1] | 119/239 | 26 | 61 | 93 | 178 | 0.68 (0.38-1.22) p=0.24 | NIIM. NA | Low risk bias |
| Smith et al | 24/87 | 3 | 10 | 21 | 77 | 1.10 (0.28-4.36)* p = 1.00 | NIIM. NA | Low risk bias |

*calculated by reviewer, NR = not reported, NS = non significant, NA= not available, NIIM = not entered in model
1 Previous surgery for CHD specifically

**Table 154: Previous IE and IE**

| | | | | | | Effect Estimate | | Quality comment |
|---|---|---|---|---|---|---|---|---|
| **Study ID** | **N with risk factor/ total** | **N with RF with outcome** | **N without RF with outcome** | **N With RF without outcome** | **N without RF Without outcome** | **Univariate Analysis OddsRatio(OR) 95% CI P-Value** | **Multivariate analysis OR (95% CI) P Value** | |
| **Outcome: Mortality (in hospital)** | | | | | | | | |
| Alonso-Valle et al[1] | NR | NR | NR | NR | NR | 1.7 (RR) 0.7-4.4 p=NR | NR. NS | High risk bias |
| Erbay et al | 10/107 | 6 | 29 | 4 | 78 | NR. 0.023 | HR 3.5 (1.2-11.0) p=0.026 | Low risk bias |
| San Roman et al | 28/317 | 16 | 187 | 12 | 130 | 0.93 (0.42-2.03)* p = 0.80 | NIIM. NA. | Low risk bias |
| Yoshinaga et al | 12/137 | 3 | 14 | 9 | 123 | 3.46 (0.81-14.7) p=0.09 | NR. NS | High risk bias |
| **Outcome: Cardiac Surgery** | | | | | | | | |
| Bannay et al | 38/449 | 24 | 240 | 14 | 209 | 1.49 (0.75-2.96)* p=0.237 | NR | Low risk bias |
| Murakami | 21/239 | 4 | 61 | 17 | 178 | 0.67 (0.22-2.06) p=0.61 | NIIM. NS | Low risk bias |

| | | | | | | Effect Estimate | | Quality comment |
|---|---|---|---|---|---|---|---|---|
| Study ID | N with risk factor/ total | N with RF with outcome | N without RF with outcome | N With RF without outcome | N without RF Without outcome | Univariate Analysis OddsRatio(OR) 95% CI P-Value | Multivariate analysis OR (95% CI) P Value | |
| Tleyjeh | 59/546 | 16 | 129 | 43 | 417 | 1.20 (0.66-2.21)* p = 0.50 | NA | High risk bias |

*calculated by reviewer, NR = not reported, NS = non significant, NA= not available, NIIM = not entered in model
1 Population was previous IE in patients with prosthetic valve endocarditis

# H.34 Review question 6a

**Table 155: Antibiotic vs placebo/no prophylaxis for infective endocarditis in those undergoing interventional procedures (dichotomous outcomes)**

| Quality assessment | | | | | | | No of patients | | Effect estimate | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Indirectness | Inconsistency | Imprecision | Other considerations | Antibiotic | No antibiotic | Relative (96% CI) | Absolute | |
| **Outcome: incidence of IE** | | | | | | | | | | | |
| *Reported in study as incidence of prosthetic valve endocarditis in those undergoing various interventional procedures (dental, urological, oropharyngeal and gynaecological)* | | | | | | | | | | | |
| 1 (Horstkotte, 1987) | Retrospective cohort | Serious[1] | None | N/A[2] | Very serious[3] | None | 0/287 (0%). | 6/390 (1.5%) | RR: 0.1 (0.01 to 1.85) | 14 fewer per 1000 (from 15 fewer to 13 more) | Very low |
| *Reported in study as incidence of IE in those undergoing dental procedures* | | | | | | | | | | | |
| 1 (Lacassin, 1995) | Case-control | Serious[4] | None | N/A[2] | Very serious[3] | None | 6/12 (50%) | 20/36 (56%) | RR: 0.9 (0.48 to 1.7) | 56 fewer per 1000 (from 289 fewer to 389 more) | Very low |
| *Reported in study as incidence of IE in those undergoing largely dental procedures* | | | | | | | | | | | |
| 1 (Vander | Case-contro | Serious[5] | None | N/A[2] | Very serious[3] | None | 8/34 (24%) | 40/214 (19%) | RR: 1.26 (0.65 to | 49 more per 1000 | Very low |

| Quality assessment | | | | | | | No of patients | | Effect estimate | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Meer, 1992) | I | | | | | | | | 2.45) | (from 65 fewer to 271 more) | |

[1] Serious risk of bias because 1) study design unclear 2) retrospective study reliant on patient's memory for data regarding interventional procedures undergone and prophylaxis use, no indication that data provided by subject was verified in any way 3) unclear how similar the interventional procedures the 2 groups underwent were; numbers not reported 4) unclear whether confounding factors were taken into account 5) age, gender not reported 6) Some subjects underwent more than one procedure 7) Power calculation not reported

[2] Single study analysis

[3] Very serious risk of imprecision as 95%Cis crosses both the default appreciable benefit and harm (0.75 and 1.25)

[4] Serious risk of bias because 1) retrospective nature of study reliant on subjects memory for interventional procedures undergone and antibiotic use 2) of the 171 cases, only 34% had definite infective endocarditis; 48% probable IE and 18% possible IE 3) in the case of medical consultation or procedure, information cited was checked by the cited practitioner; unclear whether what proportion of subjects this was possible for 4) Power calculation not reported

[5] Serious risk of bias because 1) retrospective study; data collected via structured questionnaire which although checked with medical and dental specialists, was highly reliant on patient's memory and reliability of medical records 2) cases who were very ill or who died were included in the analysis via the use of proxy responders, however this did not occur for the 53/889 controls who died 3) cases and controls did not undergo entirely the 'same' procedure however % undergoing dental procedures in both groups was comparable (92% and 91% cases and controls)

# H.42 Review question 7a

**Table 156: Antibiotic vs placebo/no prophylaxis for bacteraemia in those undergoing dental procedures (dichotomous outcomes)**

| Quality assessment | | | | | | | No of patients | | Effect estimate | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Indirectness** | **Inconsistency** | **Imprecision** | **Other considerations** | **Antibiotic** | **No prophylaxis/ placebo** | **Relative (95% CI)** | **Absolute** | |
| **Outcome: Incidence of positive blood culture following prophylaxis versus before** | | | | | | | | | | | |
| 1 (Maharaj et al., 2012) | RCT | Serious[1] | No serious | N/A[2] | No serious for amoxicillin and serious[3] for clindamycin | No serious | **At baseline** | | **At baseline** | | **At baseline** |
| | | | | | | | NR | NR | NR | NR | - |
| | | | | | | | **At 3 minutes post extraction; amoxicillin** | | **At 3 minutes post extraction; amoxicillin** | | **At 3 minutes post extraction; amoxicillin** |
| | | | | | | | 3/40 (7.5%) | 14/40 (35%) | RR: 0.21 (0.07 to 0.69) | 276 fewer per 1000 (from 108 fewer to | Moderate |

| Quality assessment | | | | | | | No of patients | | Effect estimate | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | 325 fewer) | |
| | | | | | | | **At 3 minutes post extraction; clindamycin** | | **At 3 minutes post extraction; clindamycin** | | **At 3 minutes post extraction; clindamycin** |
| | | | | | | | 8/40 (20%) | 14/40 (35%) | RR: 0.57 (0.27 to 1.21) | 150 fewer per 1000 (from 255 fewer to 74 more) | Low |
| 1 (Duvall et al., 2013) | RCT | Serious[4] | No serious | N/A[2] | Very serious[5] | No serious | **Reported in study as incidence of at least one positive culture of the 4 blood draws per subject including baseline; amoxicillin** | | **Reported in study as incidence of at least one positive culture of the 4 blood draws per subject including baseline; amoxicillin** | | |
| | | | | | | | 4/10 (40%) | 5/10 (50%) | RR: 0.8 (0.3 to 2.13) | 100 fewer per 1000 (from 350 fewer to 565 more) | Very low |
| 1 (Diz et al., 2006) | RCT | Serious[6] | No serious | N/A[2] | Not assessable[7] | No serious | **Amoxicillin: at baseline** | | **Amoxicillin: at baseline** | | Low |
| | | | | | | | 5% | 9.4% | - | - | |
| | | | | | | | **Amoxicillin: at 30 seconds** | | **Amoxicillin: at 30 seconds** | | |
| | | | | | | | 46.4% | 96.2% | P<0.001[8] | | |
| | | | | | | | **Amoxicillin: at 1 hour** | | **Amoxicillin: at 1 hour** | | |
| | | | | | | | 3.7% | 20% | P≤0.01[8] | | |
| | | | | | | | **Clindamycin: at** | | **Clindamycin: at** | | |

| Quality assessment | | | | | | | No of patients | | Effect estimate | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | **baseline** | | **baseline** | | |
| | | | | | | | 12.5% | 9.4% | - | - | |
| | | | | | | | **Clindamycin: at 30 seconds** | | **Clindamycin: at 30 seconds** | | |
| | | | | | | | 85.1% | 96.2% | P=NS[8] | | |
| | | | | | | | **Clindamycin: at 1 hour** | | **Clindamycin: at 1 hour** | | |
| | | | | | | | 22.2% | 20% | P=NS[8] | | |
| | | | | | | | **Moxifloxacin: at baseline** | | **Moxifloxacin: at baseline** | | |
| | | | | | | | 7.5% | 9.4% | - | - | |
| | | | | | | | **Moxifloxacin: at 30 seconds** | | **Moxifloxacin: at 30 seconds** | | |
| | | | | | | | 56.9% | 96.2% | P<0.001[8] | | |
| | | | | | | | **Moxifloxacin: at 1 hour** | | **Moxifloxacin: at 1 hour** | | |
| | | | | | | | 7.1% | 20% | P<0.05[8] | | |
| 1 (Hall et al., 1993) | RCT | Serious[9] | No serious | N/A[2] | No serious during extraction; penicillin V; very serious[5] 10 minutes after extraction; penicillin V; serious[3] during extraction; amoxicillin, serious[3] 10 minutes after extraction; amoxicillin | No serious | **At baseline** | | **At baseline** | | |
| | | | | | | | 0/20 (0%) | 0/20 (0%) | - | - | - |
| | | | | | | | **During extraction; penicillin V** | | **During extraction; penicillin V** | | |
| | | | | | | | 18/20 (90%) | 18/20 (90%) | RR: 1.00 (0.81 to 1.23) | 0 fewer per 1000 (from 171 fewer to 207 more) | Moderate |
| | | | | | | | **10 minutes after extraction; penicillin V** | | **10 minutes after extraction; penicillin V** | | |
| | | | | | | | 14/20 (70%) | 16/20 (80%) | RR: 0.88 (0.61 to 1.26) | 96 fewer per 1000 (from 312 | Very low |

| Quality assessment | | | | | | | No of patients | | Effect estimate | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | fewer to 208 more) | |
| | | | | | | | **During extraction; amoxicillin** | | **During extraction; amoxicillin** | | |
| | | | | | | | 17/20 (85%) | 18/20 (90%) | RR: 0.94 (0.75 to 1.19) | 54 fewer per 1000 (from 225 fewer to 171 more) | Low |
| | | | | | | | **10 minutes after extraction: amoxicillin** | | **10 minutes after extraction: amoxicillin** | | |
| | | | | | | | 12/20 (60%) | 16/20 (80%) | RR: 0.75 (0.49 to 1.14) | 200 fewer per 1000 (from 408 fewer to 112 more) | Low |
| 1 (Roberts et al., 1987) | RCT | Serious[10] | No serious | N/A[2] | Very serious[5] 2 minutes post intubation, no serious 2 minutes post extraction | No serious | **At baseline pre-intubation; amoxicillin** | | **At baseline pre-intubation; amoxicillin** | | |
| | | | | | | | 0/47 (0%) | 0/47 (0%) | - | - | |
| | | | | | | | **2 minutes after intubation** | | **2 minutes after intubation** | | |
| | | | | | | | 0/47 (0%) | 3/47 (6.4%) | RR: 0.14 (0.01 to 2.69) | 55 fewer per 1000 (from 63 fewer to 108 more) | Very low |
| | | | | | | | **2 minutes post extraction** | | **2 minutes post extraction** | | |
| | | | | | | | 1/47 | 18/47 | RR: 0.06 (0.01 to | 360 fewer per 1000 | Moderate |

| Quality assessment | | | | | | | No of patients | | Effect estimate | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | (2.1%) | (38.3%) | 0.40) | (from 230 fewer to 379 fewer) | |
| 1 (Hall et al., 1996) | RCT | Serious[11] | No serious | N/A[2] | Very serious[5] | No serious | **At baseline; cefaclor** | | **At baseline; cefaclor** | | Very low |
| | | | | | | | 0/19 (0%) | 0/20 (0%) | - | - | |
| | | | | | | | **During extraction[12]** | | **During extraction** | | |
| | | | | | | | 15/19 (79%) | 17/20 (85%) | RR: 0.93 (0.69 to 1.25) | 59 fewer per 1000 (from 264 fewer to 213 more) | |
| | | | | | | | **10 minutes after extraction[13]** | | **10 minutes after extraction** | | |
| | | | | | | | 10/19 (53%) | 9/19 (47%) | RR: 1.11 (0.59 to 2.10) | 52 more per 1000 (from 194 fewer to 521 more) | |
| 1 (Shanson et al., 1985) | RCT | Serious[14] | No serious | N/A[2] | Serious[3] | No serious | **At baseline; erythromycin** | | **At baseline; erythromycin** | | Low |
| | | | | | | | NR | NR | - | - | |
| | | | | | | | **1 to 2 minutes post extraction; erythromycin** | | **1 to 2 minutes post extraction; erythromycin** | | |
| | | | | | | | 6/40 (15%) | 18/42 (43%) | RR: 0.35 (0.15 to 0.79) | 279 fewer per 1000 (from 90 fewer to 364 fewer) | |
| 1 (Wahlm | RCT | Serious[15] | No serious | N/A[2] | No serious | No serious | **At baseline; cefuroxime** | | **At baseline; cefuroxime** | | |

| Quality assessment | | | | | | | No of patients | | Effect estimate | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ann et al., 1999) | | | | | | | NR | NR | - | - | |
| | | | | | | | **10 minutes after surgery; cefuroxime** | | **10 minutes after surgery; cefuroxime** | | |
| | | | | | | | 7/30 (23%) | 23/29 (79%) | RR: 0.29 (0.15 to 0.58) | 563 fewer per 1000 (from 333 fewer to 674 fewer) | Moderate |
| | | | | | | | **30 minutes after surgery ; cefuroxime** | | **30 minutes after surgery ; cefuroxime** | | |
| | | | | | | | 6/30 (20%) | 20/29 (69%) | RR: 0.29 (0.14 to 0.62) | 490 fewer per 1000 (from 262 fewer to 593 fewer) | Moderate |
| 1 (Lockhart et al., 2004) | RCT | Serious[16] | No serious | N/A[b] | Not assessable [7] | No serious | **At baseline after intubation; amoxicillin** | | **At baseline after intubation; amoxicillin** | | Low |
| | | | | | | | 4% | 18% | P=0.05[8] | | |
| | | | | | | | **15 minutes after extraction; amoxicillin** | | **15 minutes after extraction; amoxicillin** | | |
| | | | | | | | ~2% | 18% | P=0.04[8] | | |
| | | | | | | | **45 minutes after extraction; amoxicillin** | | **45 minutes after extraction; amoxicillin** | | |
| | | | | | | | 0% | 14% | P=0.03[8] | | |
| 1 (Morozumi et al., 2010) | RCT | Serious[17] | No serious | N/A[2] | Serious[3] | No serious | **Baseline; azithromycin** | | **Baseline; azithromycin** | | |
| | | | | | | | 0/10 (0%) | 0/10 (0%) | - | - | |
| | | | | | | | **6 minutes after scaling** | | **6 minutes after** | | |

| Quality assessment | | | | | | | No of patients | | Effect estimate | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | **and root planning; azithromycin** | | **scaling and root planning; azithromycin** | | |
| | | | | | | | 2/10 (20%) | 9/10 (90%) | RR: 0.22 (0.06 to 0.78) | 702 fewer per 1000 (from 198 fewer to 846 fewer) | Low |
| 1 (Lockhart et al., 2008) | RCT | Serious[18] | No serious | N/A[2] | Serious[3] | No serious | **At baseline** | | **At baseline** | | |
| | | | | | | | 0/96 (0%) | 0/96 (0%) | - | - | |
| | | | | | | | **First 5 minutes of procedure; amoxicillin** | | **First 5 minutes of procedure; amoxicillin** | | |
| | | | | | | | 29/89 (32.6%) | 49/84 (58.3%) | RR: 0.56 (0.39 to 0.79) | 257 fewer per 1000 (from 122 fewer to 356 fewer) | Low |
| | | | | | | | **20 minutes after; amoxicillin** | | **20 minutes after; amoxicillin** | | |
| | | | | | | | 1/88 (1.1%) | 8/83 (9.6%) | RR: 0.12 (0.02 to 0.92) | 85 fewer per 1000 (from 8 fewer to 94 fewer) | Low |
| **Adverse events** | | | | | | | | | | | |
| ***Reported in study as side effects including mild or transient nausea, abdominal discomfort or flatulence usually occurring within a few hours of extraction (no vomiting)*** | | | | | | | | | | | |
| 1 (Shanson et al., 1985) | RCT | Serious[19] | No serious | N/A[2] | No serious | No serious | 29/56 (52%) | 10/53 (19%) | RR: 2.74 (1.49 to 5.07) | 328 more per 1000 (from 92 more to 768 more) | Moderate |

[1] Serious risk of bias because 1) allocation concealment not described 2) blinding not described 3) number of positive blood cultures before extraction not reported – unclear if subjects were tested for bacteraemia 4) Power calculation not reported
[2] Single study analysis
[3] Serious imprecision as the 95%CIs are wide and crosses over the default appreciable benefit (0.75)
[4] Blinding not described, insufficient information to judge whether subjects and/or assessors blind. Incidence of positive blood cultures at baseline not reported separately but together with incidence at any of the blood draws, power calculation not reported
[5] Very serious imprecision as the 95%CIs are wide and crosses over both the default appreciable benefit and harm (0.75 and 1.25)
[6] Allocation concealment not described, baseline blood samples obtained in 40 subjects in each group (reasons for missing cultures not given), unclear if same subjects bacteraemic at different timepoints, incidence of bacteraemia at baseline not comparable between groups. Number of subjects at different timepoints unclear
[7] Imprecision could not be assessed due to the way data was presented in the article
[8] P value as reported in study. Relative risk and absolute risk could not be calculated as denominator unclear
[9] Randomisation, concealment and blinding not described. Unclear if subjects bacteraemic at 10 minutes were same subjects bacteraemic during surgery and power calculation not reported.
[10] Randomisation, concealment and blinding not described, subjects 'satisfactorily' consumed antibiotic, unclear whether those positive post extraction were those positive post intubation and power calculation not reported.
[11] Randomisation, concealment not described, unclear if those positive after extraction are those positive during extraction, unclear if one subject lost from control group at 10 minutes measurement and power calculation not reported.
[12] Based on percentages reported in study, assumption is that data was available for all subjects
[13] Study reports 47% for placebo group so assumption is that a subject was lost from control group although this is not clearly stated
[14] Number bacteraemic at baseline not reported and power calculation not reported.
[15] Randomisation, concealment and blinding not described, number bacteraemic at baseline not reported, unclear how many of the same subjects were bacteraemic at different time points and power calculation not reported.
[16] Unclear if same subjects bacteraemic at different time points, some subjects lost for measurements taken 15 minutes or later – unclear how many subjects lost from each group
[17] Randomisation, concealment and blinding not described, power calculation not reported.
[18] Unclear whether same subjects bacteraemic at different time points
[19] Number bacteraemic at baseline not reported

**Table 157: Antibiotic vs placebo/no prophylaxis for bacteraemia in those undergoing dental procedures (continuous outcomes)**

| Quality assessment | | | | | | | No of patients | | Effect estimate | Quality |
|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Indirectness | Inconsistency | Imprecision | Other considerations | Antibiotic | Placebo | Mean difference (95% CI) | |
| **Outcome: Bacteraemia levels/intensity following prophylaxis versus before** | | | | | | | | | | |
| **Reported in study as total mean magnitude of bacteraemia (cfu/ml)** | | | | | | | | | | |
| 1 (Duvall et al., 2013) | RCT | Serious[1] | None | N/A[2] | Very serious[3] | No serious | N=10 Mean (SD): 0.63 (1.33) | N=10 Mean (SD): 3.61 (7.09) | MD: -2.98 (-7.45 to 1.49) | Very low |
| **Reported in study as mean magnitude of bacteraemia per blood draw (cfu/ml):** | | | | | | | | | | |
| ***Blood draw 1 (at baseline once the IV access line was established)*** | | | | | | | | | | |
| 1 (Duvall et al., 2013) | RCT | Serious[1] | None | N/A[2] | Not assessable[4] | No serious | N=10 Mean (SD): 0.05 (0.16) | N=10 Mean (SD): 0 (0) | - | Moderate |
| ***Blood draw 2 (1.5 minutes following initiation of the mucogingival flap#32)*** | | | | | | | | | | |

| Quality assessment | | | | | | | No of patients | | Effect estimate | Quality |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 (Duvall et al., 2013) | RCT | Serious[1] | None | N/A[2] | Very serious[3] | No serious | N=10 Mean (SD): 0.02 (0.06) | N=10 Mean (SD): 1.26 (3.67) | MD: -1.24 (-3.51 to 1.03) | Very low |
| ***Blood draw 3 (1.5 minutes following initiation of mucogingival flap #17)*** | | | | | | | | | | |
| 1 (Duvall et al., 2013) | RCT | Serious[1] | None | N/A[2] | Very serious[3] | No serious | N=10 Mean (SD): 0.30 (0.73) | N=10 Mean (SD): 1.90 (5.36) | MD: -1.60 (-4.95 to 1.75) | Very low |
| ***Blood draw 4 (10 minutes following initiation of mucogingival flap #17)*** | | | | | | | | | | |
| 1 (Duvall et al., 2013) | RCT | Serious[1] | None | N/A[2] | Serious[5] | No serious | N=10 Mean (SD): 0.26 (0.60) | N=10 Mean (SD): 0.45 (0.83) | MD: -0.19 (-0.82 to 0.44) | Low |

[1] Serious risk of bias because blinding not described and incidence of positive blood cultures at baseline not reported separately but together with incidence at any of the blood Draws, power calculation not reported.
[2] Single study analysis
[3] Very serious imprecision as 95%CIs crosses over both the default appreciable benefit and harm (-0.5 and 0.5)
[4] Not assessable as mean and SD in comparator arm is zero
[5] Serious imprecision as 95%CI crosses over the default appreciable benefit (-0.5)

**Table 158: Antibiotic vs placebo/no prophylaxis for bacteraemia in those undergoing respiratory procedures**

| Quality assessment | | | | | | | No of patients | | Effect estimate | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Indirectness** | **Inconsistency** | **Imprecision** | **Other considerations** | **Antibiotic** | **No prophylaxis/ placebo** | **Relative (95% CI)** | **Absolute** | |
| **Outcome: Incidence of positive blood culture following prophylaxis versus before** | | | | | | | | | | | |
| 1 (Sanchez-Carrion et al., 2006) | RCT | Serious[1] | No serious | N/A[2] | No serious at 30 seconds, very serious[3] at 20 minutes | No serious | **At baseline** | | **At baseline** | | |
| | | | | | | | NR | NR | - | - | |
| | | | | | | | **30 seconds after adenoidectomy; cefazolin** | | **30 seconds after adenoidectomy** | | |
| | | | | | | | 2/51 (3.9%) | 16/50 (32.7%) | RR: 0.12 (0.03 to 0.51) | 282 fewer per 1000 (from 157 | Moderate |

| Quality assessment | | | | | | | No of patients | | Effect estimate | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | fewer to 310 fewer) | |
| | | | | | | | **20 minutes after adenoidectomy; cefazolin** | | **20 minutes after adenoidectomy; cefazolin** | | |
| | | | | | | | 2/51 (3.9%) | 7/50 (14.3%) | RR: 0.28 (0.06 to 1.28) | 101 fewer per 1000 (from 132 fewer to 39 more) | Very low |

[1] Randomisation, concealment not described. Incidence of bacteraemia at baseline not reported and power calculation not reported.
[2] Single study analysis
[3] Very serious imprecision as 95%Cis crosses over both the default appreciable benefit and harm (0.75 and 1.25)

**Table 159: Antibiotic vs placebo/no prophylaxis for bacteraemia in those undergoing gastrointestinal procedures**

| Quality assessment | | | | | | | No of patients | | Effect estimate | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Indirectness** | **Inconsistency** | **Imprecision** | **Other considerations** | **Antibiotic** | **No prophylaxis/ placebo** | **Relative (95% CI)** | **Absolute** | |
| **Outcome: Incidence of positive blood culture following prophylaxis versus before** | | | | | | | | | | | |
| 1 (Selby et al., 1994) | RCT | Serious[1] | No serious | N/A[2] | Very serious[3] | No serious | **At baseline** | | **At baseline** | | Very low |
| | | | | | | | 0/19 | 1/20[4] | RR: 0.35 (0.02 to 8.1) | 33 fewer per 1000 (from 49 fewer to 355 more) | |
| | | | | | | | **5 minutes after endoscopic sclerotherapy; cefotaxime** | | **5 minutes after endoscopic sclerotherapy; cefotaxime** | | |
| | | | | | | | 1/19 (5.3%) | 6/19 (31.6%) | RR: 0.17 (0.02 to 1.26) | 262 fewer per 1000 (from 309 fewer to | |

| Quality assessment | | | | | | | No of patients | | Effect estimate | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | 82 more) | |
| | | | | | | | **20 minutes after endoscopic sclerotherapy; cefotaxime** | | **20 minutes after endoscopic sclerotherapy; cefotaxime** | | |
| | | | | | | | 0/19 (0%) | 0/19 (0%) | - | - | |
| 1 (Rolando et al., 1993) | RCT | Serious[5] | No serious | N/A[2] | Very serious[3] | No serious | **At baseline[4]** | | **At baseline** | | Very low |
| | | | | | | | NR | NR | - | - | |
| | | | | | | | **30 minutes post-sclerotherapy; imipenem/cilastatin** | | **30 minutes post-sclerotherapy; imipenem/cilastatin** | | |
| | | | | | | | 1/57[7] (2%) | 5/58[6] (8%) | RR: 0.2 (0.02 to 1.69) | 69 fewer per 1000 (from 84 fewer to 59 more) | |
| 1 (Harris et al., 1999) | Meta-analysis of 4 RCTs | Serious[8] | No serious | No serious | Very serious[3] | No serious | **At baseline** | | **At baseline** | | Very low |
| | | | | | | | NR | NR | - | - | |
| | | | | | | | **Post ERCP** | | **Post ERCP** | | |
| | | | | | | | NR | NR | RR: 0.39 (0.12 to 1.29)[9] | NR | |
| **Adverse events** | | | | | | | | | | | |
| *Mortality* | | | | | | | | | | | |
| 1 (Selby et al., 1994) | RCT | Serious[1] | No serious | N/A[2] | Very serious[3] | No serious | 2/19 (10.5%) | 5/19 (26.3%) | RR: 0.4 (0.09 to 1.81) | 158 fewer per 1000 (from 239 fewer to 213 more) | Very low |

[1] Blinding not described and power calculation not reported.
[2] Single study analysis
[3] Very serious imprecision as the 95%Cis crosses over both the default appreciable benefit and harm (0.75 and 1.25)
[4] Excluded from further analysis as subject positive before procedure
[5] Serious risk of bias as concealment and blinding not described, power calculation not reported.

[6] 2/97 subjects were positive for bacteraemia before the endoscopy and therefore excluded; unclear which group subjects were from
[7] Some subjects had more than one sclerotherapy session
[8] Serious risk of bias because overall quality of individual studies assessed but not reported, also unclear whether any subjects were bacteraemic before the procedure in the individual studies
[9] As reported in study

**Table 160: Antibiotic vs placebo/no prophylaxis for bacteraemia in those undergoing genitourinary procedures**

| Quality assessment | | | | | | | No of patients | | Effect estimate | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Indirectness | Inconsistency | Imprecision | Other considerations | Antibiotic | No prophylaxis/ placebo | Relative (95% CI) | Absolute | |
| **Outcome: Incidence of positive blood culture following prophylaxis versus before** | | | | | | | | | | | |
| 1 (Allan et al., 1985) | RCT | Serious[1] | No serious | N/A[2] | No serious | No serious | **At baseline** | | **At baseline** | | |
| | | | | | | | NR | NR | - | - | |
| | | | | | | | **After completion of transurethral prostatectomy; mezlocillin** | | **After completion of transurethral prostatectomy; mezlocillin** | | |
| | | | | | | | 2/50 (4%) | 16/50 (32 %)[3] | RR: 0.12 (0.03 to 0.52) | 282 fewer per 1000 (from 154 fewer to 310 fewer) | Moderate |
| | | | | | | | **First day post-op and after removal of catheter** | | **First day post-op and after removal of catheter** | | |
| | | | | | | | NR | NR | NS[4] | | |
| 1 (Bhattacharya et al., 1995) | RCT | Serious[5] | No serious | N/A[2] | Serious[6] | No serious | **At baseline** | | **At baseline** | | |
| | | | | | | | NR | NR | - | - | |
| | | | | | | | **Immediately after transcervical resection or laser ablation of endometrium; augmentin** | | **Immediately after transcervical resection or laser ablation of endometrium; augmentin** | | |
| | | | | | | | 1/55 (2%) | 10/61 (16%) | RR: 0.11 (0.01 to | 146 fewer per 1000 (from 26 | Low |

| Quality assessment | | | | | | | No of patients | | Effect estimate | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | 0.84) | fewer to 162 fewer) | |
| 1 (Qiang et al., 2005) | Systematic review of 10 RCTs | Serious[7] | No serious | N/A[8] | Not assessable | No serious | **After transurethral resection of prostate** | | **After transurethral resection of prostate** | | Moderate |
| | | | | | | | 8/792 (1%) | 24/602 (4%) | Risk difference: -0.02 (-0.04 to 0.00)[9] | 31 fewer per 1000 (from 12 fewer to 37 fewer) | |
| **Adverse events** | | | | | | | | | | | |
| ***Reported in study as post-operative outcome within 2 weeks of endometrial ablation:*** | | | | | | | | | | | |
| *Pain* | | | | | | | | | | | |
| 1 (Bhattacharya et al., 1995) | RCT | Serious[10] | No serious | N/A[2] | Serious[11] | No serious | 29/55 (52.7%) | 26/61 (42.6%) | RR: 1.24 (0.84 to 1.82) | 102 more per 1000 (from 68 fewer to 350 more) | Low |
| *Offensive discharge* | | | | | | | | | | | |
| 1 (Bhattacharya et al., 1995) | RCT | Serious[12] | No serious | N/A[2] | Very serious[13] | No serious | 14/55 (25.5%) | 14/61 (23%) | RR: 1.11 (0.58 to 2.11) | 25 more per 1000 (from 96 fewer to 255 more) | Very low |
| *Fever* | | | | | | | | | | | |
| 1 (Bhattacharya et al., 1995) | RCT | Serious[14] | No serious | N/A[2] | Serious[9] | No serious | 9/55 (16.4%) | 4/61 (6.6%) | RR: 2.5 (0.81 to 7.65) | 98 more than per 1000 (from 12 fewer to 436 more) | Low |

[1] Unclear if subjects lost from control arm as percentages do not match up to number randomised, blood culture methods not reported, number bacteraemic before procedure not reported. power calculation not reported.
[2] Single study analysis
[3] Percentage calculated by reviewer based on assumption that denominator is 50 (i.e. no subjects lost)

[4] As reported in study. Relative risk and absolute measures could not be calculated as raw data not reported in study
[5] Characteristics of subjects not reported, incidence of bacteraemia before procedure not reported
[6] Serious imprecision as 95%Cis wide and crosses over the default appreciable benefit (0.75)
[7] Serious risk of bias as unclear how heterogeneity was assessed
[8] Not reported in study therefore could not be assessed
[9] As reported in study
[10] Characteristics of subjects not reported, incidence of bacteraemia before procedure not reported
[11] Serious imprecision as 95%CI crosses over the default appreciable harm (1.25)
[12] Characteristics of subjects not reported, incidence of bacteraemia before procedure not reported
[13] Very serious imprecision as 95% CIs crosses over both the default appreciable benefit and harm (0.75 and 1.25)
[14] Characteristics of subjects not reported, incidence of bacteraemia before procedure not reported

# H.52 Review question 7b

**Table 161: 0.12% chlorhexidine studies vs no prophylaxis/placebo for bacteraemia (dichotomous outcomes)**

| Quality assessment | | | | | | | No of patients | | Effect estimate | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Indirectness** | **Inconsistency** | **Imprecision** | **Other considerations** | **0.12% chlorhexidine rinse** | **No prophylaxis/ placebo** | **Relative (96% CI)** | **Absolute** | |
| **Outcome: Incidence of positive blood culture following prophylaxis versus before** | | | | | | | | | | | |
| 1 (Duvall et al., 2013) | RCT | Serious[1] | None | N/A[2] | Very serious[3] | No serious | **Reported in study as incidence of at least one positive culture of the 4 blood draws per subject (including baseline)** | | RR: 1.2 (0.54 to 2.67) | 100 more per 1000 (from 230 fewer to 835 more) | Very low |
| | | | | | | | 6/10 (60%) | 5/10 (50%) | | | |
| 1 (Brown et al., 1998) | RCT | Serious[4] | None | N/A[2] | Very serious[3] | No serious | **At baseline** | | **At baseline** | | Very low |
| | | | | | | | 0/31 (0%) | 0/24 (0%) | - | - | |
| | | | | | | | **At 90 seconds after intraoral suture removal** | | **At 90 seconds after intraoral suture removal** | | |
| | | | | | | | 4/31 (12.9%) | 2/24 (8.3%) | RR: 1.55 (0.31 to 7.76) | 46 more per 1000 (from 57 fewer to 563 | |

| Quality assessment | | | | | | | No of patients | | Effect estimate | Quality |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | more) | |

[1] Serious risk of bias because blinding not described and incidence of positive blood cultures at baseline not reported separately but together with incidence at any of the blood Draws, power calculation not reported and study only gave one dose of rinse before procedure.
[2] Single study analysis
[3] Very serious imprecision as 95%CIs are wide and cross over both the default appreciable benefit and harm (0.75 and 1.25)
[4] Serious risk of bias because randomisation, allocation concealment and blinding not described. Power calculation not reported and study only gave one dose of rinse before procedure.

**Table 162: 0.12% chlorhexidine studies vs no prophylaxis/placebo for bacteraemia (continuous outcomes)**

| Quality assessment | | | | | | | No of patients | | Effect estimate | Quality |
|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Indirectness | Inconsistency | Imprecision | Other considerations | 0.12% chlorhexidine | Placebo | Mean difference (95% CI) | |
| **Outcome: Bacteraemia levels/intensity following prophylaxis versus before** | | | | | | | | | | |
| **Reported in study as total mean magnitude of bacteraemia (cfu/ml)** | | | | | | | | | | |
| 1 (Duvall et al., 2013) | RCT | Serious[1] | None | N/A[2] | Very serious[3] | No serious | N=10 Mean (SD): 2.76 (4.28) | N=10 Mean (SD): 3.61 (7.09) | MD = 0.85 lower (5.98 lower 4.28 higher) | Very low |
| **Reported in study as mean magnitude of bacteraemia per blood draw (cfu/ml)** | | | | | | | | | | |
| ***Blood draw 1 (at baseline once the IV access line was established)*** | | | | | | | | | | |
| 1 (Duvall et al., 2013) | RCT | Serious[1] | None | N/A[2] | Not assessable[4] | No serious | N=10 Mean (SD): 0.04 (0.13) | N=10 Mean (SD): 0 (0) | MD = 0 higher (0 to 0 higher) | Moderate |
| ***Blood draw 2 (1.5 minutes following initiation of the mucogingival flap#32)*** | | | | | | | | | | |
| 1 (Duvall et al., 2013) | RCT | Serious[1] | None | N/A[2] | Very serious[3] | No serious | N=10 Mean (SD): 0.18 (0.29) | N=10 Mean (SD): 1.26 (3.67) | MD = 1.08 lower (3.36 lower to 1.2 higher) | Very low |
| ***Blood draw 3 (1.5 minutes following initiation of mucogingival flap #17)*** | | | | | | | | | | |
| 1 (Duvall et al., 2013) | RCT | Serious[1] | None | N/A[2] | Very serious[3] | No serious | N=10 Mean (SD): 2.37 (4.11) | N=10 Mean (SD): 1.90 (5.36) | MD = 0.47 higher (3.72 lower to 4.66 higher) | Very low |
| ***Blood draw 4 (10 minutes following initiation of mucogingival flap #17)*** | | | | | | | | | | |

| Quality assessment | | | | | | | No of patients | | Effect estimate | Quality |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 (Duvall et al., 2013) | RCT | Serious[1] | None | N/A[2] | Serious [5] | No serious | N=10 Mean (SD): 0.17 (0.24) | N=10 Mean (SD): 0.45 (0.83) | MD = 0.28 lower (0.82 lower to 0.26 higher) | Low |

[1] Serious risk of bias because blinding not described and incidence of positive blood cultures at baseline not reported separately but together with incidence at any of the blood draws, power calculation not reported and study only gave one dose of rinse before procedure.
[2] Single study analysis
[3] Very serious imprecision as 95%CIs are wide and cross over the default appreciable benefit and harm (-0.5 and +0.5)
[4] Not assessable as mean and SD in comparator arm is zero
[5] Serious imprecision as 95%CIs are wide and cross over the default appreciable benefit (-0.5)

**Table 163: 0.2% chlorhexidine vs no prophylaxis/placebo for bacteraemia**

| Quality assessment | | | | | | | No of patients | | Effect estimate | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Indirectness** | **Inconsistency** | **Imprecision** | **Other considerations** | **0.2% chlorhexidine rinse** | **No prophylaxis/ placebo** | **Relative (95% CI)** | **Absolute** | |
| **Outcome: Incidence of positive blood culture following prophylaxis versus before** | | | | | | | | | | | |
| 1 (Maharaj et al., 2012) | RCT | Serious[1] | No serious | N/A[2] | Very serious[3] | No serious | **At baseline** | | **At baseline** | | Very low |
| | | | | | | | NR | NR | NR | NR | |
| | | | | | | | **At 3 minutes post extraction** | | **At 3 minutes post extraction** | | |
| | | | | | | | 16/40 (40%) | 14/40 (35%) | RR: 1.14 (0.65 to 2.02) | 49 more per 1000 (from 123 fewer to 357 more) | |
| 1 (Pineiro et al., 2010) | RCT | Serious[4] | No serious | N/A[2] | Very serious[3] | No serious | **At baseline** | | **At baseline** | | Very low |
| | | | | | | | 0/20 (0%) | 1/30 (3.3%) | RR: 0.49 (0.02 to 11.51) | 17 fewer per 1000 (from 33 fewer to 350 more) | |
| | | | | | | | **At 30 seconds following dental implant placement** | | **At 30 seconds following dental implant placement** | | |

| Quality assessment | | | | | | | No of patients | | Effect estimate | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | 0/20 (0%) | 2/30 (6.7%) | RR: 0.30 (0.01 to 5.84) | 47 fewer per 1000 (from 66 fewer to 323 more) | |
| | | | | | | | **At 15 minutes following dental implant placement** | | **At 15 minutes following dental implant placement** | | |
| | | | | | | | 0/20 (0%) | 1/30 (3.3%) | RR: 0.49 (0.02 to 11.51) | 17 fewer per 1000 (from 33 fewer to 350 more) | |
| 1 (Tuna et al., 2012) | RCT | Serious[5] | No serious | N/A[2] | Very serious[3] | No serious | **At baseline[6]** | | **At baseline** | | Very low |
| | | | | | | | 0/12 (0%) | 0/10 (0%) | - | - | |
| | | | | | | | **At 1st minute following extraction** | | **At 1st minute following extraction** | | |
| | | | | | | | 3/12 (25%) | 4/10 (40%) | RR: 0.62 (0.18 to 2.16) | 152 fewer per 1000 (from 328 fewer to 464 more) | |
| | | | | | | | **At 15th minute following extraction** | | **At 15th minute following extraction** | | |
| | | | | | | | 2/12 (17%) | 3/10 (30%) | RR: 0.56 (0.11 to 2.7) | 132 fewer per 1000 (from 267 fewer to 510 more) | |
| 1 | RCT | Serious[7] | None | N/A[2] | No serious | No serious | **At baseline** | | **At baseline** | | Moderat |

| Quality assessment | | | | | | | No of patients | | Effect estimate | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| (Lockhart et al., 1996) | | | | | | | NR | NR | - | - | e |
| | | | | | | | **At 1 or 3 minute postextraction** | | **At 1 or 3 minute postextraction** | | |
| | | | | | | | 31/37 (84%) | 31/33 (94%) | RR: 0.89 (0.76 to 1.05) | 103 fewer per 1000 (from 225 fewer to 47 more) | |
| 1 (Tomas et al., 2007) | RCT | Serious[8] | None | N/A[2] | **At baseline** | No serious | **At baseline** | | **At baseline** | | **At baseline** |
| | | | | | Very serious[3] | | 5/53 (9%) | 4/53 (8%) | RR: 1.25 (0.36 to 4.4) | 19 more per 1000 (from 48 fewer to 257 more) | Very low |
| | | | | | **At 30 seconds** | | **At 30 seconds** | | **At 30 seconds** | | **At 30 seconds** |
| | | | | | Serious[9] | | 42/53 (79%) | 51/53 (96%) | RR: 0.82 (0.71 to 0.95) | 173 fewer per 1000 (from 48 fewer to 279 fewer) | Low |
| | | | | | **At 1 hour** | | **At 1 hour postextraction** | | **At 1 hour postextraction** | | **At 1 hour** |
| | | | | | Serious[9] | | 1/50 (2%) | 10/50 (20%) | RR: 0.1 (0.01 to 0.75) | 180 fewer per 1000 (from 50 fewer to 198 fewer) | Low |
| 1 (Rahn et al., | RCT | Serious[10] | None | N/A[2] | Very serious[3] | No serious | **At baseline** | | **At baseline** | | Very low |
| | | | | | | | 0/40 | 0/40 | - | - | |

| Quality assessment | | | | | | | No of patients | | Effect estimate | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1995) | | | | | | | (0%) | (0%) | | | |
| | | | | | | | **At post dental treatment (2, 4 and 6 minutes cultures)** | | **At post dental treatment (2, 4 and 6 minutes cultures)** | | |
| | | | | | | | 18/40 (45%) | 21/40 (52.5%) | RR: 0.86 (0.55 to 1.35) | 73 fewer per 1000 (from 236 fewer to 184 more) | |

[1] Serious risk of bias because 1) allocation concealment not described 2) blinding not described 3) number of positive blood cultures before extraction not reported – unclear if subjects were tested for bacteraemia 4) Power calculation not reported 5) Study only gave one dose of rinse before procedure.
[2] Single study analysis
[3] Very serious imprecision as the 95%CIs are wide and crosses over both the default appreciable benefit and harm (0.75 and 1.25)
[4] Serious risk of bias because randomisation, allocation concealment and blinding not described, power calculation not reported, study only gave one dose of rinse before procedure.
[5] Serious risk of bias because allocation concealment and blinding not described, unclear whether it's the same subjects bacteraemic at different time points (possible double counting of subjects), power calculation not reported and study only gave one dose of rinse before procedure.
[6] Those with bacteraemia in the preoperative blood culture were excluded (n=2 from chlorhexidine group)
[7] Numbers in each group not explicitly stated – calculated by reviewer based on percentages reported in study. Incidence of bacteraemia at baseline not reported, power calculation not reported and study only gave one dose of rinse before procedure.
[8] Serious risk of bias because allocation concealment and blinding not described. Unclear if same subjects bacteraemic at different time points, power calculation not reported, study only gave one dose of rinse before procedure.
[9] Serious imprecision as 95%CIs are wide and cross over the default appreciable benefit (0.75)
[10] Serious risk of bias because randomisation and concealment not described. Also, single blind only, details not described. Unclear whether same subjects were bacteraemic at the 2, 4 and 6 minutes cultures as data presented together, power calculation not reported and study only gave one dose of rinse before procedure.

**Table 164: 0.5% chlorhexidine studies vs control for bacteraemia**

| Quality assessment | | | | | | | No of patients | | Effect estimate | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Indirectness** | **Inconsistency** | **Imprecision** | **Other considerations** | **0.5% chlorhexidine rinse** | **Sterile cotton rolls and saliva ejector** | **Relative (96% CI)** | **Absolute** | |
| **Outcome: Incidence of positive blood culture following prophylaxis versus before** | | | | | | | | | | | |
| 1 (Jokinen et al., 1978) | RCT | Very serious[1] | None | N/A[2] | Serious[3] | None | **At baseline** | | **At baseline** | | Very low |
| | | | | | | | NR | NR | - | - | |
| | | | | | | | **At 30 to 60 seconds post extraction** | | **At 30 to 60 seconds post extraction** | | |
| | | | | | | | 5/38 (13%) | 13/38 (34%) | RR: 0.38 (0.15 to 0.97) | 212 fewer per 1000 (from 10 | |

| Quality assessment | | | | | | | No of patients | | Effect estimate | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | fewer to 291 fewer) | |

[1] Study design not clearly described, randomisation, concealment and blinding not described, outcome not pre-specified (therefore selective reporting difficult to judge), incidence of bacteraemia before extraction not reported, power calculation not reported and study only gave one dose of rinse before procedure.
[2] Single analysis study
[3] Serious imprecision as 95%CIs are wide and cross over the default appreciable benefit (0.75)

**Table 165: 1% chlorhexidine vs placebo for bacteraemia**

| Quality assessment | | | | | | | No of patients | | Effect estimate | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Indirectness** | **Inconsistency** | **Imprecision** | **Other considerations** | **1% chlorhexidine rinse** | **Placebo** | **Relative (95% CI)** | **Absolute** | |
| **Outcome: Incidence of positive blood culture following prophylaxis versus before** | | | | | | | | | | | |
| 1 ( MacFarlane et al., 1984) | RCT | Serious[1] | No serious | N/A[2] | No serious | No serious | **At baseline** | | **At baseline** | | Moderate |
| | | | | | | | 0/20 (0%) | 0/20 (0%) | - | - | |
| | | | | | | | **At 30 seconds post extraction** | | **At 30 seconds post extraction** | | |
| | | | | | | | 5/20 (25%) | 16/20 (80%) | RR: 0.31 (0.14 to 0.69) | 528 fewer per 1000 (from 248 fewer to 668 fewer) | |

[1] Serious risk of bias because study design not described in detail, randomisation, allocation concealment and blinding not described, power calculation not reported and study only gave one dose of rinse before procedure.
[2] Single study analysis

# Appendix I: Economic search strategy

Databases that were searched, together with the number of articles retrieved from each database are shown in Table 166. The economic search strategy is shown in Table 167. The same strategy was translated for the other databases listed.

**Table 166: Economic search summary**

| Databases | Date searched | No. retrieved |
|---|---|---|
| MEDLINE (Ovid) | 20/11/2014 | 144 |
| MEDLINE In-Process (Ovid) | 20/11/2014 | 8 |
| EMBASE (Ovid) | 20/11/2014 | 629 |
| NHS Economic Evaluation Database - NHS EED (CRD, Ovid, Wiley)* | 20/11/2014 | 3 |
| Health Economic Evaluations Database – HEED (Wiley) | 20/11/2014 | 13 |
| PubMed | 20/11/2014 | 323 |
| HTA database (Wiley) | 20/11/2014 | 1 |

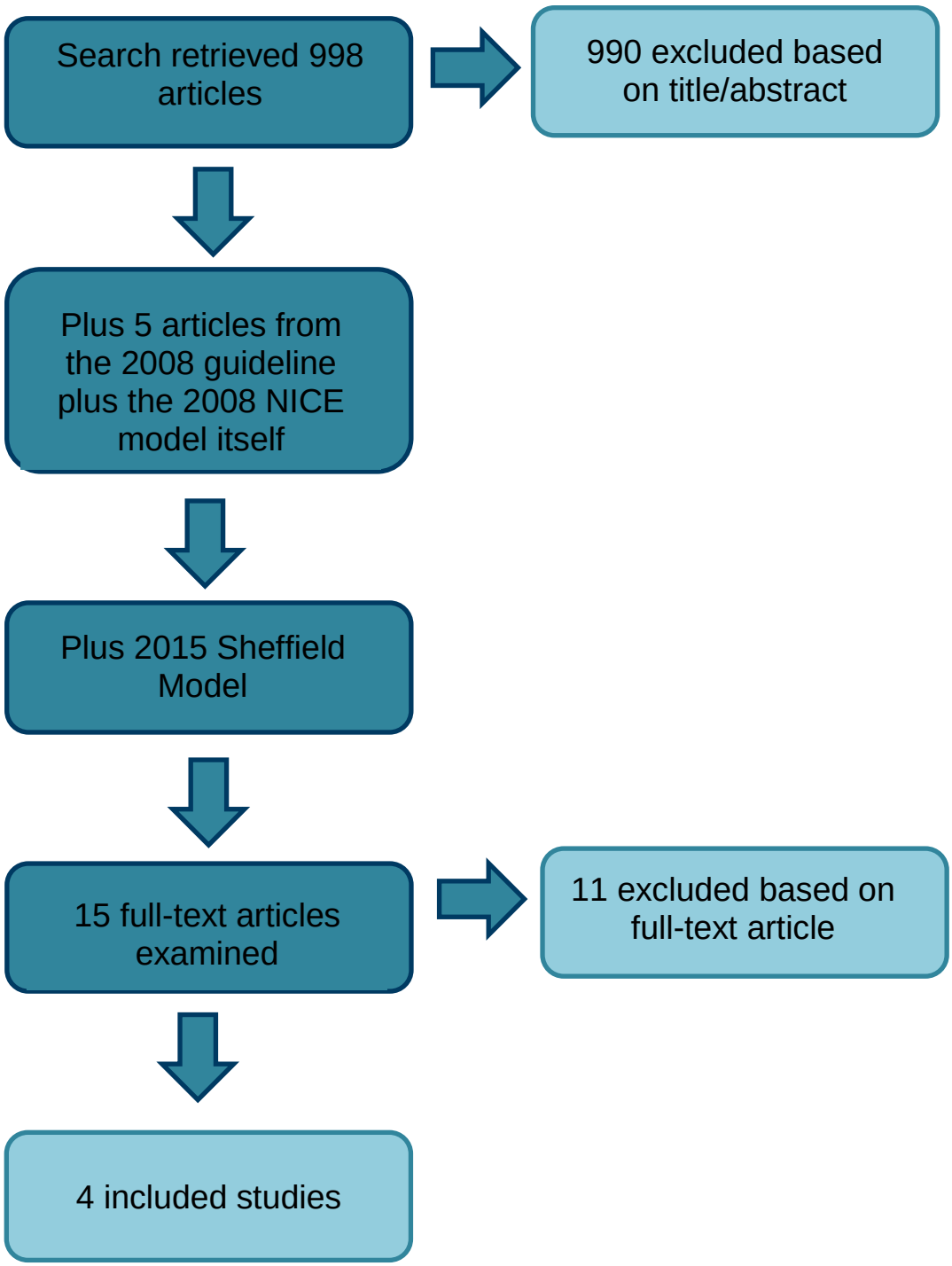
**Table 167: Economic search strategy**

| Database: Medline |
|---|
| Database: Ovid MEDLINE(R) <1946 to November Week 1 2014><br>Search Strategy:<br>---<br>1 exp Endocarditis/ (24453)<br>2 endocardit$.tw. (25708)<br>3 1 or 2 (31159)<br>4 Economics/ (27421)<br>5 exp "Costs and Cost Analysis"/ (189530)<br>6 Economics, Dental/ (1867)<br>7 exp Economics, Hospital/ (20161)<br>8 exp Economics, Medical/ (13982)<br>9 Economics, Nursing/ (4025)<br>10 Economics, Pharmaceutical/ (2601)<br>11 Budgets/ (9957)<br>12 exp Models, Economic/ (10669)<br>13 Markov Chains/ (10687)<br>14 Monte Carlo Method/ (21237)<br>15 Decision Trees/ (9157)<br>16 econom$.tw. (162263)<br>17 cba.tw. (8891)<br>18 cea.tw. (16656)<br>19 cua.tw. (819)<br>20 markov$.tw. (12445)<br>21 (monte adj carlo).tw. (21903)<br>22 (decision adj3 (tree$ or analys$)).tw. (8758)<br>23 (cost or costs or costing$ or costly or costed).tw. (319228)<br>24 (price$ or pricing$).tw. (23936)<br>25 budget$.tw. (17705)<br>26 expenditure$.tw. (36910)<br>27 (value adj3 (money or monetary)).tw. (1418) |

**Database: Medline**

28 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (3521)
29 or/4-28 (680212)
30 "Quality of Life"/ (125912)
31 quality of life.tw. (145261)
32 "Value of Life"/ (6025)
33 Quality-Adjusted Life Years/ (7609)
34 quality adjusted life.tw. (6428)
35 (qaly$ or qald$ or qale$ or qtime$).tw. (5256)
36 disability adjusted life.tw. (1266)
37 daly$.tw. (1235)
38 Health Status Indicators/ (20938)
39 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (16200)
40 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1012)
41 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (2822)
42 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (22)
43 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (344)
44 (euroqol or euro qol or eq5d or eq 5d).tw. (4098)
45 (qol or hql or hqol or hrqol).tw. (25908)
46 (hye or hyes).tw. (54)
47 health$ year$ equivalent$.tw. (39)
48 utilit$.tw. (118446)
49 (hui or hui1 or hui2 or hui3).tw. (895)
50 disutili$.tw. (228)
51 rosser.tw. (72)
52 quality of wellbeing.tw. (7)
53 quality of well-being.tw. (350)
54 qwb.tw. (176)
55 willingness to pay.tw. (2290)
56 standard gamble$.tw. (678)
57 time trade off.tw. (778)
58 time tradeoff.tw. (205)
59 tto.tw. (616)
60 or/30-59 (336218)
61 29 or 60 (970661)
62 3 and 61 (566)
63 animals/ not humans/ (3998169)
64 62 not 63 (540)
65 limit 64 to english language (455)
66 limit 65 to ed=20070921-20141120 (144)

# Appendix J: Economic review flowchart



# Appendix K: Ecomonic excluded studies

| Reference | Reason for exclusion |
|---|---|
| CADTH (2013) Antibiotic prophylaxis for patients with cardiac or orthopedic implants undergoing dental procedures: a review of the clinical effectiveness and guidelines (Structured abstract). Health Technology Assessment Database | Not an economic evaluation, narrative review only |
| Clemens JD, Ransohoff DF (1984) A quantitative assessment of pre-dental antibiotic prophylaxis for patients with mitral-valve prolapse. Journal of Chronic Diseases, 37 (7): 531-544. | Insufficiently applicable and the analysis has been superseded by more recent studies (NICE 2008; Agha et al. 2005) that are more applicable |
| Devereux RB, Cynthia JF, Kramer-Fox R, Roberts RB, Ruchlin HS (1994) Cost-effectiveness of infective endocarditis prophylaxis for mitral valve prolapse with or without a mitral regurgitant murmur. Valvular Heart Disease, 74: 1024-1029. | Insufficiently applicable and the analysis has been superseded by more recent studies (NICE 2008; Agha et al. 2005) that are more applicable |
| Glenny AM, Oliver R, Roberts GJ et al. (2013) Antibiotics for the prophylaxis of bacterial endocarditis in dentistry. [Review][Update of Cochrane Database Syst Rev. 2008;(4):CD003813; PMID: 18843649]. Cochrane Database of Systematic Reviews 10: CD003813. | No economic evaluations included |
| Guay DR (2012) Antimicrobial prophylaxis in noncardiac prosthetic device recipients. [Review]. Hospital practice (1995) Hospital practice 40: 44-74. | Narrative review only |
| Gould IM, Buckingham JK (1993) Cost effectiveness of prophylaxis in dental practice to prevent infective endocarditis. British Heart Journal. 70:79-83. | Insufficiently applicable and the analysis has been superseded by more recent studies (NICE 2008; Agha et al. 2005) that are more applicable |
| Kaye D, Zuckerman JM (2003) Antibiotic Prophylaxis of Endocarditis: What Is Accomplished and at What Cost? Curr Infect Dis Rep 5: 1-3. | Not an economic evaluation |
| Lockhart PB, Blizzard J, Maslow AL et al. (2013) Drug cost implications for antibiotic prophylaxis for dental procedures. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology 115: 345-53. | Analysis of national spending on antibiotic prophylaxis in the United States |
| Marks DJ, Hyams C, Koo CY et al. (2014) Clinical features, microbiology and surgical outcomes of infective endocarditis: a 13-year study from a UK tertiary cardiothoracic referral centre. QJM. | Not an economic evaluation |
| Oliver R, Roberts GJ, Hooper L et al. (2008) Antibiotics for the prophylaxis of bacterial endocarditis in dentistry. Cochrane Database of Systematic Reviews | No economic evaluations included |
| Tempelhof MW, Reeves G (2012) Infective endocarditis and antibiotic prophylaxis: A systematic review of efficacy and safety of the AHA guidelines. Research Journal of Medical Sciences.6 (4) (pp 193-202), 2012. 193-202. | Narrative review only |

# 1 Appendix L:Economic evidence tables

## L.1 2 Full economic evidence for dental procedures

| Bibliographic reference | Agha Z, Lofgren RP, VanRuiswyk JV (2005) Is antibiotic prophylaxis for bacterial endocarditis cost-effective? Medical Decision Making 25:308-320. |
|---|---|

**Evaluation design**

| | |
|---|---|
| **Interventions** | Predental antibiotic prophylaxis regimens as per the American Heart Association guidelines at the time:<br>1. Oral amoxicillin 2 gm, administered 1 hour before the procedure<br>2. Oral clarithromycin 500 mg, administered 1 hour before the procedure<br>3. Oral clindamycin 600 mg, administered 1 hour before the procedure<br>4. Oral cephalexin 2 mg, administered 1 hour before the procedure<br>5. Intravenous or intramuscular ampicillin 2 mg, administered 30 minutes before the procedure<br>6. Intravenous or intramuscular cefazolin 1 gm, administered 30 minutes before the procedure<br>7. Intravenous clindamycin 600 mg, administered 30 minutes before the procedure |
| **Comparator** | No prophylaxis |
| **Base-line cohort characteristics** | Patients with underlying heart disease with moderate or high risk for developing endocarditis<br>40 years old |
| **Type of Analysis** | Cost-utility analysis and cost-effectiveness sub-analyses (cases of endocarditis prevented and lives saved) |
| **Structure** | Decision tree for short term consequences and Markov model for long term survival |
| **Cycle length** | 1 year |
| **Time horizon** | 55 years |
| **Perspective** | Societal perspective for costs and benefits |
| **Country** | United States |
| **Currency unit** | US dollars |
| **Cost year** | 2003 |
| **Discounting** | 3% |
| **Other comments** | The authors note that there is no evidence for the effectiveness of antibiotics in preventing endocarditis, citing 4 small case-control studies, 2 of these failing to show any protective effect, 1 of these showing a protective effective that did not meet statistical significance, and 1 showing a benefit but limited by the potential for recall and misclassification bias.<br><br>Key assumptions: |

| Bibliographic reference | Agha Z, Lofgren RP, VanRuiswyk JV (2005) Is antibiotic prophylaxis for bacterial endocarditis cost-effective? Medical Decision Making 25:308-320. |
|---|---|
| | • Antibiotic effectiveness and compliance is similar for all regimens due to a lack of evidence of effectiveness.<br>• There is no disutility applied to the base case study cohort despite having underlying cardiac conditions associated with moderate or high risk of endocarditis. In other words, it is assumed this health state is equivalent to good health. |

**Results**

| | |
|---|---|
| **Comparison** | 7 antibiotic prophylaxis regimes vs. no prophylaxis for **moderate or high risk** cardiac conditions |
| **Incremental cost** | Not reported |
| **Incremental effects** | Incremental QALYs gained per 10 million patients<br>1. Oral amoxicillin: -3303<br>2. Oral clarithromycin: +1125<br>3. Oral clindamycin: +1118<br>4. Oral cephalexin: +827<br>5. Intravenous or intramuscular ampicillin: -3030<br>6. Intravenous or intramuscular cefazolin: +827<br>7. Intravenous clindamycin: +1118<br><br>Deaths per 10 million patients<br>1. Oral amoxicillin: +181 (net loss of life)<br>2. Oral clarithromycin: -19<br>3. Oral clindamycin: -19<br>4. Oral cephalexin: -9<br>5. Intravenous or intramuscular ampicillin: +181 (net loss of life)<br>6. Intravenous or intramuscular cefazolin: -9<br>7. Intravenous clindamycin: -19<br><br>Cases of endocarditis prevented<br>1. Oral amoxicillin: 119<br>2. Oral clarithromycin: 119<br>3. Oral clindamycin: 119<br>4. Oral cephalexin: 119<br>5. Intravenous or intramuscular ampicillin: 119<br>6. Intravenous or intramuscular cefazolin: 119<br>7. Intravenous clindamycin: 119 |
| **Incremental cost** | Per quality adjusted life year [a] |

| Bibliographic reference | Agha Z, Lofgren RP, VanRuiswyk JV (2005) Is antibiotic prophylaxis for bacterial endocarditis cost-effective? Medical Decision Making 25:308-320. | |
|---|---|---|
| | **effectiveness ratio** | 1. Oral amoxicillin: dominated<br>2. Oral clarithromycin: US$88,007 (2003) or £76,155 (2015)<br>3. Oral clindamycin: US$101,142 (2003) or £87,522 (2015)<br>4. Oral cephalexin: US$99,373 (2003) or £85,991 (2015)<br>5. Intravenous or intramuscular ampicillin: dominated<br>6. Intravenous or intramuscular cefazolin: US$199,430 (2003) or £172,574 (2015)<br>7. Intravenous clindamycin: US$411,093 (2003) or £355,733 (2015) |
| | **Conclusion** | "Our results suggest that the routine use of amoxicillin and ampicillin for endocarditis prophylaxis is not safe. If the decision to provide prophylaxis for moderate-risk lesions is made, then clarithromycin should be recommended as the 1st-choice regimen, followed by oral cephalexin and oral clindamycin as 2nd-line drugs." |

| | | |
|---|---|---|
| | **Comparison** | 7 antibiotic prophylaxis regimes vs. no prophylaxis for **high risk** cardiac conditions due to **prior endocarditis** |
| | **Incremental cost** | Not reported |
| | **Incremental effects** | Incremental QALYs gained per 10 million patients<br>1. Oral amoxicillin: -1885<br>2. Oral clarithromycin: +2271<br>3. Oral clindamycin: +2271<br>4. Oral cephalexin: +1973<br>5. Intravenous or intramuscular ampicillin: -1885<br>6. Intravenous or intramuscular cefazolin: +1973<br>7. Intravenous clindamycin: +2271<br><br>Deaths per 10 million patients<br>1. Oral amoxicillin: +162 (net loss of life)<br>2. Oral clarithromycin: -38<br>3. Oral clindamycin: -38<br>4. Oral cephalexin: -28<br>5. Intravenous or intramuscular ampicillin: +162 (net loss of life)<br>6. Intravenous or intramuscular cefazolin: -28<br>7. Intravenous clindamycin: -38<br><br>Cases of endocarditis prevented<br>1. Oral amoxicillin: 237 |

| Bibliographic reference | Agha Z, Lofgren RP, VanRuiswyk JV (2005) Is antibiotic prophylaxis for bacterial endocarditis cost-effective? Medical Decision Making 25:308-320. | |
|---|---|---|
| | | 2. Oral clarithromycin: 237<br>3. Oral clindamycin: 237<br>4. Oral cephalexin: 237<br>5. Intravenous or intramuscular ampicillin: 237<br>6. Intravenous or intramuscular cefazolin: 237<br>7. Intravenous clindamycin: 237 |
| | **Incremental cost effectiveness ratio** | Per quality adjusted life year [a]<br>1. Oral amoxicillin: dominated<br>2. Oral clarithromycin: US$40,334 (2003) or £34,902 (2015)<br>3. Oral clindamycin: US$199,029 (2003) or £172,227 (2015)<br>4. Oral cephalexin: US$37,916 (2003) or £32,810 (2015)<br>5. Intravenous or intramuscular ampicillin: dominated<br>6. Intravenous or intramuscular cefazolin: US$79,886 (2003) or £69,128 (2015)<br>7. Intravenous clindamycin: US$199,029 (2003) or £172,226 (2015) |
| | **Conclusion** | "For patients with high-risk cardiac lesions (prosthetic valve or history of prior endocarditis) cephalexin should be the 1st choice and clarithromycin or clindamycin 2nd-choice agents. Intravenous regimens are less cost-effective, except in the case of cefazolin for patients with prosthetic valves." |

| | |
|---|---|
| **Comparison** | 7 antibiotic prophylaxis regimes vs. no prophylaxis for **high risk** cardiac conditions due to **a prosthetic valve** |
| **Incremental cost** | Not reported |
| **Incremental effects** | Incremental QALYs gained per 10 million patients<br>1. Oral amoxicillin: +407<br>2. Oral clarithromycin: +4562<br>3. Oral clindamycin: +4562<br>4. Oral cephalexin: +4264<br>5. Intravenous or intramuscular ampicillin: +407<br>6. Intravenous or intramuscular cefazolin: +4264<br>7. Intravenous clindamycin: +4562<br><br>Deaths per 10 million patients<br>1. Oral amoxicillin: +124 (net loss of lives)<br>2. Oral clarithromycin: -76 |

| Bibliographic reference | Agha Z, Lofgren RP, VanRuiswyk JV (2005) Is antibiotic prophylaxis for bacterial endocarditis cost-effective? Medical Decision Making 25:308-320. | |
|---|---|---|
| | | 3. Oral clindamycin: -76<br>4. Oral cephalexin: -66<br>5. Intravenous or intramuscular ampicillin: +124 (net loss of lives)<br>6. Intravenous or intramuscular cefazolin: -66<br>7. Intravenous clindamycin: -76<br><br>Cases of endocarditis prevented<br>1. Oral amoxicillin: 475<br>2. Oral clarithromycin: 475<br>3. Oral clindamycin: 475<br>4. Oral cephalexin: 475<br>5. Intravenous or intramuscular ampicillin: 475<br>6. Intravenous or intramuscular cefazolin: 475<br>7. Intravenous clindamycin: 475 |
| | **Incremental cost effectiveness ratio** | Per quality adjusted life year [a]<br>1. Oral amoxicillin: US$160,871 (2003) or £139,207 (2015)<br>2. Oral clarithromycin: US$16,818 (2003) or £14,553 (2015)<br>3. Oral clindamycin: US$19,936 (2003) or £17,251 (2015)<br>4. Oral cephalexin: US$14,060 (2003) or £12,167 (2015)<br>5. Intravenous or intramuscular ampicillin: US$498,488 (2003) or £431,359 (2015)<br>6. Intravenous or intramuscular cefazolin: US$33,480 (2003) or £28,971 (2015)<br>7. Intravenous clindamycin: US$19,936 (2003) or £17,251 (2015) |
| | **Conclusion** | “For patients with high-risk cardiac lesions (prosthetic valve or history of prior endocarditis) cephalexin should be the 1st choice and clarithromycin or clindamycin 2nd-choice agents. Intravenous regimens are less cost-effective, except in the case of cefazolin for patients with prosthetic valves.” |

| Bibliographic reference | Agha Z, Lofgren RP, VanRuiswyk JV (2005) Is antibiotic prophylaxis for bacterial endocarditis cost-effective? Medical Decision Making 25:308-320. |
|---|---|
| Data sources | |

| | |
|---|---|
| **Base-line data** | • Moderate or high risk cardiac conditions and dental procedures requiring endocarditis prophylaxis defined by American Heart Association criteria at the time<br>• Population incidence of bacterial endocarditis from 1 study from the literature, 3.8/100,000 person years<br>• Endocarditis cases that occur in patients after a high-risk dental procedure estimated from 1 study, base case 16.8%, range 4% to 23%<br>• Endocarditis cases with a pre-existing cardiac lesion estimated from 1 study as 53%, range 21% to 91%<br>• Number of dental visits in patients with underlying cardiac lesions from a survey from the literature, 2.7 visits per year<br>• Dental procedures requiring antibiotic prophylaxis from 1 study from the literature, 75%<br>• Prevalence of moderate or high risk cardiac lesions was estimated as 10% for the base case, range 5% to 35% |
| **Effectiveness data** | • Antibiotic effectiveness in preventing bacterial endocarditis from 4 studies from the literature, base case RR 0.46, range 0.01 to 1<br>• Mortality from an acute episode of endocarditis from 1 study from the literature, base case 16%, range 5% to 55%<br>• Valve replacement surgery during or immediately following an acute endocarditis infection, base case 28%, range 20% to 80%<br>• Fatal anaphylactic reactions due to oral amoxicillin or IV ampicillin estimated from two studies from the literature, base case 20 per million, range 0.5 to 40 per million<br>• Fatal anaphylactic reactions due to cephalexin or cefazolin, base case 1 per million, range 0.5 to 5 per million<br>• Fatal anaphylactic reactions due to clarithromycin and clindamycin was estimated, base case 0 per million, varied up to 5 per million in sensitivity analysis<br>• Nonfatal hypersensitivity to amoxicillin or ampicillin estimated from 1 study from the literature, base case 2%, range 0.5% to 10%<br>• Nonfatal hypersensitivity to clarithromycin estimated from 1 study from the literature, base case 0.3%, range 0.1% to 5%<br>• Nonfatal hypersensitivity to clindamycin estimated from 1 study from the literature, base case 0.4%, range 0.1% to 10%<br>• Nonfatal hypersensitivity to cephalexin or cefaxolin estimated from 1 study from the literature, base case 1.7% to 0.5% to 3%<br>• Patients that survived endocarditis go on to require valve surgery at a rate of 4.2% per year for years 1 through 15 and then decreases to 1% per year, from 1 study from the literature<br>• The risk of death was obtained from 1 study from the literature, 12.5% |

| Bibliographic reference | Agha Z, Lofgren RP, VanRuiswyk JV (2005) Is antibiotic prophylaxis for bacterial endocarditis cost-effective? Medical Decision Making 25:308-320. | |
|---|---|---|
| | | • Patients who require valve replacement after endocarditis have a 50% annual probability of developing congestive heart failure, from 2 studies from the literature<br>• Patients who do not require valve replacement have a 5% annual probability of developing congestive heart failure, from 2 studies from the literature<br>• Patients who transition to valve replacement or valve replacement with congestive heart failure health states were assigned 3.3 times greater annual mortality compared to the general population based on 3 studies from the literature |
| | **Cost data** | • Antibiotics from the Drug Topics Red Book 2000<br>• Hospital costs based on Medicare diagnosis related groups<br>• Outpatient visits based on published estimates<br>• Treating an antibiotic side effect based on a published estimate<br>• Indirect cost of patient or caregiver time lost were estimated |
| | **Utility data** | • Utility score for congestive heart failure was based on a study from the literature that used to the Quality of Well-Being measure, base case 0.63, range 0.25 to 1<br>• Utility score for valve replacement was an estimate obtained from the literature, base case 0.9, range 0.25 to 1<br>• Utility score for valve replacement and congestive heart failure was derived by multiplying these two utility scores, base case 0.57, range 0.25 to 1 |
| **Uncertainty** | | |
| | **One-way sensitivity analysis** | One way sensitivity analyses for many input parameters were conducted with the target thresholds of US$50,000 and US$100,000 per QALY in mind. All interventions below were compared against no prophylaxis. All ICERs are reported in 2003 US dollars.<br><br>Risk of antibiotic fatal side effects<br>• Raising the risk of fatal anaphylaxis for clarithromycin from zero to 0.65 per million reached the $100,000 per QALY threshold.<br>• Amoxicillin became the favoured strategy with an ICER of $85,421 per QALY when the rate of fatal anaphylaxis was reduced from a base case of 20 per million to 2 per million and the nonfatal side effects rate was reduced to 0.5% from a base case rate of 2% (two way sensitivity analysis).<br><br>Incidence of bacterial endocarditis<br>• When the incidence of bacterial endocarditis was increased to 62 per million:<br>  ○ the ICER was $49,997 per QALY for cephalexin and<br>  ○ the ICER was $56,372 per QALY for clarithromycin.<br><br>Potentially preventable cases |

| Bibliographic reference | Agha Z, Lofgren RP, VanRuiswyk JV (2005) Is antibiotic prophylaxis for bacterial endocarditis cost-effective? Medical Decision Making 25:308-320. | |
|---|---|---|
| | | • When the proportion of BE cases in the population with underlying valve disease was raised from the base case value of 53% to 87%:<br>  ○ cephalexin had an ICER of $49,586 per QALY and<br>  ○ clarithromycin had an ICER of $56,372 per QALY.<br><br>Cost of antibiotics<br>• When the cost of clarithromycin was reduced by 42% from $10.43 to $6.10 the ICER was $49,592 per QALY.<br>• When the cost of oral clindamycin was reduced by 49% from $11.77 to $6.00 the ICER was $49,715 per QALY.<br>• When the price of oral cephalexin was reduced by 54% from $7.65 to $3.50 the ICER was $49,552 per QALY.<br><br>Incidence of dental visits that require prophylaxis<br>• When the average number of dental visits was decreased from 2 to 1 per year:<br>  ○ cephalexin had an ICER of $37,916 per QALY and<br>  ○ clarithromycin had an ICER of $56,371 per QALY.<br><br>Age of population<br>• When the population age was reduced from 40 years of age to 20:<br>  ○ cephalexin had an ICER of $41,651 per QALY and<br>  ○ clarithromycin had an ICER of $50,788 per QALY.<br>• All prophylaxis interventions had ICERs greater than $100,000 per QALY for ages greater than 43 years.<br>• All prophylaxis interventions had ICERs greater than $200,000 per QALY for ages above 55 years.<br><br>Discount rate<br>• At a discount rate of 0% clarithromycin had an ICER of $48,719 per QALY.<br>• At a discount rate of 5% clarithromycin had an ICER of $120,329 per QALY.<br><br>One way sensitivity analyses of all other variables did not result in any of the antibiotic prophylaxis strategies achieving the thresholds of $50,000 or $100,000 per QALY. |
| | **Probabilistic sensitivity analysis** | Not conducted |

| | |
|---|---|
| **Bibliographic reference** | **Agha Z, Lofgren RP, VanRuiswyk JV (2005) Is antibiotic prophylaxis for bacterial endocarditis cost-effective? Medical Decision Making 25:308-320.** |
| **Applicability** | **Partially Applicable**<br><br>• The analysis was based on the United States healthcare system.<br>• A societal perspective was adopted for both cost and health consequences.<br>• The discount rate used in the base case was 3% rather than 3.5%.<br>• Utilities used to derive quality adjusted life years were based on the Quality of Well-being index of a United States population rather than the EQ-5D with United Kingdom general population preferences. Some utility values were also estimated or a combination of the QWB and the estimations. |
| **Limitations** | **Potentially Serious Limitations**<br><br>• Many of the key parameters driving the model are based on poor and conflicting evidence from literature sources.<br>• Estimates of resource use include productivity losses due to the societal perspective.<br>• Probabilistic sensitivity analysis was not conducted.<br><br>**Conflicts**<br>No declarations were provided. |

1

| | |
|---|---|
| **Bibliographic reference** | **National Institute for Health and Clinical Excellence (2008) NICE clinical guideline 64 Prophylaxis against infective endocarditis: antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures.** |
| **Evaluation design** | |

| | |
|---|---|
| **Interventions** | Pre-dental antibiotic prophylaxis regimens as specified in the British National Formulary at the time:<br>1. Oral amoxicillin, 3 g, 1 hour before procedure for people who have not received more than a single dose of a penicillin in the previous, including those with a prosthetic valve (but not those who have had infective endocarditis)<br>2. Oral clindamycin, 600 mg, 1 hour before procedure for people who are penicillin-allergic or have received more than a single dose of a penicillin in the previous month<br>3. Intravenous amoxicillin, 1 g, at induction, then oral amoxicillin 500 mg, 6 hours later for people with no special risk including people who have not received more than a single dose of a penicillin in the previous month<br>4. Oral amoxicillin, 3 g, 4 hours before induction, then oral amoxicillin, 3 g, as soon as possible after the procedure for people with no special risk including people who have not received more than a single dose of a penicillin in the previous month |

| Bibliographic reference | National Institute for Health and Clinical Excellence (2008) NICE clinical guideline 64 Prophylaxis against infective endocarditis: antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures. | |
|---|---|---|
| | | 5. Amoxicillin plus gentamicin as under general anaesthesia for people with previous endocarditis<br>6. Intravenous vancomycin, 1 g, over at least 100 minutes, then intravenous gentamicin, 120 mg, at induction or 15 minutes before the procedure for patients who are penicillin-allergic or who have received more than a single dose of a penicillin in the previous month<br>7. Intravenous teicoplanin 400 mg, plus gentamicin, 120 mg, at induction or 15 minutes before procedure for patients who are penicillin-allergic or who have received more than a single dose of a penicillin in the previous month<br>8. Intravenous clindamycin, 300 mg, over at least 10 minutes at induction or 15 minutes before procedure, then oral or intravenous clindamycin, 150 mg, 6 hours later for patients who are penicillin-allergic or who have received more than a single dose of a penicillin in the previous month |
| | **Comparators** | No prophylaxis |
| | **Base-line cohort characteristics** | 50 years of age<br>Male |
| | **Type of Analysis** | Cost-utility analysis |
| | **Structure** | Decision tree for short term impacts, Markov model for long term outcomes |
| | **Cycle length** | 1 year |
| | **Time horizon** | Lifetime |
| | **Perspective** | NHS |
| | **Country** | United Kingdom |
| | **Currency unit** | £ |
| | **Cost year** | Not stated, 2005-06 reference costs were used |
| | **Discounting** | Costs and health outcomes at 3.5% |
| | **Other comments** | "Given the paucity of data in key parameters (e.g. risk of developing infective endocarditis following a dental procedure, antibiotic efficacy), the analysis aimed to estimate cost effectiveness based on certain 'what if' scenarios."<br><br>Key assumptions:<br>• Individual dental procedures can lead directly to the development of infective endocarditis<br>• Antibiotic prophylaxis can reduce that risk<br>• All antibiotic strategies were of equal effectiveness |

| Bibliographic reference | **National Institute for Health and Clinical Excellence (2008) NICE clinical guideline 64 Prophylaxis against infective endocarditis: antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures.** |
|---|---|

**Results**

| | |
|---|---|
| **Comparison** | Antibiotic regimens vs. no prophylaxis **excluding** costs and benefits of future antibiotic prophylaxis<br>1. Oral amoxicillin<br>2. Oral clindamycin<br>3. Intravenous amoxicillin then oral amoxicillin<br>4. Oral amoxicillin before and oral amoxicillin after<br>5. Amoxicillin plus gentamicin<br>6. Intravenous vancomycin then intravenous gentamicin<br>7. Intravenous teicoplanin plus gentamicin<br>8. Intravenous clindamycin then oral or intravenous clindamycin |
| **Incremental cost** | 1. Oral amoxicillin: £1<br>2. Oral clindamycin: £6<br>3. Intravenous amoxicillin then oral amoxicillin: £2<br>4. Oral amoxicillin before and oral amoxicillin after: £2<br>5. Amoxicillin plus gentamicin then oral amoxicillin: £186<br>6. Intravenous vancomycin then intravenous gentamicin: £29<br>7. Intravenous teicoplanin plus gentamicin: £58<br>8. Intravenous clindamycin then oral or intravenous clindamycin: £14 |
| **Incremental effects** | 1. Oral amoxicillin: 0.00001<br>2. Oral clindamycin: 0.00001<br>3. Intravenous amoxicillin then oral amoxicillin: 0.00001<br>4. Oral amoxicillin before and oral amoxicillin after: 0.00001<br>5. Amoxicillin plus gentamicin: 0.00001<br>6. Intravenous vancomycin then intravenous gentamicin: 0.00001<br>7. Intravenous teicoplanin plus gentamicin: 0.00001<br>8. Intravenous clindamycin then oral or intravenous clindamycin: 0.00001 |
| **Incremental cost effectiveness ratio** | 1. Oral amoxicillin: £88,069<br>2. Oral clindamycin: £551,284<br>3. Intravenous amoxicillin then oral amoxicillin: £179,356<br>4. Oral amoxicillin before and oral amoxicillin after: £179,769<br>5. Amoxicillin plus gentamicin: £17,953,043<br>6. Intravenous vancomycin then intravenous gentamicin: £2,750,466<br>7. Intravenous teicoplanin plus gentamicin: £5,571,067<br>8. Intravenous clindamycin then oral or intravenous clindamycin: £1,340,889 |

| Bibliographic reference | National Institute for Health and Clinical Excellence (2008) NICE clinical guideline 64 Prophylaxis against infective endocarditis: antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures. | |
|---|---|---|
| | **Conclusion** | The model suggested that prophylactic antibiotic strategies are not cost effective under all scenarios explored in the present analysis unless optimistic assumptions are made with regard to a number of parameters, chiefly the risk of developing IE following a dental procedure. |
| | **Comparison** | Antibiotic regimens vs. no prophylaxis **including** costs and benefits of future antibiotic prophylaxis<br>1. Oral amoxicillin<br>2. Oral clindamycin<br>3. Intravenous amoxicillin then oral amoxicillin<br>4. Oral amoxicillin before and oral amoxicillin after<br>5. Amoxicillin plus gentamicin<br>6. Intravenous vancomycin then intravenous gentamicin<br>7. Intravenous teicoplanin plus gentamicin<br>8. Intravenous clindamycin then oral or intravenous clindamycin |
| | **Incremental cost** | 9. Oral amoxicillin: £26<br>10. Oral clindamycin: £160<br>11. Intravenous amoxicillin then oral amoxicillin: £53<br>12. Oral amoxicillin before and oral amoxicillin after: £53<br>13. Amoxicillin plus gentamicin then oral amoxicillin: £5193<br>14. Intravenous vancomycin then intravenous gentamicin: £796<br>15. Intravenous teicoplanin plus gentamicin: £1612<br>16. Intravenous clindamycin then oral or intravenous clindamycin: £389 |
| | **Incremental effects** | 9. Oral amoxicillin: 0.00001<br>10. Oral clindamycin: 0.00001<br>11. Intravenous amoxicillin then oral amoxicillin: 0.00001<br>12. Oral amoxicillin before and oral amoxicillin after: 0.00001<br>13. Amoxicillin plus gentamicin: 0.00001<br>14. Intravenous vancomycin then intravenous gentamicin: 0.00001<br>15. Intravenous teicoplanin plus gentamicin: 0.00001<br>16. Intravenous clindamycin then oral or intravenous clindamycin: 0.00001 |
| | **Incremental cost effectiveness ratio** | 9. Oral amoxicillin: £248,912<br>10. Oral clindamycin: £1,513,095<br>11. Intravenous amoxicillin then oral amoxicillin: £498,047<br>12. Oral amoxicillin before and oral amoxicillin after: £499,175<br>13. Amoxicillin plus gentamicin: £49,005,022<br>14. Intravenous vancomycin then intravenous gentamicin: £7,514,982 |

| | | |
|---|---|---|
| **Bibliographic reference** | **National Institute for Health and Clinical Excellence (2008) NICE clinical guideline 64 Prophylaxis against infective endocarditis: antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures.** | |
| | | 15. Intravenous teicoplanin plus gentamicin: £15,212,810<br>16. Intravenous clindamycin then oral or intravenous clindamycin: £3,668,040 |
| | **Conclusion** | The model suggested that prophylactic antibiotic strategies are not cost effective under all scenarios explored in the present analysis unless optimistic assumptions are made with regard to a number of parameters, chiefly the risk of developing IE following a dental procedure. |
| **Data sources** | | |
| | **Base-line data** | • Risk of IE following a dental procedure from one study from the literature, base case 4.1 per million procedures, range 22 to 93 per million<br>• Dental procedures per year estimated, base case 1.5 procedures per year<br>• Probability of mortality from infective endocarditis, native valves from two studies from the literature, base case 16.4%, range +/- 50%<br>• Probability of mortality from acute endocarditis, prosthetic valves, base case 22.8% from one study from the literature, not varied<br>• Annual probability of developing congestive heart failure following endocarditis estimated from one study from the literature, 8.3%, range +/- 50%<br>• Annual probability of developing congestive heart failure in non-endocarditis cases estimated from one study from the literature, 0.6%, range +/- 50%<br>• Annual probability of valve replacement during or immediately following IE from one study from the literature, base case 34%, range +/- 50%<br>• Probability of valve replacement in years 1 to 10 for endocarditis cases from one study from the literature based on UK valve registry data, base case 1.3%, range +/- 0%<br>• Probability of redo valve replacement, years 1 to 10 from one study from the literature based on UK valve registry data, base case 1.3%, range +/- 50%<br>• Probability of valve replacement after ten years all people from one study from the literature, base case 0.4%, range +/- 50%<br>• Probability of death from valve surgery from one study from the literature, base case 8.2%, range +/- 50%<br>• Overall mortality risk by age and sex from national data set |
| | **Effectiveness data** | • Efficacy of prophylaxis assumed, base case RR 0.5, range 0.25 to 0.75<br>• Probability of non-fatal hypersensitivity to amoxicillin from one study in the literature, base case 0, range 0 to 0.1 per million<br>• Probability of non-fatal hypersensitivity to clindamycin assumed, base case 0, range 0 to 0.1 per million<br>• Probability of non-fatal hypersensitivity to vancomycin assumed, base case 0, range 0 to 0.1 per |

| Bibliographic reference | National Institute for Health and Clinical Excellence (2008) NICE clinical guideline 64 Prophylaxis against infective endocarditis: antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures. | |
|---|---|---|
| | | million<br>• Probability of non-fatal hypersensitivity to gentamicin assumed, base case 0, range 0 to 0.1 per million<br>• Probability of non-fatal hypersensitivity to teicoplanin assumed, base case 0, range 1 to 0.1 per million<br>• Probability of fatal anaphylaxis from amoxicillin from two studies from the literature, base case 0 per million, range 0 to 40 per million<br>• Probability of fatal anaphylaxis from other antibiotics assumed and one study from the literature for clindamycin, base case 0 per million, range from 0 to 5 per million |
| | **Cost data** | • Hospitalisation costs – NHS reference costs 2005-06<br>• Medication costs – BNF September 2007<br>• Labour costs – Personal Social Services Research Unit's Unit Costs of Health and Social Care 2005-06 |
| | **Utility data** | Most utilities were based on the New York Heart Association functional classification scheme with values estimated from literature sources.<br>• Well – NYHA class I – base case 0.930, range 0.923 to 0.945<br>• Valve replacement / repair needed – NYHA classes III and IV – base case 0.525, range 0.506 to 0.546<br>• Successful valve replacement – NYHA classes I and II – base case 0.855, range 0.838 to 0.879<br>• Congestive heart failure – NYHA class III – base case 0.610, range 0.591 to 0.631<br>• Hospitalisation with heart failure – one study from the literature – base case 0.570, range 0.480 to 0.800 |
| **Uncertainty** | | |
| | **One-way sensitivity analysis** | • The risk of developing IE had to be at least 16 per million procedures for the ICER to reduce to £20,000 per QALY.<br>• When the estimated costs and potential benefits of future prophylaxis are included in the analysis, this threshold rises to 48 per million.<br>• When a 10 year timeframe was adopted, the scenario excluding estimated costs and potential benefits of future antibiotic prophylaxis resulted in a minimum ICER of £204,167 per QALY for amoxicillin (strategy 1) and a maximum ICER of £41,562,056 per QALY for IV amoxicillin and IV gentamycin then oral amoxicillin (strategy 5).<br>• When a 10 year timeframe was adopted, the scenario including the estimated costs and potential benefits of future prophylaxis, the minimum ICER was £427,682 per QALY for strategy 1 (oral amoxicillin) and the maximum ICER was £85,231,144 per QALY for strategy 5 (IV amoxicillin and IV gentamycin followed by oral amoxicillin).<br>• When costs were varied between their upper and lower limits, ICERs ranged from £248,723 per QALY for strategy 1 (oral amoxicillin) to £49,004,833 per QALY for strategy 5 (IV amoxicillin and |

| Bibliographic reference | National Institute for Health and Clinical Excellence (2008) NICE clinical guideline 64 Prophylaxis against infective endocarditis: antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures. | |
|---|---|---|
| | | IV gentamycin followed by oral amoxicillin).<br>• When utilities were varied between their upper and lower estimates, ICERs ranged from £244,636.69 per QALY for strategy 1 (oral amoxicillin) to £48,163,308 for strategy 5 (IV amoxicillin plus IV gentamycin followed by oral amoxicillin).<br>• When the starting age of the cohort was reduced to 20 years of age (from 50), the ICER of strategy 1 (oral amoxicillin) was £234,000 per QALY.<br>• When overall mortality risk was changed from an estimate of all-cause mortality to one that excluded deaths from cardiac causes, the ICER was £244,000 per QALY.<br>• When the efficacy of prophylaxis was varied between 25% to 75%, the ICER for strategy 1 was £503,448 and £164,069 per QALY respectively, and the ICER for strategy 2 was £3,031,864 and £1,006,853 respectively.<br>• When the risk of developing IE for all patients with a pre-existing cardiac condition was increased to 22 per million cases per dental procedure (from 4.1 per million), the ICERs ranged from £44,880 per QALY for strategy 1 to £9,057,252 per QALY for strategy 5.<br>• When the risk of developing IE for all patients with a pre-existing cardiac condition was increased to 93 per million cases per dental procedure, strategies 1, 3 and 4 had ICERs that were below the £20,000 per QALY cost-effectiveness threshold with ICERs of £5,124, £12,187 and £12,219 per QALY respectively. The ICERs for all other strategies ranged from £40,962 to £1,387,296 per QALY.<br>• All other one way sensitivity analyses resulted in ICERs that ranged from £169,728 to £867,343 per QALY for strategy 1. |
| | **Three-way sensitivity analysis** | The risk of fatal anaphylaxis with amoxicillin, antibiotic efficacy and the risk of developing IE for all patients with a pre-existing cardiac condition per dental procedure were varied concurrently and there were 4 scenarios under which strategy 1 was considered cost-effective:<br>• Risk of developing IE per dental procedure 93 per million, fatal anaphylaxis 0.9 per million, antibiotic efficacy 75%: ICER was £1,667 per QALY<br>• Risk of developing IE per dental procedure 93 per million, fatal anaphylaxis 0.9 per million, antibiotic efficacy 50%: ICER was £5,531 per QALY<br>• Risk of developing IE per dental procedure 93 per million, fatal anaphylaxis 0.9 per million, antibiotic efficacy 25%: ICER was £18,497 per QALY<br>• Risk of developing IE per dental procedure 93 per million, fatal anaphylaxis 10 per million, antibiotic efficacy 75%: ICER was £3416<br>All other multi-way sensitively analysis results were ICERs ranging from £25,483 to dominated (strategy was more costly and less effective than no phrophylaxis). |
| | **Probabilistic sensitivity analysis** | Not conducted |

| | |
|---|---|
| **Bibliographic reference** | **National Institute for Health and Clinical Excellence (2008) NICE clinical guideline 64 Prophylaxis against infective endocarditis: antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures.** |
| **Applicability** | **Directly Applicable** |
| **Limitations** | **Minor Limitations**<br><br>No probabilistic sensitivity analysis<br>No reasonable evidence was identified to support the assumptions that individual dental procedures can lead directly to the development of infective endocarditis or that antibiotic prophylaxis reduces that risk.<br><br>**Conflicts**<br>Refer to 2008 guideline documentation |

*Acronyms*
*ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; AHA: American Heart Association; BE: bacterial endocarditis; IE: infective endocarditis; RR: relative risk; NYHA: New York Heart Association*
*(a) ICERs converted to 2015 UK pounds by using the Campbell and Cochrane Economics Methods Group EPPI Cost Converter available at http://www.c-cemg.org/, accessed 21-22 January 2015*

# L.26 Full economic evidence for non-dental procedures

| | |
|---|---|
| **Bibliographic reference** | **Caviness AC, Cantor SB, Coburn HA, Ward MA (2004) A cost-effectiveness analysis of bacterial endocarditis prophylaxis for febrile children who have cardiac lesions and undergo urinary catheterization in the emergency department. Pediatrics, 113 (5), 1291-1296.** |
| **Evaluation design** | |

| | |
|---|---|
| **Interventions** | 1. Amoxicillin 500 mg<br>2. Vancomycin 200 mg |
| **Comparator** | No prophylaxis |
| **Base-line cohort characteristics** | • Aged 0 to 24 months, have moderate-risk cardiac lesions, present to the ED with fever, and require urine collection to evaluate the possibility of an underlying urinary tract infection<br>• Moderate-risk cardiac lesions were based on the American Heart Association guidelines at the time and included most congenital cardiac malformations such as ventricular septal defects, acquired valvular dysfunction such as rheumatic heart disease, hypertrophic cardiomyopathy, and mitral valve prolapse with valvular regurgitation and/or thickened leaflets. |
| **Type of Analysis** | Cost-utility analysis |
| **Structure** | Decision tree |
| **Cycle length** | Not applicable |

| Bibliographic reference | Caviness AC, Cantor SB, Coburn HA, Ward MA (2004) A cost-effectiveness analysis of bacterial endocarditis prophylaxis for febrile children who have cardiac lesions and undergo urinary catheterization in the emergency department. Pediatrics, 113 (5), 1291-1296. |
|---|---|

| | |
|---|---|
| **Time horizon** | Lifetime |
| **Perspective** | Societal |
| **Country** | United States |
| **Currency unit** | $ |
| **Cost year** | 2000 |
| **Discounting** | 3% |
| **Other comments** | Clinical assumptions:<br>• Prophylaxis before urinary catheterisation prevents all bacterial endocarditis by preventing bacteraemia.<br>• Amoxicillin and vancomycin are equally effective in preventing bacteraemia.<br>• In the presence of bacteraemia with organisms that cause endocarditis, the incidence of bacterial endocarditis, no matter the cause for the bacteraemia or the type of moderate-risk cardia lesion.<br>• In the absence of bacteraemia or in the presence of organisms not typically associated with endocarditis, bacterial endocarditis does not occur.<br>• There is no increased risk of bacteraemia or bacterial endocarditis with contaminated urine specimens.<br>• Bacteraemia occurs immediately after instrumentation and is followed immediately by bacterial seeding of the endocardium. |

| **Bibliographic reference** | **Caviness AC, Cantor SB, Coburn HA, Ward MA (2004) A cost-effectiveness analysis of bacterial endocarditis prophylaxis for febrile children who have cardiac lesions and undergo urinary catheterization in the emergency department. Pediatrics, 113 (5), 1291-1296.** |
|---|---|

**Results**

| **Comparison** | **Amoxicillin** vs. no prophylaxis |
|---|---|
| **Incremental cost** | US$495.30 (2000) |
| **Incremental effects** | -0.00045 |
| **Incremental cost effectiveness ratio** | Dominated |
| **Conclusion** | "Antiobiotic prophylaxis for urinary catheterisation of febrile children who are aged 0 to 2 years and have moderate-risk cardiac lesions is not a cost-effective use of health care resources. This is true for the regimen using amoxicillin and for the regimen using vancomycin." |

| **Comparison** | **Vancomycin** vs. no prophylaxis |
|---|---|
| **Incremental cost** | US$666.16 (2000) |
| **Incremental effects** | 0.00005 |
| **Incremental cost effectiveness ratio** | US$13,323,200 (2000) or £12,213,677 (2015) [a] |
| **Conclusion** | "Antiobiotic prophylaxis for urinary catheterisation of febrile children who are aged 0 to 2 years and have moderate-risk cardiac lesions is not a cost-effective use of health care resources. This is true for the regimen using amoxicillin and for the regimen using vancomycin." |

**Data sources**

| | |
|---|---|
| **Base-line data** | • Prevalence of urinary tract infection in febrile children from 3 studies from the literature, base case 3.9%, range 3.3% to 5.3%<br>• Prevalence of bacterial endocarditis causing organisms among urinary tract infection causing organisms from 2 studies from the literature, base case 3.4%, range 0% to 100%<br>• Incidence of bacteraemia after urinary catheterisation from 2 adult studies, base case 23.1%, range 14.3% to 26.3%<br>• Incidence of endocarditis in children with rheumatic heart disease after bacteraemia from tooth extractions from two studies, 1.1% and 2.2% |
| **Effectiveness data** | • Prophylactic efficacy of antibiotics in preventing bacteraemia from 1 clinical trial and 2 decision analyses, base case 89%, range 0% to 100%<br>• Mortality from bacterial endocarditis from 4 studies from the literature, base case 11.6%, range 0% to 13.5%<br>• Rate of decompensation requiring surgery for survivors from 4 studies from the literature, base case 18.6%, range 0% to 25%<br>• Incidence of CHF attributable to bacterial endocarditis from 1 study from the literature, base case 27.1% (95% CI 14.5 to 39.7%) |

| Bibliographic reference | **Caviness AC, Cantor SB, Coburn HA, Ward MA (2004) A cost-effectiveness analysis of bacterial endocarditis prophylaxis for febrile children who have cardiac lesions and undergo urinary catheterization in the emergency department. Pediatrics, 113 (5), 1291-1296.** | |
|---|---|---|
| | | • Average survival in children who recover from bacterial endocarditis with congestive heart failure from 1 adult study from the literature, 6.2 years<br>• Mild reactions due to amoxicillin from 1 study from the literature, base case 1%, range 0.7% to 10%<br>• Anaphylaxis due to amoxicillin estimated, base case 0.03%, range 0.02% to 0.04%<br>• Mortality due to penicillin estimated, base case 0.002%, range 0% to 0.004%<br>• Allergic or anaphylactic reactions due to vancomycin nil from 2 study from the literature |
| | **Cost data** | • Antibiotics from 2001 Drug Topics Red Book<br>• Nursing labour for delivery from national data sets<br>• Parental time from work missed based on average wages from national data sets<br>• Mild anaphylactic reactions in the emergency department taken one study from the literature<br>• Medical care preceding death from anaphylaxis assumed to be $2000<br>• Endocarditis, mitral valve replacement, congestive heart failure from one study from the literature<br>• Outpatient visits from Medicaid charges for 2000 |
| | **Utility data** | • Endocarditis utility score from the Years of Healthy Life Measure, base case 0.58, range 0.29 to 0.84<br>• Patients recovering fully from endocarditis return to their baseline quality of life, represented by mitral valve disorder with a utility score of 0.81, range 0.72 to 0.92 (range derived from other moderate-risk lesions) (Years of Healthy Life Measure)<br>• Utility score for congestive heart failure from the Years of Healthy Life Measure, base case 0.40, range 0.17 to 0.55 |
| **Uncertainty** | | |
| | **One-way sensitivity analysis** | • When all antibiotic-related deaths due to amoxicillin were excluded, the ICER was US$9,875,800 (2000) or £9,053,368 (2015).<br>• When the prevalence of urinary tract infections is increased to 100% (from 3.9%), the ICER for amoxicillin was $311,507 and $427,966 for vancomycin.<br>• The conclusions were robust to all other sensitivity analyses. |
| | **Probabilistic sensitivity analysis** | Not undertaken |

| Bibliographic reference | **Caviness AC, Cantor SB, Coburn HA, Ward MA (2004) A cost-effectiveness analysis of bacterial endocarditis prophylaxis for febrile children who have cardiac lesions and undergo urinary catheterization in the emergency department. Pediatrics, 113 (5), 1291-1296.** |
|---|---|
| **Applicability** | **Partially Applicable**<br><br>• Study based on the US healthcare system<br>• Societal perspective taken for costs<br>• Discount rate of 3% used<br>• Years of Healthy Life Measure used for utilities to derive quality adjusted life years |
| **Limitations** | **Minor Limitations**<br><br>• Decision tree used for model structure whereas a Markov model may have been more appropriate to model long term consequences<br>• Parameters used for effectiveness were based on the limited evidence available in the literature<br>• Full range of sensitivity analyses not reported<br>• Probabilistic sensitivity analysis not done<br><br>**Conflicts**<br>No declaration provided |

*Acronyms*
*ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; AHA: American Heart Association; BE: bacterial endocarditis; IE: infective endocarditis; CI: confidence interval*
*(a) ICERs converted to 2015 UK pounds by using the Campbell and Cochrane Economics Methods Group EPPI Cost Converter available at http://www.c-cemg.org/, accessed 21-22 January 2015*

# Appendix M: Quality assessment

## Q3

### Quality criteria for prognostic/clinical prediction question (Hayden's checklist)

| Author | Criteria | | | | | | Quality |
|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | |
| Mohee (2014) | Y | U | Y | Y | Y | N | LRB |
| Chen (2013) | Y | U | Y | Y | N | Y | LRB |
| Ammar (2013) | Y | U | N | Y | U | N | HRB |
| Duval (2006) | Y | U | Y | Y | N | N | HRB |
| Lacassin (1995) | Y | U | Y | N | U | Y | HRB |
| Strom (2000) | Y | U | Y | Y | U | N | HRB |

Y = Yes; N = No; U = Unclear

### Hayden's checklist for prognostic/clinical prediction studies

| | Criteria | Circle or highlight one option for each question | | |
|---|---|---|---|---|
| 1 | The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results | Yes | No | Unclear |
| 2 | Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias | Yes | No | Unclear |
| 3 | The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias | Yes | No | Unclear |
| 4 | The outcome of interest is adequately measured in study participants, sufficient to limit potential bias | Yes | No | Unclear |
| 5 | Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest | Yes | No | Unclear |
| 6 | The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results | Yes | No | Unclear |

## Q4

### Quality criteria for controlled before and after (CBA) designs

| Author | Criteria | | | | | | | Quality |
|---|---|---|---|---|---|---|---|---|
| | A | B | C | D | E | F | G | |
| Tuna (2012) | D | D | NC | ND | ND | N/A | D | HRB |
| DuVall (2013) | D | D | NC | ND | ND | N/A | D | HRB |
| Lockhart (2008) | D | D | D | ND | ND | N/A | D | LRB |
| Cherry (2007) | D | D | NC | ND | ND | N/A | D | HRB |
| Morozumi (2010) | D | D | ND | ND | ND | N/A | D | HRB |
| Pineiro (2010) | D | D | NC | ND | ND | N/A | D | HRB |
| Sonbol (2009) | D | D | NC | ND | ND | N/A | D | HRB |
| Lucas (2002) | D | D | NC | NC | ND | N/A | D | HRB |
| Roberts (2000) | D | D | NC | ND | ND | N/A | D | HRB |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Roberts (2006) | D | D | NC | ND | ND | N/A | D | HRB |
| Roberts (1998) | D | D | ND | ND | ND | N/A | D | HRB |
| Tomas (2007) | D | D | NC | ND | ND | N/A | D | HRB |
| Yokoyama (2014) | D | D | ND | ND | ND | N/A | D | HRB |
| Zuccaro (1998) | D | D | NC | ND | ND | N/A | D | HRB |
| Assaf (2007) | D | D | NC | D | ND | N/A | D | LRB |
| Yagci (2013) | D | ND | NC | ND | ND | N/A | D | HRB |
| Zhang (2013) | D | ND | NC | ND | ND | N/A | D | HRB |
| Sharif-Kashani (2010) | D | ND | NC | ND | ND | N/A | D | HRB |
| El Batrawy (2014) | D | ND | NC | ND | ND | N/A | D | HRB |
| Saayman (2009) | D | ND | NC | ND | ND | N/A | D | HRB |
| Ho (1991) | D | NC | NC | NC | ND | N/A | D | HRB |
| London (1986) | D | ND | NC | ND | ND | N/A | D | HRB |
| Melendez (1991) | D | ND | NC | ND | ND | N/A | D | HRB |
| Roudaut (1993) | D | D | NC | NC | ND | N/A | D | HRB |
| Shyu (1992) | D | ND | NC | ND | ND | N/A | D | HRB |
| Yildirim (2003) | D | NC | NC | NC | ND | N/A | D | HRB |
| Min (2008) | D | D | NC | NC | ND | N/A | D | HRB |
| Chun (2012) | D | ND | NC | ND | ND | N/A | D | HRB |
| Weickert (2006) | D | D | NC | NC | ND | N/A | D | HRB |
| Kullman (1992) | D | ND | NC | ND | ND | N/A | D | HRB |

D = Done; NC= Not clear; ND = Not done; NRB = No risk of bias; LRB = Low risk of bias; HRB = High risk of bias

**Cochrane Effective Practice and Organisation of Care Review Group (EPOC)**

**Quality Checklist for before-and-after study (as suggested in Appendix H, Developing NICE guidelines - the Manual, NICE 2014)**

**(Reference)**

**http://epoc.cochrane.org/sites/epoc.cochrane.org/files/uploads/datacollectionchecklist.pdf**

**Quality criteria for controlled before and after (CBA) designs**

**Seven standard criteria are used for CBAs included in EPOC reviews:**

*A) Baseline measurement*

Score DONE if performance or patient outcomes were measured prior to the intervention, and no substantial differences were present across study groups (e.g. where multiple pre intervention measures describe similar trends in intervention and control groups);

Score NOT CLEAR if baseline measures are not reported, or if it is unclear whether baseline measures are substantially different across study groups;

Score NOT DONE if there are differences at baseline in main outcome measures likely to undermine the post intervention differences (e.g. are differences between the groups before the intervention similar to those found post intervention).

*b) Characteristics for studies using second site as control*

Score DONE if characteristics of study and control providers are reported and similar;

Score NOT CLEAR if it is not clear in the paper e.g. characteristics are mentioned in the text but no data are presented;

Score NOT DONE if there is no report of characteristics either in the text or a table OR if baseline characteristics are reported and there are differences between study and control providers.

*c) Blinded assessment of primary outcome(s)* (protection against detection bias)*

Score DONE if the authors state explicitly that the primary outcome variables were assessed blindly OR the outcome variables are objective e.g. length of hospital stay, drug levels as assessed by a standardised test;

Score NOT CLEAR if not specified in the paper;

Score NOT DONE if the outcomes were not assessed blindly.

Primary outcome(s) are those variables that correspond to the primary hypothesis or question as defined by the authors. In the event that some of the primary outcome variables were assessed in a blind fashion and others were not, score each separately and label each outcome variable clearly.

*d) Protection against contamination*

Studies using second site as control

Score DONE if allocation was by community, institution, or practice and is unlikely that the control group received the intervention;

Score NOT CLEAR if providers were allocated within a clinic or practice and communication between experimental and group providers was likely to occur;

Score NOT DONE if it is likely that the control group received the intervention (e.g. cross-over studies or if patients rather than providers were randomised).

*e) Reliable primary outcome measure(s)*

Score DONE if two or more raters with at least 90% agreement or kappa greater than or equal to 0.8 OR the outcome is obtained from some automated system e.g. length of hospital stay, drug levels as assessed by a standardised test;

Score NOT CLEAR if reliability is not reported for outcome measures that are obtained by chart extraction or collected by an individual;

Score NOT DONE if agreement is less than 90% or kappa is less than 0.8.

In the event that some outcome variables were assessed in a reliable fashion and others were not, score each separately and label each outcome variable clearly.

*f) Follow-up of professionals (protection against exclusion bias)*

Score DONE if outcome measures obtained 80-100% subjects allocated to groups. (Do not assume 100% follow-up unless stated explicitly.);

Score NOT CLEAR if not specified in the paper;

Score NOT DONE if outcome measures obtained for less than 80% of patients allocated to groups.

*g) Follow-up of patients*

Score DONE if outcome measures obtained 80-100% of patients allocated to groups or for patients who entered the study. (Do not assume 100% follow-up unless stated explicitly.);

Score NOT CLEAR if not specified in the paper;

Score NOT DONE if outcome measures obtained for less than 80% of patients allocated to groups or for less than 80% of patients who entered the study.

# Appendix N: Supporting information

## N.1 Incidence of bacteraemia over time in those receiving antibiotics vs no prophylaxis/placebo

| Study | Timepoints and incidence of bacteraemia | | | | Trend |
|---|---|---|---|---|---|
| Sanchez-Carrion 2006 | B: NR | 30 secs: 3.9% | 20 mins: 3.9% | - | |
| | B: NR | 30 secs: 32.7% | 20 mins: 14.3% | - | ↓ |
| Diz 2006 | B: 5% | 30 secs: 46.4% | 15 mins: 10.7% | 1 hr: 3.7% | ↓ (Amoxicillin) |
| | B: 12.5% | 30 secs: 85.1% | 15 mins: 70.4% | 1hr: 22.2% | ↓ (Clindamycin) |
| | B: 7.5% | 30 secs: 56.9% | 15 mins: 24.1% | 1hr: 7.1% | ↓ (Moxifloxacin) |
| | B: 9.4% | 30 secs: 96.2% | 15 mins: 64.2% | 1 hr: 20% | ↓ |
| Hall 1993 | B: 0% | During extraction: 90% | 10 mins after: 70% | - | ↓ (Penicillin V) |
| | B: 0% | During extraction: 85% | 10 mins after: 60% | - | ↓ (Amoxicillin) |
| | B: 0% | During extraction: 90% | 10 mins after: 80% | - | ↓ |
| Hall 1996 | B: 0% | During extraction: 79% | 10 mins after: 53% | - | ↓ |
| | B: 0% | During extraction: 85% | 10 mins after: 47% | - | ↓ |
| Wahlman 1999 | B: NR | 10 mins after surgery: 23% | 30 mins after surgery: 20% | - | ↓ |
| | B: NR | 10 mins after surgery: 79% | 10 mins after surgery: 69% | - | ↓ |
| Selby 1994 | B: 0% | 5 mins: 5.3% | 4 hrs: 0% | 24 hrs: 0% | ↓ |
| | B: 0% | 5 mins: | 4 hrs: 5% | 24 hrs: 0% | ↓ |

| | | | | | |
|---|---|---|---|---|---|
| | | 31.6% | | | |
| Lockhart 2004 | B after intubation: 4% | 15mins: 2% | 30mins: 0% | 45mins: 0% | ↓ |
| | B after intubation: 18% | 15mins: 18% | 30mins: 16% | 45mins: 14% | ↓ |
| Lockhart 2008 | B: 0% | 5 mins: 33% | 20 mins: 1% | - | ↓ |
| | B: 0% | 5 mins: 58% | 20 mins: 10% | - | ↓ |

1 NR: not reported

2 B: baseline

3 Antibiotic prophylaxis

4 No prophylaxis/placebo

## N.25 Incidence of bacteraemia over time in those receiving
## 6 chlorhexidine compared to no prophylaxis/placebo

| Study | Timepoints and incidence of bacteraemia | | | | Trend |
|---|---|---|---|---|---|
| Pineiro 2010 | B: 0% | 30 secs: 0% | 15 mins: 0% | - | - |
| | B: 3% | 30 secs: 7% | 15 mins: 3% | - | ↓ |
| Tuna 2012 | B: 0% | 1 mins: 25% | 15 mins: 17% | - | ↓ |
| | B: 0% | 1 mins: 40% | 15 mins: 30% | - | ↓ |
| Tomas 2007 | B: 9% | 30 secs: 79% | 15 mins: 30% | 1 hr: 2% | ↓ |
| | B: 8% | 30 secs: 96% | 15 mins: 64% | 1 hr: 20% | ↓ |

7 B: baseline

8 Chlorhexidine prohylaxis

9 No prophylaxis/placebo

10

11

12

13

14

15

# Appendix O: Critique of Dayer et al. (2014) study by Ramsay (2015)

## Methods Critique

### Incidence of infective endocarditis in England, 2000–13: a secular trend, interrupted time-series analysis by Dayer *et al*

**Produced by:** Craig Ramsay

Health Services Research Unit, University of Aberdeen

3rd Floor, Health Sciences Building, Foresterhill

Aberdeen, AB25 2ZD

**Date completed:** **4th February 2015**

**Declared competing interests of the author**

The author is statistical editor for the Cochrane Effective Practice and Organisation of Care Group and as such was involved in developing the risk of bias assessment tool for interrupted time series used in this report.

**Rider on responsibility for report**

The Health Services Research Unit is supported by a core grant from the Chief Scientist Office of the Scottish Government Health and Social Care Directorates. The views and opinions expressed herein are those of the author and do not necessarily reflect those of the Chief Scientist Office or the Department of Health.

This report contains a summary, description, critique and quality assessment of the methods used in Dayer MJ *et al*. Incidence of infective endocarditis in England, 2000–13: a secular trend, interrupted time-series (ITS) analysis. *Lancet* http://dx.doi.org/10.1016/S0140-6736(14)62007-9.

#### 1. Summary

A brief summary of the critique is given below:

- There was no factual error with modelling approach undertaken in paper
- Data for incidence of endocarditis (Figure 2 in original paper) and incidence of high and low risk cases (Figure 3 in original paper) were abstracted from the graph and original paper analysis confirmed
- Exploratory investigation of data suggested that two straightlines might not be an adequate description of the series, implying that the change in slope in original paper is likely biased

- Multiple change-points seem possible rather than only one at the point of guideline introduction
- Reanalysis of series suggests the change in slope estimate is primarily driven by whether the post-intervention data is a straightline (as in the original paper) or not
- If an additional interruption is incorporated at June 2011, the change in slope at guideline introduction is reduced to zero, suggesting no effect of guidance on trends
- Applying the Cochrane Effective Practice and Organisation of Care risk of bias assessment for interrupted time series suggests the study is at high risk of bias
- Taking all evidence into account, I believe the effect of change in slope is biased and the published estimates are likely too high

## 2. Description of methods used by Dayer paper

### *2.1 Interrupted time series*

Dayer *et al* applied a segmented regression time series model to monthly data points from January 2000 until end March 2013 (159 data points in total). The interruption was assumed to have occurred at end of March 2008, therefore 99 data points were assumed in the pre-intervention data and 60 data points in the post-intervention data. No other interruptions were assumed to have occurred. The regression lines before and after the interruption were assumed to be linear (straight lines). Recognising that the data may contain serial correlation (also known as autocorrelation) (i.e. that points closer in time may be more correlated with each other than points further away), investigation of autocorrelation functions and partial autocorrelation functions was undertaken. If serial correlation was identified, it could be adjusted for in the regression model though it was not stated in the paper exactly how this was performed.

Two effect sizes were produced by the regression model. A *change in level* and a *change in slope*. A change in level relates to an instantaneous change (or "interruption") in the time series at March 2008. If the effect is positive, then there is predicted to have been more cases of endocarditis in March 2008 than would have been predicted by the trend in the pre-intervention data. If the effect is negative then there are fewer cases than would have been expected. The change in slope relates to the difference in the monthly trend pre-intervention versus the monthly trend post-intervention (after the interruption). If the change in slope effect is positive then there is predicted to have been more cases of endocarditis per month than would have been predicted by the trend in the pre-intervention data.

Figure 2 in Dayer et al provides the main finding from the interrupted time series analysis. The change in slope was +0.11 (95% CI 0.05, 0.16; p<0.0001) and the change in level was -0.45 (95% CI -2.54, 1.63; p=0.670). These effects were interpreted as providing no statistically significant evidence for an instantaneous change in level in March 2008, but there was strong evidence for a change in the slope that suggested there was an increase in the incidence of endocarditis by 0.11 per ten million per month than would have been expected by chance.

### *2.2 Change-point analysis*

In an attempt to confirm the robustness of the segmented regression, Dayer *et al* used change-point analysis to calculate the optimum positioning and number of data changepoints using the R change-point package that implements the Hinkley algorithm. In simple terms, the Hinkley algorithm is a form of binary segmentation whereby a single changepoint test-statistic is applied to the whole series and then if one is identified the data set is then split into two at that changepoint and each portion before and after the changepoint is then searched individually for further changepoints and the analysis recursively cuts the data set up into increasingly smaller chunks searching for significant changes in

mean levels before and after the cuts. The method is distribution-free and assumes that the datapoints are identical and independent. Given the chance of spuriously picking up changepoints because the entire sample space is being recursively searched, a variety of "penalties" can be applied to the data. It is not clear which, if any, approach was used in the Dayer *et al* model.

## 3. Critique of the methods used by Dayer *et al* paper

### *3.1 Critique of Interrupted time series*

*Abstracting Dayer et al data*

The robustness of the interrupted time series analysis rests on how well one believes that the data are represented by the trends before and after the interruption. As part of the critique, the raw data from Dayer *et al* Figure 2 (incidence of infective endocarditis) and Figure 3 (incidence by risk group) was abstracted using Plot Digitizer software (http://plotdigitizer.sourceforge.net/). The accuracy of the abstraction can be seen in Table 1, where the Dayer *et al* result and the application of the Dayer *et al* model to the abstracted data can be compared.

**Table 1 Comparison of Dayer *et al* estimates and abstracted data**

| Estimate | Dayer et al<br>Estimate (95% CI) | Abstracted data<br>Estimate (95% CI) |
|---|---|---|
| **Fig 2 – incidence of endocarditis** | | |
| Change in level | -0.45 (-2.54, 1.63) | -0.45 (-2.69, 1.78) |
| Change in slope | +0.11 (0.05, 0.16) | +0.11 (0.05, 0.16) |
| **Fig 3 – incidence of endocarditis (high risk)** | | |
| Change in level | -0.04 (-1.35, 1.27) | -0.09 (-1.67, 1.49) |
| Change in slope | +0.04 (0.01, 0.07) | +0.04 (0.00, 0.08) |
| **Fig 3 – incidence of endocarditis (low risk)** | | |
| Change in level | -0.46 (-1.86, 1.09) | -0.47 (-2.08, 1.14) |
| Change in slope | +0.07 (0.03, 0.10) | +0.07 (0.02, 0.11) |

Notwithstanding abstraction variability because of the resolution of Figures 2 and 3, the very slight discrepancy in the confidence intervals relates primarily to the method used to derive the trend lines. In the Dayer *et al* paper, the authors do not describe the actual model they fitted to the data in terms of any autocorrelation found, the paper only describes the approach they used to identify the autocorrelation. For the model I fitted to the data in Table 1, I assumed first order autocorrelation (see autocorrelation section below) and adjusted the data using the Cochran-Orcutt method and fitted the lines exactly as described by the Dayer *et al* paper (i.e. using the Wagner *et al* approach to model fitting). Note, however, this approach was an attempt to illustrate that the abstracted data was good enough to do further robust analysis on, it was not (in my opinion) the suboptimal model to fit to the data. In my opinion given the statistical estimates are accurate to within 2 decimal places for most of the estimates, the abstracted data is robust. Appendix 1 contains the abstracted data from each timepoint that is used in subsequent analyses.

*Autocorrelation*

The level of autocorrelation in a series is identified, as the Dayer *et al* paper suggests, by interpretation of autocorrelation function (ACF) and partial autocorrelation function (PACF). These functions are applied to the pre-intervention data only. The one method stipulation in using these functions is that the series should be "stationary". This means that any trend in the data should be removed before using. A trend can be removed by "differencing" and is a standard approach when using these functions. Figures 1a and 1b show the results of applying the functions to the differenced incidence data.

**Figure 1a ACF of incidence**

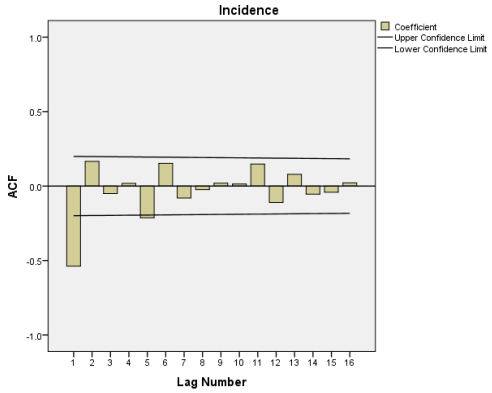
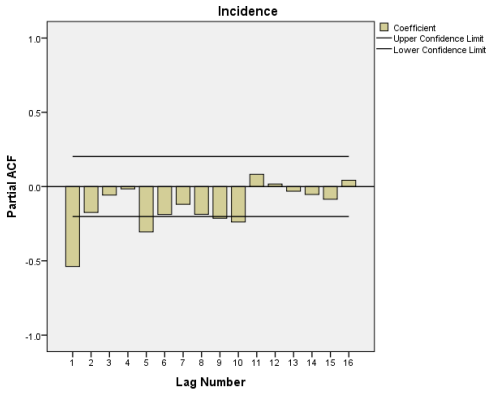



**Figure 1b PACF of incidence**




The above graphs are highly suggestive (monotonically decreasing ACF and PACF with one significant lag close to low lag numbers) that the series have what is known as **first order autocorrelation**. As Dayer *et al* suggested, there is no evidence of seasonality in the data (lag 12 would be significant if seasonality was present). I have assumed in subsequent analyses that the data have first order autocorrelation, but Dayer *et al* paper did not state what they found.

*Time series modelling*

Given it has been possible to replicate the Dayer *et al* results, I am confident that the model as they developed it, has been successfully implemented. The approach Dayer *et al* used fitted a straight line to the data pre-intervention and a straight line post-intervention. All their reported results are therefore robust to that model. Although I cannot be 100% confident, it does appear that Dayer *et al* have also correctly adjusted for autocorrelation in their series. So, the main distributional assumption in the modelling is that the residual error term is first order autocorrelated.

Where I have real uncertainty however is the assumption that a straight-line fits the pre-and post-intervention data. It is crucial that assumption is correct because the main finding of the Dayer study is for a change in slope at March 2008.

*Shape of pre-intervention line*

Visual interpretation of the incidence data would suggest that the pattern up to around point 60 (December 2003) looks different to points after December 2003. Prior to December 2003 the points appear to be quite flat (no trend or maybe even slightly downward) and then after 2003 increasing. Instead of fitting a straight line it is possible to test whether a curve fits the data better. The simplest curve to fit is a parabolic shape where

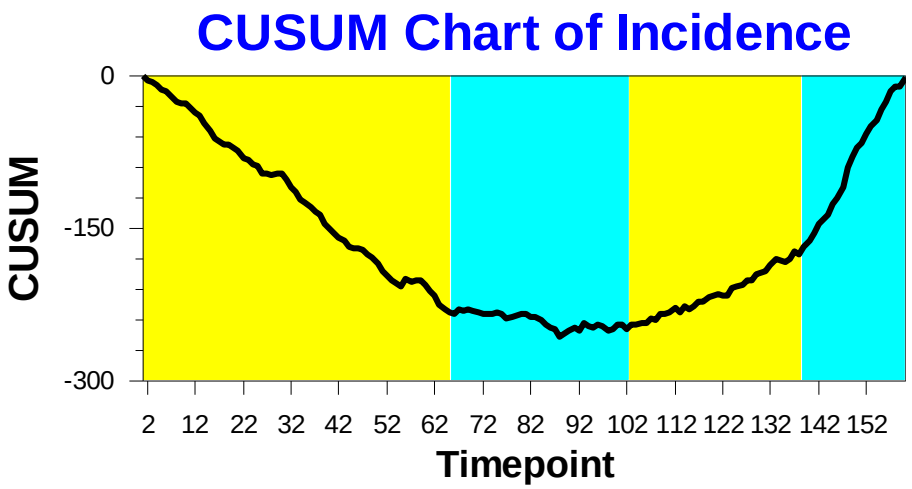
$$\text{Incidence} = \text{constant} + \text{time} + (\text{time})^2$$

When applying the above model to the pre-intervention data the $(\text{time})^2$ parameter was highly

significant (p<0.001) and positive thereby suggesting a 'U' shape fitted better. There was therefore strong evidence that the pre-intervention data was not linear.

An alternative way to look for patterns in time series data is to plot the CUSUM chart. In the CUSUM chart each observation is sequentially compared to the series mean. If the CUSUM chart is going downwards the data are trending to below the series mean, if flat they are at the series mean and if increasing they are above the series mean. If the data were increasing straight lines (as Dayer *et al* have assumed) we would expect the CUSUM chart to go in one direction before and after the guidelines were introduced. The CUSUM plot for the Incidence data is shown in Figure 2.

**Figure 2 – CUSUM chart for Incidence data**




The CUSUM plot demonstrates that the pre-intervention phase is not linear. There is a flattening out of the CUSUM curve around point 65.

So two approaches for investigating a non-linear relationship both provide strong evidence that a straightline relationship is not appropriate. The implications are that the reported change in slope is biased. I provide alternative estimates of the likely change in slope in the *Revised estimates of effect* section below.

There are other time series methods available that may provide a better test of the intervention effect compared to simple time series regression such as autoregressive integrated moving average models, which are particularly amenable to longer time series such as is found in this paper. Dayer *et al* have not discussed using any other interrupted time series method to crosscheck their time series regression findings. Instead, they chose to look for any changes in the series using a change-point technique, which is discussed below.

### *3.2 Critique of change-point analysis*

Dayer *et al* used change-point analysis to calculate the optimum positioning and number of data changepoints using the R change-point package that implements the Hinkley algorithm. As described earlier the Hinkley algorithm is a form of binary segmentation whereby a single change-point test-statistic is applied to the whole series and then if one is identified the data set is then split into two at that changepoint and each portion before and after the changepoint is then searched individually for further changepoints and the analysis recursively cuts the data set up into increasingly smaller chunks searching for significant changes in mean levels before and after the cuts. The method is distribution-free and assumes that the datapoints are identical and independent. I have not had access to the R change-point package and therefore cannot replicate the analysis they performed. There are a variety of algorithms that could be used within the change-point package (Killick, R., Eckley, I.A. (2014) changepoint: An R package for changepoint analysis. *Journal of Statistical Software* 58(3) 1-19.), but there are insufficient details in the Dayer *et al* paper to determine which one they used. However, because they have referred to the Hinkley method it seems plausible that they have opted for the simplest of mean change models. I ran the data

through an alternative multiple change-point programme (Taylor, Wayne (2000a), Change-Point Analyzer 2.0 shareware program, Taylor Enterprises, Libertyville, Illinois. Web: http://www.variation.com/cpa) that performs distribution free change-point methodology akin to the Hinkley method. The results are shown in Table 2 and Figure 3.

**Table 2 Results of change-point analysis on incidence data**

Table of Significant Changes for Incidence

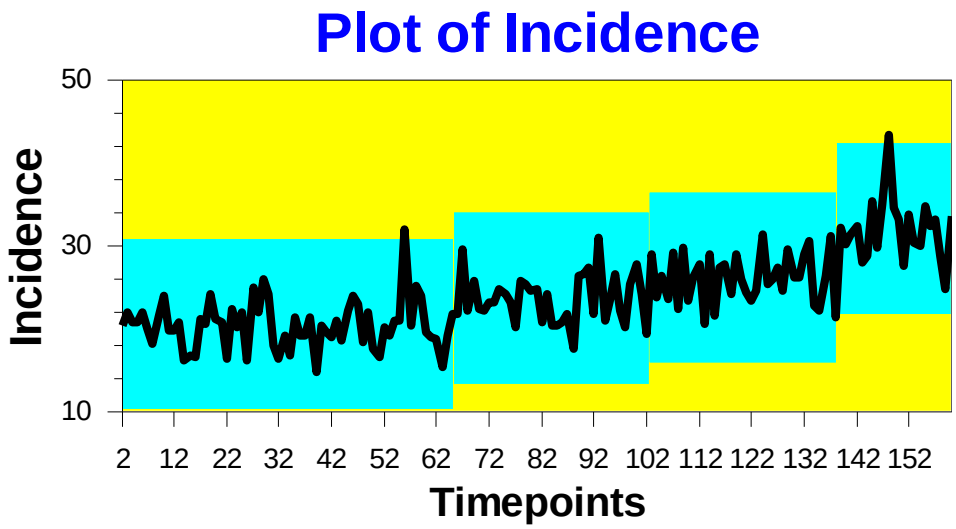
Confidence Level for Candidate Changes = 50%, Confidence Level for Inclusion in Table = 90%, Confidence Interval = 95%, Bootstraps = 1000, Without Replacement, MSE Estimates

| Row | Confidence Interval | Conf. Level | From | To | Level |
|---|---|---|---|---|---|
| 66 | (54, 75) | 99% | 20.543 | 23.695 | 2 |
| 103 | (88, 121) | 99% | 23.695 | 26.208 | 4 |
| 139 | (136, 142) | 100% | 26.208 | 32.118 | 2 |

Table 2 illustrates that there is strong evidence of a change in the mean level of the data at data point 103 (this is 4 months after the guidelines were introduced) – this corresponds very closely with the Dayer *et al* result. However, the change-point analysis also identified two other significant change-points. One at point 66 and one at point 103. Graphically the data can be considered in four separate chunks as displayed in the shaded areas in Figure 3.

Dayer *et al* are unclear on number of change-points in their paper. Whilst they stated that a change-point occurred at 3 months post guideline introduction, they have not explicitly stated whether they did or did not identify any other change-points. According to my reanalysis, it is likely that there were other potential change-points in the series and these also seem to correspond with my earlier findings that a linear relationship was not appropriate. One is left to conjecture on what "events" occurred at these points in time to increase the incidence of endocarditis.

**Figure 3 – Plot of incidence with change-points in shaded areas**




### *3.3 Critique of Study Quality*

The Cochrane Effective Practice and Organisational Care (EPOC) Group have developed seven risk of bias criteria for interrupted time series studies (https://epoc.cochrane.org/epoc-specific-

resources-review-authors). A description of the tool is given in Appendix 2. Applying the tool to Dayer *et al* (Table 2), the study has two criteria at high risk of bias (pre-specification of the intervention effect and biased statistical analysis). The study findings therefore are at a high risk of bias.

**Table 2 – Risk of bias assessment**

| |
|---|
| **Was the intervention independent of other changes? YES** |
| Reasonably convincing evidence that nothing else occurred at time of guideline introduction<br>Eg "..dental statistics for England show that dental extractions have remained fairly constant.." or "a sudden<br>large increase in the number of individuals at risk of infective endocarditis might have occurred. However, for<br>many of the factors that put an individual at high risk of infective endocarditis, we have shown that this situation<br>is unlikely to be the case…" |
| **Was the shape of the intervention effect pre-specified? NO** |
| A linear trend before and after the intervention was conducted, but no rationale was given or tested that this was the correct, pre-specified shape. |
| **Was the intervention unlikely to affect data collection? YES** |
| Unlikely intervention affected routine data collection<br>e.g. "…because the coding was done independently of our study, it was not subject to study related bias or affected in any other way by the introduction of the NICE guidelines…" |
| **Was knowledge of the allocated interventions adequately prevented during the study? YES** |
| The routine data collection could not have been affected by knowledge of the guidelines |
| **Were incomplete outcome data adequately addressed? YES** |
| Whilst some cases may be missing, it is likely that they are random error<br>e.g. "…the size of the dataset and the consistency of the underlying coding process are likely to negate the effect of any systematic error…" |
| **Was the study free from selective outcome reporting? YES** |
| The outcome has included all known reported cases of endocarditis and it is unlikely there were any other outcomes that could have been used. |
| **Was the study free from other risks of bias? NO** |

The statistical analysis does not correctly model the trends in the data and likely biases the estimates.

## 4 Revised estimates of effect section

Taking all of the above evidence into account there is, in my opinion, a strong case for revising the model proposed by Dayer *et al*. The simplest amendment to make, would be to use the same methodology as Dayer *et al* (linear time series regression with first order autocorrelation), but to fit an additional interruption at an earlier time point. To maximise the data points pre-intervention I selected the lower bound from the confidence interval around point 66 interruption so this meant the time point for the first interruption was point 54 (June 2004). So the model fits a straightline to the first 54 datapoints, a straightline from point 54 to 99 and makes no change to the post-intervention data. A second analysis incorporated an additional interruption at time point 139 (June 2011). The results are displayed in Table 3.

**Table 3 Comparison of Dayer *et al* estimates and "reviewer sensitivity analyses"**

| **Incidence** | **Dayer et al** | **Abstracted data** | **Abstracted data** |
|---|---|---|---|
| | | **Two change-points[1]** | **Three change-points[2]** |
| | **Estimate (95% CI); p** | **Estimate (95% CI); p** | **Estimate (95% CI); p** |
| **All cases** | | | |
| Change in level | -0.45 (-2.54, 1.63);0.670 | -0.81 (-3.30, 1.71);0.562 | +0.68 (-1.94, 3.31);0.606 |
| Change in slope | +0.11 (0.05, 0.16);0.000 | +0.10 (0.01, 0.19);0.021 | -0.00 (-0.11, 0.11);0.970 |
| **high risk** | | | |
| Change in level | -0.04 (-1.35, 1.27);0.951 | -0.27 (-2.10,1.60);0.777 | +0.17 (-1.87,2.21);0.870 |
| Change in slope | +0.04 (0.01, 0.07);0.025 | +0.03 (-0.04,0.09);0.373 | -0.00 (-0.09, 0.08);0.938 |
| **low risk** | | | |
| Change in level | -0.46 (-1.86, 1.09);0.547 | -0.71 (-2.45,1.02);0.419 | +0.35 (-1.50,2.21);0.705 |
| Change in slope | +0.07 (0.03, 0.10);0.000 | +0.07 (0.01,0.13);0.02 | -0.00 (-0.08, 0.07);0.941 |

[1] change-points considered at point 54 and 99

[2] change-points considered at point 54, point 99 and point 139

The results in Table 3 suggest that the impact of the interruption at the point of guideline introduction is highly sensitive to whether there are multiple change-points. If three changes are modelled, the effects show no significant change in slope or level. The data suggests that the more datapoints are collected in the future, the more the model will move away from a single straightline describing it adequately. There is likely to be some minor change around the time of the guideline intervention, but there are also other substantive changes in the series that remain unexplained (i.e. what happened around June 2011?). It is worth considering these results in light of Dayer et al earlier published paper with fewer data points. At that point (2 years follow-up) they did not observe any change in incidence. The results above would also be in line with that original finding because much of the new data is possibly from a different shape of effect and unlikely to be due to the guideline introduction per se.

My final conclusion on the methods is that the methodology in the paper is relatively robust, but the size of the change in slopes are highly sensitive to whether you believe a single straightline describes the post-guideline data. My personal opinion based upon the reanalysed data is that it is likely that the Dayer *et al* change in slopes is biased too high, and that the real change is likely to be smaller. Due consideration must be given to whether it is plausible that the trends observed 3 or 4 years after the guideline introduction could be considered to be influenced by the guideline rather than some other external event(s).

**Appendix 1 – Abstracted data from Dayer *et al***

| Year/Month | Incidence | Incidence High risk | Incidence Low risk |
|---|---|---|---|
| 2000m1 | 20.595856 | 2.04969 | 18.4206 |
| 2000m2 | 22.10708 | 1.35759 | 20.8696 |
| 2000m3 | 20.811745 | 2.44898 | 18.5271 |
| 2000m4 | 20.854921 | 2.84827 | 18.0479 |
| 2000m5 | 22.193438 | 4.9512 | 17.4623 |
| 2000m6 | 20.034542 | 3.96628 | 16.85 |
| 2000m7 | 18.393782 | 1.75688 | 16.6371 |
| 2000m8 | 21.675303 | 4.89796 | 16.8234 |
| 2000m9 | 24.136442 | 4.65839 | 19.5918 |
| 2000m10 | 19.861832 | 3.00799 | 16.8767 |
| 2000m11 | 19.905008 | 2.79503 | 17.3558 |
| 2000m12 | 20.811745 | 4.92458 | 16.3975 |

| | | | |
|---|---|---|---|
| 2001m1 | 16.321243 | 2.12955 | 14.2147 |
| 2001m2 | 16.968912 | 2.63531 | 14.3744 |
| 2001m3 | 16.753023 | 2.20941 | 14.5608 |
| 2001m4 | 21.373056 | 4.73824 | 16.9033 |
| 2001m5 | 20.768566 | 3.56699 | 17.1695 |
| 2001m6 | 24.309155 | 5.29725 | 19.3256 |
| 2001m7 | 21.243523 | 3.83319 | 17.5688 |
| 2001m8 | 20.984455 | 3.1677 | 17.835 |
| 2001m9 | 16.58031 | 3.4339 | 13.15 |
| 2001m10 | 22.582039 | 2.95475 | 19.6451 |
| 2001m11 | 20.336788 | 4.15262 | 16.4241 |
| 2001m12 | 22.193438 | 6.68146 | 15.6256 |
| 2002m1 | 16.234888 | 2.79503 | 13.4428 |
| 2002m2 | 25 | 6.70807 | 18.4206 |
| 2002m3 | 22.020725 | 5.61668 | 16.8234 |
| 2002m4 | 26.165804 | 13.5226 | 13.0701 |
| 2002m5 | 24.309155 | 6.78793 | 16.9299 |
| 2002m6 | 18.048359 | 3.96628 | 14.2413 |
| 2002m7 | 16.450777 | 2.4756 | 13.8421 |
| 2002m8 | 19.386873 | 4.25909 | 15.4126 |
| 2002m9 | 16.925734 | 3.75333 | 13.2298 |
| 2002m10 | 21.459414 | 5.08429 | 16.4508 |

| | | | |
|---|---|---|---|
| 2002m11 | 19.343697 | 4.15262 | 15.3061 |
| 2002m12 | 19.343697 | 4.60515 | 14.827 |
| 2003m1 | 21.416235 | 7.2937 | 14.268 |
| 2003m2 | 14.896373 | 2.12955 | 12.8305 |
| 2003m3 | 20.595856 | 5.48358 | 15.2795 |
| 2003m4 | 19.732298 | 5.66992 | 14.268 |
| 2003m5 | 19.170984 | 4.17924 | 15.2795 |
| 2003m6 | 21.027634 | 3.4339 | 17.7019 |
| 2003m7 | 18.609673 | 2.76841 | 16.0248 |
| 2003m8 | 22.366148 | 4.685 | 17.7019 |
| 2003m9 | 24.17962 | 8.06566 | 16.2644 |
| 2003m10 | 23.18653 | 6.38864 | 16.8767 |
| 2003m11 | 18.43696 | 3.80657 | 14.7471 |
| 2003m12 | 22.150259 | 4.84472 | 17.4623 |
| 2004m1 | 17.746115 | 4.79148 | 13.3097 |
| 2004m2 | 16.62349 | 5.43035 | 11.3132 |
| 2004m3 | 20.207254 | 3.93966 | 16.2112 |
| 2004m4 | 19.343697 | 4.73824 | 14.6673 |
| 2004m5 | 21.027634 | 4.36557 | 16.7968 |
| 2004m6 | 21.070812 | 3.51375 | 17.5155 |
| 2004m7 | 32.038 | 8.62467 | 23.5847 |
| 2004m8 | 20.595856 | 5.72316 | 14.9068 |

| | | | |
|---|---|---|---|
| 2004m9 | 25.388601 | 7.77285 | 17.7019 |
| 2004m10 | 24.136442 | 6.54836 | 17.8882 |
| 2004m11 | 19.602764 | 3.88642 | 15.8385 |
| 2004m12 | 19.08463 | 5.85626 | 13.496 |
| 2005m1 | 18.998272 | 3.67347 | 15.3327 |
| 2005m2 | 15.457685 | 3.75333 | 11.8722 |
| 2005m3 | 19.343697 | 4.20586 | 15.0665 |
| 2005m4 | 21.804836 | 4.79148 | 17.0364 |
| 2005m5 | 21.891191 | 4.25909 | 17.5954 |
| 2005m6 | 29.792746 | 8.14552 | 21.7746 |
| 2005m7 | 22.322971 | 4.49867 | 17.7551 |
| 2005m8 | 25.82038 | 7.53327 | 18.4472 |
| 2005m9 | 22.582039 | 6.25555 | 16.504 |
| 2005m10 | 22.366148 | 6.28217 | 16.1579 |
| 2005m11 | 23.35924 | 7.2937 | 16.2112 |
| 2005m12 | 23.272884 | 6.44188 | 16.9033 |
| 2006m1 | 24.913645 | 6.44188 | 18.5537 |
| 2006m2 | 24.352331 | 8.27862 | 16.0515 |
| 2006m3 | 23.229706 | 5.11091 | 18.3141 |
| 2006m4 | 20.29361 | 6.20231 | 14.2946 |
| 2006m5 | 25.863558 | 7.50665 | 18.5271 |
| 2006m6 | 25.474957 | 7.66637 | 17.8083 |

| | | | |
|---|---|---|---|
| 2006m7 | 24.611399 | 6.28217 | 18.4738 |
| 2006m8 | 24.827288 | 6.4685 | 18.4206 |
| 2006m9 | 20.941278 | 6.4685 | 14.7205 |
| 2006m10 | 24.352331 | 6.30878 | 18.2609 |
| 2006m11 | 20.552677 | 5.08429 | 15.4392 |
| 2006m12 | 20.552677 | 5.21739 | 15.4392 |
| 2007m1 | 20.8981 | 6.44188 | 14.5874 |
| 2007m2 | 21.891191 | 5.85626 | 15.9982 |
| 2007m3 | 17.702936 | 4.126 | 13.6291 |
| 2007m4 | 26.468048 | 5.19077 | 21.2689 |
| 2007m5 | 26.770294 | 6.86779 | 20.2839 |
| 2007m6 | 27.504318 | 9.95563 | 17.622 |
| 2007m7 | 21.891191 | 7.74623 | 14.268 |
| 2007m8 | 31.088083 | 14.0816 | 17.1695 |
| 2007m9 | 21.070812 | 5.7764 | 15.2795 |
| 2007m10 | 23.704662 | 5.27063 | 18.8731 |
| 2007m11 | 26.64076 | 7.40018 | 19.4587 |
| 2007m12 | 22.322971 | 4.8181 | 17.7019 |
| 2008m1 | 20.250431 | 5.82964 | 14.5342 |
| 2008m2 | 25.561312 | 9.74268 | 15.8917 |
| 2008m3 | 27.806562 | 8.62467 | 19.4587 |
| 2008m4 | 24.265976 | 7.10736 | 17.3292 |

| | | | |
|---|---|---|---|
| 2008m5 | 19.516407 | 5.98935 | 13.6823 |
| 2008m6 | 29.058722 | 5.7764 | 23.425 |
| 2008m7 | 23.834196 | 6.76131 | 17.1961 |
| 2008m8 | 26.468048 | 6.76131 | 19.9645 |
| 2008m9 | 23.704662 | 8.46495 | 15.0133 |
| 2008m10 | 29.231434 | 10.0887 | 19.299 |
| 2008m11 | 22.53886 | 6.89441 | 15.6788 |
| 2008m12 | 29.965458 | 8.73114 | 21.402 |
| 2009m1 | 23.57513 | 8.86424 | 14.8004 |
| 2009m2 | 26.20898 | 9.92902 | 15.8651 |
| 2009m3 | 27.979275 | 11.7657 | 16.3177 |
| 2009m4 | 20.639032 | 6.14907 | 14.5342 |
| 2009m5 | 29.145079 | 9.50311 | 19.8314 |
| 2009m6 | 21.718481 | 6.49512 | 15.2795 |
| 2009m7 | 27.590673 | 8.83762 | 18.6335 |
| 2009m8 | 27.936096 | 10.7276 | 17.1961 |
| 2009m9 | 24.265976 | 6.89441 | 17.3824 |
| 2009m10 | 29.015545 | 10.9405 | 18.1012 |
| 2009m11 | 26.079447 | 9.87578 | 16.2378 |
| 2009m12 | 24.438688 | 9.18367 | 15.1464 |
| 2010m1 | 23.445597 | 9.13043 | 14.3478 |
| 2010m2 | 24.654577 | 9.79592 | 14.8536 |

| | | | |
|---|---|---|---|
| 2010m3 | 31.433506 | 13.4161 | 18.0745 |
| 2010m4 | 25.43178 | 8.33185 | 17.1961 |
| 2010m5 | 26.122625 | 7.21384 | 19.0328 |
| 2010m6 | 27.417961 | 7.66637 | 20.0177 |
| 2010m7 | 24.654577 | 8.9441 | 15.732 |
| 2010m8 | 29.792746 | 7.74623 | 22.3336 |
| 2010m9 | 26.295338 | 6.57498 | 19.7249 |
| 2010m10 | 26.25216 | 7.4268 | 18.8731 |
| 2010m11 | 29.1019 | 9.55634 | 18.7933 |
| 2010m12 | 30.74266 | 12.9104 | 17.9947 |
| 2011m1 | 22.970638 | 7.50665 | 15.7054 |
| 2011m2 | 22.366148 | 6.04259 | 16.5839 |
| 2011m3 | 26.597582 | 8.33185 | 17.7551 |
| 2011m4 | 31.303972 | 14.0018 | 17.3558 |
| 2011m5 | 21.50259 | 7.32032 | 14.2147 |
| 2011m6 | 32.38342 | 9.44987 | 23.0524 |
| 2011m7 | 30.35406 | 8.70452 | 21.6948 |
| 2011m8 | 31.56304 | 11.1269 | 20.4969 |
| 2011m9 | 32.599308 | 11.2866 | 21.4818 |
| 2011m10 | 28.108809 | 9.9024 | 18.181 |
| 2011m11 | 28.842833 | 10.488 | 18.394 |
| 2011m12 | 35.405872 | 15.7853 | 19.6983 |

| | | | |
|---|---|---|---|
| 2012m1 | 29.92228 | 11.6859 | 18.394 |
| 2012m2 | 35.060448 | 13.3363 | 20.6832 |
| 2012m3 | 43.566494 | 18.2875 | 25.5013 |
| 2012m4 | 34.715027 | 17.3026 | 17.5688 |
| 2012m5 | 33.333332 | 12.1118 | 21.5617 |
| 2012m6 | 27.677029 | 9.13043 | 18.6868 |
| 2012m7 | 33.981003 | 10.6477 | 23.4516 |
| 2012m8 | 30.52677 | 11.3665 | 19.1925 |
| 2012m9 | 30.138168 | 9.87578 | 20.3372 |
| 2012m10 | 34.974094 | 11.606 | 23.5315 |
| 2012m11 | 32.599308 | 8.9441 | 23.7178 |
| 2012m12 | 33.37651 | 14.7205 | 18.8465 |
| 2013m1 | 28.972366 | 10.2484 | 19.0062 |
| 2013m2 | 24.827288 | 9.66282 | 15.2263 |
| 2013m3 | 33.678757 | 10.2218 | 23.6912 |

## Appendix 2 - Risk of bias for interrupted time series (ITS) studies

Seven standard criteria are used for all ITS studies. Further information can be obtained from the Cochrane handbook section on Risk of Bias and from the draft methods paper on risk of bias under the EPOC specific resources section of the EPOC website.

Note: If the ITS study has ignored secular (trend) changes and performed a simple t-test of the pre versus post intervention periods without further justification, the study should not be included in the review unless reanalysis is possible.

| **Was the intervention independent of other changes?** |
|---|
| Score “Yes” if there are compelling arguments that the intervention occurred independently of other changes over time and the outcome was not influenced by other confounding variables/historic events during study period. *If Events/variables identified, note what they are.* Score “NO” if reported that intervention was not independent of other |

| |
|---|
| changes in time. |
| **Was the shape of the intervention effect pre-specified?** |
| Score ”Yes” if point of analysis is the point of intervention OR a rational explanation for the shape of intervention effect was given by the author(s). Where appropriate, this should include an explanation if the point of analysis is NOT the point of intervention;Score “No” if it is clear that the condition above is not met |
| **Was the intervention unlikely to affect data collection?** |
| Score “Yes” if reported that intervention itself was unlikely to affect data collection (for example, sources and methods of data collection were the same before and after the intervention); Score “No” if the intervention itself was likely to affect data collection (for example, any change in source or method of data collection reported). |
| **Was knowledge of the allocated interventions adequately prevented during the study?[3]** |
| Score “Yes” if the authors state explicitly that the primary outcome variables were assessed blindly, or the outcomes are objective, e.g. length of hospital stay. Primary outcomes are those variables that correspond to the primary hypothesis or question as defined by the authors. Score “No” if the outcomes were not assessed blindly. Score “unclear” if not specified in the paper. |
| **Were incomplete outcome data adequately addressed?** |
| Score “Yes” if missing outcome measures were unlikely to bias the results (e.g. the proportion of missing data was similar in the pre- and post-intervention periods or the proportion of missing data was less than the effect size i.e. unlikely to overturn the study result). Score “No” if missing outcome data was likely to bias the results. Score “Unclear” if not specified in the paper (Do not assume 100% follow up unless stated explicitly). |
| **Was the study free from selective outcome reporting?** |
| Score “Yes” if there is no evidence that outcomes were selectively reported (e.g. all relevant outcomes in the methods section are reported in the results section). Score “No” if some important outcomes are subsequently omitted from the results. Score “unclear” if not specified in the paper. |
| **Was the study free from other risks of bias?** |
| Score “Yes” if there is no evidence of other risk of biases.<br>e.g. should consider if seasonality is an issue (i.e. if January to June comprises the preintervention period and July to December the post, could the “seasons’ have caused a spurious effect). |

# Appendix P: CG64 original scope

## 1 Guideline title

Antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures

### *1.1 Short title*

Prophylaxis against infective endocarditis

## 2 Background

a) The Department of Health has asked the National Institute for Health and Clinical Excellence ('NICE' or 'the Institute') to prepare guidance on 'antimicrobial prophylaxis against endocarditis for adults and children undergoing an interventional procedure (including dentistry)'. The guideline will provide recommendations for good practice that are based on the best available evidence of clinical and cost effectiveness.

b) The Institute's clinical guidelines will support the implementation of National Service Frameworks (NSFs) in those aspects of care where a Framework has been published. The statements in each NSF reflect the evidence that was used at the time the Framework was prepared. The clinical guidelines and technology appraisal guidance published by the Institute after an NSF has been issued will have the effect of updating the Framework.

c) NICE clinical guidelines support the role of healthcare professionals in providing care in partnership with patients, taking account of their individual needs and preferences, and ensuring that patients (and their carers and families, where appropriate) can make informed decisions about their care and treatment.

## 3 Clinical need for the guideline

a) Infective endocarditis (IE) is an inflammation of the inner lining of the heart, particularly affecting the heart valves, caused by bacterial or other

infections. It is a rare condition, with an annual incidence of less than 10 per 100,000 population. It is, however, a life-threatening disease with significant mortality (approximately 20%) and morbidity. IE predominantly affects people with underlying structural cardiac defects, both congenital and acquired, who develop bacteraemia (presence of bacteria in the blood) with organisms likely to cause IE. People with underlying structural cardiac defects constitute an important patient group ‘at risk’ of developing IE.

b) The prevention of IE has focused on the need to reduce bacteraemia in people at risk. This approach has three components: promotion of good oral health, timely treatment of sepsis and giving antimicrobial prophylaxis to at-risk people undergoing an interventional procedure that is considered likely to cause bacteraemia. The frequency of bacteraemia after healthcare procedures varies depending on type and site of the procedure. There is, however, controversy about whether procedure-based bacteraemia causes IE. There is a view that cumulative bacteraemia, caused by everyday activities like eating and tooth brushing, is more likely to cause IE, particularly in the case of dental procedures (including dentogingival manipulation).

c) It is considered biologically plausible that antimicrobial prophylaxis can reduce the risk of developing IE in people at risk. There is support for this position from laboratory animal models, although there is controversy about whether laboratory animal models can explain the pathophysiology of spontaneous IE in humans. The rarity of IE means that it is difficult to undertake controlled clinical trials, so evidence about the effectiveness of antimicrobial prophylaxis in reducing the risk of developing IE is likely to come from well conducted observational studies. Potential risks of inappropriate use of antibiotics include serious adverse events (such as anaphylaxis) and development of antimicrobial resistance.

d) There is currently conflicting UK guidance relating to prophylaxis for IE. The chief area of controversy relates to the need for antibiotic prophylaxis for dental procedures, where there is concern that the likelihood of

preventing IE by using antibiotics is less than the risk of the antibiotics causing serious adverse events.

# 4 The guideline

a) This document is the scope. It defines exactly what this guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health.

b) The areas that will be addressed by the guideline are described in the following sections.

## *4.1 Population*

### 4.1.1 Groups that will be covered

a) Adults and children with known underlying structural cardiac defects, including those who have previously had IE.

b) Adults and children who have previously had IE (irrespective of whether they have a known underlying cardiac defect).

c) There are no additional subgroups of patients who may need specific consideration in their treatment or care.

### 4.1.2 Groups that will not be covered

a) People at increased risk of IE who do not have structural cardiac defects (such as intravenous drug users).

## *4.2 Healthcare setting*

a) Primary dental care, primary medical care and community settings.

b) Secondary care.

## *4.3 Clinical management*

a) Definition of people with structural heart lesions at risk of developing IE. This will include classifying structural heart lesions into those at risk and those not at risk of IE.

b) Definition of interventional procedures considered to need antimicrobial prophylaxis for IE for specific at-risk groups. This will include:

- Dental procedures.
- Other interventional procedures if there is considered to be an increased risk of IE in at-risk people. The following sites will be covered.
  - Upper and lower gastrointestinal (GI) tract.
  - Genitourinary tract. This includes urological, gynaecological and obstetric procedures (including childbirth).
  - Upper and lower respiratory tract. This includes ear nose and throat and bronchoscopy procedures.

c) Antimicrobial regimen to be used. This will include:

- specifying antibiotics that may be used
- the role of chlorhexidine mouthwash.

d) The guideline will not offer detailed recommendations on the route of administration, timing and duration of antibiotic and antimicrobial regimen(s). It is anticipated that the GDG and technical team will liaise with the 'British National Formulary' to ensure that the March 2008 'British National Formulary' publication will provide advice for clinicians that complements this guideline.

e) The information needs of patients regarding the benefits and risks of antimicrobial prophylaxis for IE. This will specifically include advice regarding body piercing and tattooing that involves damage to mucosal tissue.

f) The guideline defines IE as bacterial endocarditis. Non-infective, fungal and atypical bacterial causes of IE will not be considered.

g) The Guideline Development Group will take reasonable steps to identify ineffective interventions and approaches to care. If robust and credible recommendations for re-positioning the intervention for optimal use, including the identification of appropriate patient subgroups, or changing the approach to care to make more efficient use of resources, can be

made, they will be clearly stated. If the resources released are substantial, consideration will be given to listing such recommendations in the 'Key priorities for implementation' section of the guideline.

## *4.4 Key outcome measures*

Key outcomes that will be considered when reviewing the evidence include:

- risk of dental and other interventional procedures causing IE
- risk of antibiotics prescribed for prophylaxis causing serious adverse events, for example anaphylaxis, in 'at risk' population
- mortality and/or morbidity (for example congestive cardiac failure)
- health-related quality of life
- resource use and costs.

## *4.5 Economic aspects*

The developers will take into account the cost-effectiveness of antimicrobial (principally antibiotic) prophylaxis against infective bacterial endocarditis in people undergoing the interventional procedures described in section 4.3b. .

## *4.6 Status*

### 4.6.1 Scope

This is the final version of the scope.

### 4.6.2 Guideline

The development of the guideline recommendations will begin in July 2007.

# 5 Further information

Information on the guideline development process is provided in:

- 'The guideline development process: an overview for stakeholders, the public and the NHS'
- 'Developing NICE guidelines - the Manual 2014'.

These booklets are available as PDF files from the NICE website (www.nice.org.uk/guidelinesmanual). Information on the progress of the guideline will also be available from the website.

The Guideline Development Group will work in accordance with the methods set out in the documents above. The short clinical guidelines programme is in development and will be consulted on.