NICE Medicines and prescribing centre

Antimicrobial stewardship

Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use

Medicines practice guideline

Appendices

August 2015

National Institute for Health and Care Excellence

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Appendices

Appendix A: Declarations of interest

A.1 Guideline development group (GDG) members

Alastair Hay (Chair)

GDG meeting	Declaration of interest	Action taken
Recruitment	None	None
First GDG meeting (3 June 2014)	Member of Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection. Would like to be aware of evidence gaps and GDG research recommendations that could influence future research programme.	Project lead will monitor for any potential conflict. Advice given regards ensuring that information learnt as part of the NICE guideline process is not shared with other committees/groups etc.
Second GDG meeting (8 September 2014)	Has an interest in the longitude prize, no financial interests, no involvement in any new antimicrobials.	None
Third GDG meeting (30 September 2014)	No changes to record	None
Fourth GDG meeting (14 November 2014)	No financial conflicts of interest to declare. Lead a group at the University of Bristol conducting research into primary care infections and antimicrobial resistance.	Advice given regards ensuring that information learnt as part of the NICE guideline process is not shared with other committees/groups etc.
Fifth GDG meeting (14 April 2015)	No changes to record	None

Tessa Lewis (Vice-chair)

GDG meeting	Declaration of interest	Action taken
Recruitment	None	None
First GDG meeting (3 June 2014)	No changes to record	None

GDG meeting	Declaration of interest	Action taken
Second GDG meeting (8 September 2014)	No changes to record	None
Third GDG meeting (30 September 2014)	No changes to record	None
Fourth GDG meeting (14 November 2014)	No changes to record	None
Fifth GDG meeting (14 April 2015)	No changes to record	None

Chris Cefai

GDG meeting	Declaration of interest	Action taken
Recruitment	None	None
First GDG meeting (3 June 2014)	No changes to record	None
Second GDG meeting (8 September 2014)	No changes to record	None
Third GDG meeting (30 September 2014)	No changes to record	None
Fourth GDG meeting (14 November 2014)	No changes to record	None
Fifth GDG meeting (14 April 2015)	No changes to record	None

Esmita Charani (until 27 November 2014)

GDG meeting	Declaration of interest	Action taken
Recruitment	None	None
First GDG meeting (3 June 2014).	Published in peer reviewed journals.	Advice given regards ensuring that information learnt as part of the NICE guideline process is not shared with other committees/groups or included within any written articles. Reminded that opinions expressed that may be relevant to

GDG meeting	Declaration of interest	Action taken
		the guideline may lead to a conflict of interest.
Emailed 31 July 2014	Published author on research into antimicrobial stewardship interventions and behaviour change in this field including Cochrane reviews (one ongoing at present). Has also published research on use of mobile health technology to deliver antimicrobial stewardship interventions. Salary is funded by the National Institute of Health Research on a grant investigating behaviour change in antimicrobial prescribing. Honorary visiting researcher to Haukeland University in Norway where advice on the implementation of the national implementation of an antimicrobial stewardship programme.	Chair and Project lead will monitor for any potential conflict. Also discussed with the Nice Medicines and prescribing centre Programme Director. Advice given regards ensuring that information learnt as part of the NICE guideline process is not shared with other committees/groups or included within any written articles.
Second GDG meeting (8 September 2014)	No changes to record	None
Third GDG meeting (30 September 2014)	No changes to record	None
Fourth GDG meeting (14 November 2014)	Undertaking research at PhD level into antibiotic prescribing behaviours in secondary care. Published author in the field of antibiotic prescribing behaviours and antimicrobial stewardship.	Chair and Project lead will monitor for any potential conflict. Advice given regards ensuring that information learnt as part of the NICE guideline process is not shared with other committees/groups or included within any written articles.

Lynne Craven

GDG meeting	Declaration of interest	Action taken
Recruitment	None	None
First GDG meeting (3 June 2014)	No changes to record	None
Second GDG meeting (8 September 2014)	No changes to record	None
Third GDG meeting (30	No changes to record	None

GDG meeting	Declaration of interest	Action taken
September 2014)		
Fourth GDG meeting (14 November 2014)	No changes to record	None
Fifth GDG meeting (14 April 2015)	No changes to record	None

Martin Duerden

GDG meeting	Declaration of interest	Action taken
Recruitment	Received personal payment (honoraria) plus reimbursement of expenses from Reckitt Benckiser (RB) to speak at 2 meetings in the last 12 months. The subject of the talks was antibiotic use in respiratory infections at each meeting but there was no promotion of products marketed by RB in the content. In the last 12 months has also received payment from the publishers of Pulse, GP and Prescriber for writing various articles on prescribing and therapeutics, including antibiotic use.	Advice given regards ensuring that information learnt as part of the NICE guideline process is not shared with other committees/groups or included within any written articles. Advised not to write for any publication until the guideline has published.
First GDG meeting (3 June 2014)	Clinical Adviser on Prescribing for the Royal College of General Practitioners but does not receive payment for this.	None
Emailed 26 August 2014	Member of the Global Respiratory Infection Partnership (work declared above with RB done in this capacity). Now spoken at 4 meetings in the last 12 months. On the Editorial Board of Drug and Therapeutics Bulletin, a BMJ Group publication, this is a paid position. On the editorial board of Prescriber (a Wiley publication) which is an unpaid position. Occasionally writes opinion based editorials and articles for this publication. Receives payments for these. In the last year was commissioned and co-wrote a report on Polypharmacy for the King's Fund and received	Advice given regards ensuring that information learnt as part of the NICE guideline process is not shared with other committees/groups or included within any written articles. Advised not to write for any publication until the guideline has published.

GDG meeting	Declaration of interest	Action taken
	payment for this. Also spoke at a King's Fund seminar on the topic. I am a member of the Paediatric Formulary Committee for the British National Formulary (BNF) payment not received for this.	
Second GDG meeting (8 September 2014)	No changes to record	None
Third GDG meeting (30 September 2014)	No changes to record	None
Fourth GDG meeting (14 November 2014)	Recently has received small payments for articles on the Lipid Modification Clinical Guideline from Pulse and from Guidelines in Practice. Member of the NICE Guideline Development Group on Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. On the Medicines Committee for the Royal College of Paediatrics and Child Health - payment not received for this. Member of the NICE technology appraisals Committee until October 2014. This is not a paid position.	Advice given regards ensuring that information learnt as part of the NICE guideline process is not shared with other committees/groups or included within any written articles. Chair and Project lead will monitor for any potential conflict.
Fifth GDG meeting (14 April 2015)	No changes to record	None

Heather Edmonds

GDG meeting	Declaration of interest	Action taken
Recruitment	None	None
First GDG meeting (3 June 2014)	No changes to record	None
Second GDG meeting (8 September 2014)	No changes to record	None

GDG meeting	Declaration of interest	Action taken
Third GDG meeting (30 September 2014)	No changes to record	None
Fourth GDG meeting (14 November 2014)	No changes to record	None
Fifth GDG meeting (14 April 2015)	Presented at workshops for commissioners introducing the proposed new national Antimicrobial Prescribing Quality Premium and guide commissioners towards resources and best practice –March 2015 in Leeds. Delivered a session on sharing success and the work that has been done within Leeds.No financial payment was received for presenting.	None

Rose Gallagher

GDG meeting	Declaration of interest	Action taken
Recruitment	None	None
Second GDG meeting (8 September 2014)	Involved in a Royal College of Nursing published position statement which was sponsored by Pfizer.	Chair and Project lead will monitor for any potential conflict Advice given regards ensuring that information learnt as part of the NICE guideline process is not shared with other committees/groups etc.
Third GDG meeting (30 September 2014)	No changes to record	None
Fourth GDG meeting (14 November 2014)	No changes to record	None
Fifth GDG meeting (14 April 2015)	No changes to record	None

Philip Howard

GDG meeting	Declaration of interest	Action taken
Recruitment	Paid consultancy work on antibiotics for the pharmaceutical industry i.e. Pfizer (Linezolid), Astellas	Advised not to undertake any further consultancy work in this area during the development of the guideline through to

GDG meeting	Declaration of interest	Action taken
	(Levofloxacin), AstraZeneca (Ceftaroline), Novartis (Daptomycin), Gilead (Ambisome).	publication.
First GDG meeting (3 June 2014)	Paid consultancy work with Danone on antimicrobial stewardship. Committee member of UK Clinical Pharmacy Association - Pharmacy Infection Network. Council member of British Infection Association (until May 2013). Council member of British Society of Antimicrobial Chemotherapy. Represented International Pharmaceutical Federation (FIP) at WHO (World Health Organisation) Antimicrobial Resistance Strategic Technical Advisory Group (May 2014). Published unpaid articles related to AMS. Spokesman on Antimicrobials for Royal Pharmaceutical Society.	Advised not to undertake any further consultancy work in this area during the development of the guideline through to publication. Advice given regards ensuring that information learnt as part of the NICE guideline process is not shared with other committees/groups etc. Chair and Project lead will monitor for any potential conflict
12 August 2014	Involved in Antimicrobial Resistance Summit at the Royal Pharmaceutical Society in November 2014.	Advised that as the evidence of the NICE MPG will have been presented he will need to ensure that information he has learnt as being on the GDG is not shared. He agreed and understood.
Second GDG meeting (8 September 2014). Interests emailed 7 September 2014.	Sponsorship to present work at international conferences (no money received directly): European Advisory Board on pipeline antibiotics (January 2014) funded by Sanofi. Lecture on *Clostridium difficile* multicentre local service evaluation of fidaxomycin Lecturing/consultancy about: • role of the pharmacist in antimicrobial stewardship • antimicrobial medicine specific topics • data warehousing	Project lead reiterated the importance that work from this group is not shared with other work that he is involved with. Chair and Project lead will monitor for any potential conflict.

GDG meeting	Declaration of interest	Action taken
	• pipeline agents Carried out in September/October 2014. Fees paid into Leeds Teaching Hospitals NHS Trust Charitable Trustees funding from Astellas, Baxter, Pfizer and Cubist. Sponsorship to present work at international conferences (no money received directly): • European Association of Hospital Pharmacy (B. Braun 2013 and 2014) • European Congress of Clinical Pharmacy and Infectious Diseases (Gilead 2014). Received expenses and conference paid directly to conference. Paid by College of Pharmacy Practice and Education to develop Antimicrobials in Focus (Antimicrobial Stewardship for Community Pharmacists). Research funding from Novartis and Astellas paid directly to an independent audit company to undertake audit. Audits not directly related to antimicrobial stewardship topic. Committee member of European Society of Clinical Microbiology and Infectious Diseases, Antimicrobial Stewardship Group (ESGAP). Member of the Department of Health/Public Health England ESPAUR group. Department of Health ARHAI (Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection) Start Smart then Focus guidance for hospitals group. PHE (Public Health England) & RCGP (Royal College of General Practitioners) TARGET AMS for primary care group. PHE (Public Health England)/Department of Health Competencies of Antimicrobial Prescribing and	

GDG meeting	Declaration of interest	Action taken
	Antimicrobial Stewardship. Lead a research project on surveying Antimicrobial Stewardship in hospitals across the world. Part of a research group developing an Antimicrobial guideline application with a European group “Panacea”. Part of a joint NIHR (National Institute for Health Research) Programme grant AMR themed call on behalf of Leeds and Oxford Universities on Antimicrobial Allergy. Antimicrobial Resistance round table group (unfunded) with AstraZeneca to help pharmaceutical industry discussion with Government. Lecture at Clinical Pharmacy Congress (2013 and 2014). Updates provided on respiratory infections in 2013. Updates provided on *C. difficile*, ESBL and drug allergy in 2014. Payment received directly.	
Third GDG meeting (30 September 2014)	No changes to record	None
Fourth GDG meeting (14 November 2014)	Speaker for Royal Pharmaceutical Society at the Royal Colleges Summit on Antimicrobial Resistance. No payment received. Introduction of proposed ESPAUR / NHS-England on Quality Premium to reduce antibiotic prescribing. Secondment to NHS England as Regional Healthcare Associated Infections Project Lead from November 2014 to March 2015. Speaker at British Society for Antimicrobial Chemotherapy Antimicrobial Stewardship conference in India. British Society of Antimicrobial Chemotherapy (BSAC) workshop on antimicrobial stewardship in India (27-28 November 2014).	Project lead reiterated the importance that work from this group is not shared with other work involved with. Chair and Project lead will monitor for any potential conflict.

GDG meeting	Declaration of interest	Action taken
Interests emailed 12 February 2015	BSAC workshop on antimicrobial stewardship in Bahrain (24-26 February 2015) BSAC round table talk on Pharmacy's role in antimicrobial stewardship Advisory board for new pipeline product, Durata (February 2015). Fees paid into Leeds Teaching Hospitals NHS Trust Charitable Trustees.	
Fifth GDG meeting (14 April 2015)	Advisory boards for: • Durata (Dalbavancin) (February 2015) • Cubist (Tedezolid) (March 2015) Payment to be made to employer (Leeds Teaching Hospitals) for time Attendance at European Association of Hospital Pharmacy conference. B.Braun paid for accommodation, travel paid and attendance. No direct payment received. Secondment to NHS England as Regional Healthcare Associated Infections Project Lead from November 2014 to March 2015. Extended to June 2015. NHS-England payment to Leeds Teaching Hospital Trust for time. Speaker at 3 Antimicrobial resistance study day for NHS Commissioners and a single C.difficile day (March 2015) (NHS-England role) GP C. difficile event in Hull (NHS-England role) Part of a Public Health England project on Tailoring Antimicrobial Programmes Speaker at British Society of Antimicrobial Chemotherapy Gulf Antimicrobial Stewardship conference in Bahrain	None. Advised that the GDG discussions remain confidential although the draft guideline contents can be used now they are in the public domain.

GDG meeting	Declaration of interest	Action taken
	National Sepsis Programme Board (March 2015 onwards) POC CRP testing in Primary Care (Alere) - Feb-15	

Sanjay Kalra

GDG meeting	Declaration of interest	Action taken
Recruitment	None	None
Second GDG meeting (8 September 2014)	No changes to record	None
Third GDG meeting (30 September 2014)	No changes to record	None
Fourth GDG meeting (14 November 2014)	No changes to record	None
Fifth GDG meeting (14 April 2015)	No changes to record	None

Kym Lowder

GDG meeting	Declaration of interest	Action taken
Recruitment	None	None
First GDG meeting (3 June 2014)	Associate for the NICE Medicines & Prescribing Centre	Advice given regards ensuring that information learnt as part of the NICE guideline process is not shared with other committees/groups etc.
Second GDG meeting (8 September 2014)	No changes to record	None
Third GDG meeting (30 September 2014)	No changes to record	None
Fourth GDG meeting (14	No changes to record	None

GDG meeting	Declaration of interest	Action taken
November 2014)		
Fifth GDG meeting (14 April 2015)	No changes to record	None

Cliodna McNulty

GDG meeting	Declaration of interest	Action taken
Recruitment	Stated no conflicts to declare, Spoken at antimicrobial resistance symposiums sponsored by public bodies and one by bioMeriuex but receives no payment. Leads the development of national Public Health England antibiotic and lab use guidance for GP's which covers the diagnosis and treatment of *Urinary tract infections.* She has received grants from several publically funded research bodies.	Advice given regards ensuring that information learnt as part of the NICE guideline process is not shared with other committees/groups etc.
First GDG meeting (3 June 2014)	Member of Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection	Advice given regards ensuring that information learnt as part of the NICE guideline process is not shared with other committees/groups etc.
6 August 2014	Observer on British Society for Antimicrobial Chemotherapy Council Member of English surveillance programme for antimicrobial utilisation and resistance Lead in the development of Treat Antibiotics Responsibly, Guidance, Education, Tool s (TARGET) and promotes the TARGET resources hosted by the Royal College of General Practitioners	Advice given regards ensuring that information learnt as part of the NICE guideline process is not shared with other committees/groups etc.
Second GDG meeting (8 September 2014)	Involved in judging the longitude prize.	None
Third GDG meeting (30 September 2014)	No changes to record	None
Fourth GDG meeting (14 November 2014)	No changes to record	None
Fifth GDG meeting (14 April 2015)	No changes to record	None

John Morris

GDG meeting	Declaration of interest	Action taken
Recruitment	None	None
First GDG meeting (3 June 2014)	No changes to record	None
Second GDG meeting (8 September 2014)	No changes to record	None
Third GDG meeting (30 September 2014)	No changes to record	None
Fourth GDG meeting (14 November 2014)	No changes to record	None
Fifth GDG meeting (14 April 2015)	No changes to record	None

Sanjay Patel

GDG meeting	Declaration of interest	Action taken
Recruitment	None	None
4 August 2014	Attended advisory board meeting organised by Hayward Medical Communications on 16/05/14 to discuss procalcitonin: event organised on behalf of Thermo Fischer. Honorarium paid to University Hospital Southampton, travel expenses reimbursed.	Advice given regards ensuring that information learnt as part of the NICE guideline process is not shared with other committees/groups etc.
Second GDG meeting (8 September 2014)	Has written a paper on AMS.	
Third GDG meeting (30 September 2014)	No changes to record	None
Fourth GDG meeting (14 November 2014)	No changes to record	None
Fifth GDG meeting (14 April 2015)	Author of book chapter about antimicrobial stewardship in paedatric care. Manuscript prepared April 2015 for Oxford University Press.	None

Wendy Thompson

GDG meeting	Declaration of interest	Action taken
Recruitment	None	None
First GDG meeting (3 June 2014)	No changes to record	None
Second GDG meeting (8 September 2014)	Has had a relevant journal article published.	Advice given regards ensuring that information learnt as part of the NICE guideline process is not shared with other committees/groups or included within any written articles.
Third GDG meeting (30 September 2014)	Lectured to foundation dentists on antimicrobial prescribing in general dental practice guidance to Foundation Dentists in Health Education (North East) Lecturer on AMS prescribing at a Local Professional Network event in Chester in in November and sponsored by Colgate.	Advice given regards ensuring that information learnt as part of the NICE guideline process is not shared with other committees/groups or included within any written articles.
Fourth GDG meeting (14 November 2014)	No changes to record	None
Fifth GDG meeting (14 April 2015)	Offer received from Leeds Unviersity re PhD sponsored financially by Leeds University entitled educating patients about dental treatment rather than antibiotic prescriptions for dental pain Lecturing at British Dental Association Conference on prescribing standards and guidance – May 2016 – no financial gain	None

Susan Walsh

GDG meeting	Declaration of interest	Action taken
Recruitment	Represents and works for organisations that support people with faulty immune systems. Antimicrobials are life-saving medicines for these patients.	None
First GDG meeting (3 June 2014)	Primary Immunodeficiency UK (PID UK) received two grants from CSL Behring in the last 12 months. They were unrestricted and were unrelated to antimicrobials.	None
Second GDG meeting (8 September 2014)	No changes to record	None

GDG meeting	Declaration of interest	Action taken
Third GDG meeting (30 September 2014)	No changes to record	None
Fourth GDG meeting (14 November 2014)	Restricted grant from Biotest UK Ltd to PID UK. Sponsorship from Bio Products Laboratory Ltd to attend European Society for an Immunodeficiencies conference – unrelated to antimicrobial stewardship.	None
Fifth GDG meeting (14 April 2015)	Appointment as community member of PHAC: guideline on 'Antimicrobial resistance: changing risk-related behaviours in the general population' (confirmed 27th January 2015).	None

Appendix B: Scope

Guideline title

Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use.

Short title

Antimicrobial stewardship.

The remit

The Department of Health and Public Health England have agreed that NICE should develop a guideline on antimicrobial stewardship.[a]

Need for the guideline

- Awareness of antimicrobial resistance is important in ensuring the antimicrobial medicines are used when needed but that use is reduced without an increase in harm when use is not indicated. Resistance to all antimicrobials is increasing and, combined with a lack of new medicines, there is an increasing risk in the future that infections may not be able to be treated.
- The Annual Report of the Chief Medical Officer, Volume Two, 2011, Infections and the rise of antimicrobial resistance states that antimicrobial stewardship 'embodies an organisational or healthcare-system-wide approach to promoting and monitoring judicious use of antimicrobials to preserve their future effectiveness'. It is not a new concept and several publications have been issued in response to combating antimicrobial resistance and ensuring appropriate use of antimicrobials. For the purpose of the guideline the World Health Organization (WHO) definition will be used to describe antimicrobial resistance.
- The Executive Board of the World Health Organization considers antimicrobial resistance to be the 'loss of effectiveness of any anti-infective medicine, including antiviral, antifungal, antibacterial and antiparasitic medicines'. The WHO states further that 'When the microorganisms become resistant to most antimicrobials they are often referred to as "superbugs". This is a major concern because a resistant infection may kill, can spread to others, and imposes huge costs to individuals and society.' The WHO Antimicrobial resistance: global report on surveillance 2014 provides 'as accurate a picture as is presently possible of the magnitude of [antimicrobial resistance] and the current state of surveillance globally'.
- The Annual Report of the Chief Medical Officer, Volume Two, 2011, Infections and the rise of antimicrobial resistance (Department of Health, 2013) reviews infectious disease in England and the rise of antimicrobial resistance. It discusses the importance of antimicrobial stewardship and preserving the effectiveness of existing antimicrobials. It describes 3 major goals that have been identified for antimicrobial stewardship:
  - optimise therapy for individual patients
  - prevent overuse, misuse and abuse
  - minimise development of resistance at patient and community levels.

  The report also states that evidence-based guidance is needed for antimicrobial use, with particular consideration given to increasing awareness of heterogeneity of prescribing to help slow the development of antimicrobial resistance.

[a] NICE is also developing public health guidance on Antimicrobial resistance: changing risk-related behaviours.

- In 2013, the Department of Health published the UK five year antimicrobial resistance strategy 2013 to 2018, which aims to slow the development and spread of antimicrobial resistance. The strategy states that antimicrobial resistance cannot be eradicated but by using a multidisciplinary approach, the risk of antimicrobial resistance can be limited and its impact on health now and in the future can be reduced. The report describes 3 strategic aims, to:
  - improve the knowledge and understanding of antimicrobial resistance
  - conserve and steward the effectiveness of existing treatments
  - stimulate the development of new antibiotics, diagnostics and novel therapies.
- The Department of Health also carried out an impact assessment (Antimicrobial resistance strategy impact assessment) alongside the 5-year strategy. This supports the introduction of the strategy and highlights issues such as the importance of preserving current effective therapies and focusing on the appropriate use of antimicrobials (including using the correct antimicrobial, dose and duration of treatment for every prescription, and using them wisely and sparingly).
- To further support the 5-year antimicrobial strategy, the document Antimicrobial prescribing and stewardship competencies (Department of Health and Public Health England, 2013) was published. The competencies aim to improve the quality of antimicrobial treatment and stewardship, and so reduce the risks and ill-effects of inadequate and inappropriate treatment.
- In 2011 the Department of Health Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection published Antimicrobial stewardship: Start smart - then focus providing guidance for antimicrobial stewardship in hospitals in England. However, the principles of this guidance can be applied to all antimicrobial prescribing. The guidance also stresses the importance of clear governance arrangements when managing antimicrobial resistance.
- The TARGET toolkit has been developed by the RCGP, PHE and The Antimicrobial Stewardship in Primary Care (ASPIC) in collaboration with professional societies as a central resource for clinicians and commissioners about safe, effective, appropriate and responsible antibiotic prescribing.
- Public Health England in its response to the antimicrobial strategy has established a new national programme, the English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR). The programme aims to monitor and enhance the use of antimicrobials in the community and in hospitals in England through measuring antimicrobial utilisation, the impact on resistance and patient safety.
- For managing infections in the community, the Health Protection Agency[b] first published Management of infection guidance for primary care for consultation and local adaption in 2000 (reviewed in 2010). The guidance provides an overview of the treatment options for managing common infections in the community, and aims to lead to more appropriate antibiotic use.
- The Health Protection Agency[1] has also published an Acute trust toolkit for the early detection, management and control of carbapenemase-producing Enterobacteriaceae (2013) provides 'practical advice for frontline clinicians and staff to prevent or reduce spread of these bacteria'.
- NICE has issued guidance on Respiratory tract infections – antibiotic prescribing (CG69) which provides recommendations for the prescribing of antibiotics for self-limiting respiratory tract infections in adult and children in primary care and Infection (CG139) which provides recommendations for prevention and control of healthcare-associated infections in primary and community care. These guidelines support effective management of these common conditions again aiming to reduce antimicrobial resistance and use antimicrobials appropriately.

[b] The Health Protection Agency (HPA) is now part of Public Health England.

- As highlighted, several initiatives and guidance have been published to attempt to tackle the growing concern of appropriate use of antimicrobials and antimicrobial resistance; despite these however, prescribing is still variable. This medicines practice guideline is needed to consider the evidence for effective interventions in this area of practice, in particular for changing prescriber and patient behaviour when using antimicrobials and for minimising antimicrobial resistance.

Data on resistance and antimicrobial use

There are still wide variations in prescribing across primary care organisations. Limited data on secondary care prescribing also shows variation, but these data are not routinely available.

- In the NHS in England, as part of the 'Quality, Innovation, Productivity and Prevention' (QIPP) medicines use and procurement work stream several specific topics relating to antimicrobials were identified. These topics are:
  - Antibiotic prescribing – especially quinolones and cephalosporins
  - Three-day courses of trimethoprim for uncomplicated urinary tract infection
  - Minocycline

  The topics are based on new guidance and important new evidence, and include prescribing data.
- NHS Prescription services annual National Antibiotic Charts show that antibiotic prescribing in general practice in England over the last 5 years has broadly remained constant in relation to breakdown of different antibiotic prescribing. However, the overall use of antibiotics has steadily increased over several years. The most common antibiotic group prescribed is penicillins, followed by tetracyclines and macrolides. Broad-spectrum penicillins comprised 36% of all antibacterial prescribing in 2012-13. However, the prescription and use of cephalosporin antibiotics has declined following initiatives to reduce prescribing.
- In 2013 the Health and Social Care Information Centre published Prescriptions dispensed in the community: England 2002-13 which provides an overview of the changes in dispensed items between 2012 and 2013. The bulletin states that 'The BNF Section with the largest increase in cost between 2011 and 2012 was Antibacterial Drugs, where costs rose by £25.1 million (14.8 per cent) to £195.4 million. The number of items dispensed increased by 2.5 million, (6.1 per cent) to 43.3 million.'
- Prescribing data collected in hospital and community are not comparable when using items. The common comparator that can be used for comparing data is the cost of prescribing. Hospital prescribing: England 2012 shows that the cost of antimicrobials is greater in the hospital setting compared to primary care. The cost of prescribing antimicrobials in both settings has increased over time. This increased cost may correspond to an increase in usage although this cannot be certain.
- Prescribing data for some services, including urgent care (out-of-hours) centres, are not available for England as the supply of medicines is directly to the patient and is funded and monitored locally. These data are not collated nationally and therefore do not appear in national datasets.

The guideline

The guideline development process is described in detail on the NICE website.

This scope defines what the 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.[c]

[c]NICE is also developing public health guidance on Antimicrobial resistance: changing risk-related behaviours.

All anti-infective therapies will be considered in the scope (antiviral, antifungal, antibacterial and antiparasitic medicines), additionally all formulations will be considered within the scope (oral, parenteral and topical agents).

The areas that will be addressed by the guideline are described in the following sections.

Population

Groups that will be covered

- Health and social care practitioners (a term used to define the wider care team including hospital staff [including microbiologists and infection control staff], community matrons and case managers, GPs, pharmacists and community nurses [including those staff working in out-of-hours services], domiciliary care workers and care home staff [registered nurses and social care practitioners working in care homes], social workers and case managers).
- Organisations commissioning (for example clinical commissioning groups or local authorities), providing or supporting the provision of care (for example national or professional bodies, Directors of Public Health, Health and Wellbeing Boards, healthcare trusts and locum agencies).
- Adults, young people and children (including neonates) using antimicrobials, or those caring for these groups.

Groups that will not be covered

- None.

Setting

- All publicly funded health and social care commissioned or provided by NHS organisations, local authorities (in England), independent organisations or independent contractors.
- This guideline may also be relevant to individual people and organisations delivering non-NHS healthcare services, and to other devolved administrations.

Key issues

Areas that will be covered

- Supporting antimicrobial use by health and social care practitioners where their use is indicated.
- Reducing the use of antimicrobials without increasing harm through changing behaviour of health and social care practitioners and patients or their carers.
- Reducing emergence of antimicrobial resistance through effective antimicrobial stewardship.

Areas that will not be covered

- The use of specific named medicines (although classes of medicines for example broad spectrum antibiotics will be referred to).
- Public health awareness of antimicrobial resistance and self-care as this will be covered by NICE Public Health guidance (see Antimicrobial resistance: changing risk-related behaviours).
- Treatment of specific clinical conditions (such as healthcare-associated infections [see CG139 – Infection] and respiratory tract infections [see CG69 – Respiratory tract infection: Antibiotic prescribing]).

- Research for new antimicrobials.
- Immunisation and vaccination.
- Antimicrobial household cleaning products.
- Antimicrobials use in animals.
- Hand-hygiene, decolonisation and infection prevention and control measures.
- Medicines adherence except where there are specific issues for health and social care practitioners to address for antimicrobials. The general principles of medicines adherence are covered by CG76 – Medicines adherence: Involving patients in decisions about prescribed medicines and supporting adherence,
- Access to medicines, including local-decision making for drugs not included on local formularies.
- Medicines shortages, including supply issues and discontinued medicines.
- Prescription charges.
- Waste medicines.

Main outcomes

- Clinical outcomes such as:
  - mortality and morbidity
  - infection cure rates or time to clinical cure
  - surgical infection rates
  - re-infection rates.
- Antimicrobial use as measured by change in the variation over time and movement of the mean over time.
- Presence, emergence and incidence of organisms resistant to antimicrobials.
- Health and social care related quality of life.
- Healthcare-associated infections.
- Community-associated infections.
- Side effects, adverse events and critical incidents.
- Hospitalisation and health and social care utilisation.
- Planned and unplanned contacts with health professionals or services.
- Patient-reported outcomes, such as medicines adherence related specifically to issues of antimicrobial stewardship, patient experience, patient satisfaction with decision-making, patient information and patient expectations.
- Professional belief systems and their attitude to the use of antimicrobials.
- No harm.

Economic aspects

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions. A review of the economic evidence will be conducted and analyses will be carried out as appropriate. The preferred unit of effectiveness is the quality-adjusted life year (QALY), and the costs considered will usually be only from an NHS and personal social services (PSS) perspective. Further detail on the methods of medicines practice guidelines can be found in interim methods guide and integrated process statement. Economic analyses of antimicrobial stewardship will demonstrate if interventions are cost effective.

Status

Scope

This is the final scope.

Timing

The development of the guideline recommendations will begin in May 2014.

Related NICE guidance

Published guidance and quality standards

Medicines practice guidelines

- Patient group directions. NICE medicines practice guideline 2 (2013).
- Developing and updating local formularies. NICE medicines practice guideline 1 (2012).

Clinical guidelines and quality standards

- Infection control NICE clinical guideline 139 (2012).
- Patient experience in adult NHS services. NICE clinical guideline 138 (2012).
- Patient experience in adult NHS services. NICE quality standard 15 (2012).
- Prevention and control of healthcare-associated infections NICE public health guidance 36 (2011).
- Medicines adherence. NICE clinical guideline 76 (2009).
- Respiratory tract infections (RTI) – antibiotic prescribing NICE clinical guideline 69 (2008).

Social care guidelines

- Managing medicines in care homes. NICE social care guideline 1 (2014).

Guidance under development

NICE is currently developing the following related guidance (details available from the NICE website):

- Drug allergy. NICE clinical guideline. Publication expected October 2014.
- Medicines optimisation. NICE clinical guideline. Publication expected TBC.
- Antimicrobial resistance: changing risk-related behaviours. NICE Public health guidance (in development).
- Antibiotics for neonatal infection. NICE Quality Standard (in development).
- Infection prevention and control. NICE Quality Standard (in development).

Further information

Information on the medicines practice guideline development process is provided in the following documents, available from the NICE website:

- 'Integrated process statement'
- 'Interim methods guide'

Information on the progress of the guideline will also be available from the NICE website.

Appendix C: How this guideline was developed

C.1 Search strategies for the guideline

C.1.1 Scoping searches

Scoping searches were undertaken on the following websites and databases (listed in alphabetical order) in January 2014 to provide information for scope development and project planning. Browsing or simple search strategies were employed. Examples of search terms included: antibiotic(s), antimicrobial(s), stewardship, “antibiotic resistance”, “antimicrobial resistance”, “antibiotic prescribing”, and “antimicrobial prescribing”.

Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection

Antibiotic Action

Association of the British Pharmaceutical Industry

bioMérieux

British Infection Association

British Medical Association

British Society for Antimicrobial Chemotherapy

CDSR (Cochrane Database of Systematic Reviews)
Clinical Knowledge Summaries
COMET (Core Outcome Measures in Effectiveness Trials)

DARE (Database of Abstracts of Reviews of Effects)

Department of Health

Department of Health, Social Services and Public Safety – Northern Ireland

DUETS (UK Database of Uncertainties about the Effects of Treatments)

EU Joint Programming Initiative on Antimicrobial Resistance

European Centre for Disease Control and Prevention

European Commission

European Public Health Alliance

European Society of Clinical Microbiology and Infectious Diseases

Health Infection Society

Health Protection Agency

Health Protection Scotland

Healthtalk Online

HTA (Health Technology Assessment) Database
Imperial College London

Infection Prevention Society

Infectious Disease Research Network

King's Fund

London School of Hygiene and Tropical Medicine

Map of Medicine

MRSA Action

National prescribing centre (NPA)

National Resource for Infection Control

NHS Choices

NHS England

NHS Wales

NICE (National Institute for Health and Care Excellence)

NICE Evidence Services

NIHR (National Institute for Health Research) Health Services and Delivery Research NIHR (National Institute for Health Research) Health Technology Assessment Programme

Patient UK

Prospero

Public Health England

ReAct (Action on Antibiotic Resistance)

Royal College of General Practitioners

Royal College of Nursing

Royal College of Pathologists

Royal College of Physicians

Scottish Government

Scottish Infection Research Network

Scottish Medicines Consortium - Scottish Antimicrobial Prescribing Group

SIGN (Scottish Intercollegiate Guidelines Network)

Society for General Microbiology

Trip (Turning Research into Practice) database

Welsh Government

World Health Organisation

YouthHealthTalk

C.1.2 Main searches

Sources searched for the guideline

- MEDLINE, MEDLINE In-Process, Embase, CDSR, DARE, CENTRAL, HTA, NHS EED

Identification of evidence for clinical questions

The searches were conducted between JULY 2014 and OCTOBER 2014.The aim of the searches was to identify evidence for each of the clinical questions. The MEDLINE search strategies and details of sources searched for each question are presented below. They were translated for use in all other databases.

C.1.2.1 Reducing antimicrobial resistance

The following search strategies were designed to identify the evidence-base for this review question. Study design filters to retrieve systematic reviews and randomised controlled trials were added to the strategies. Details of these filters can be found in section C.1.2.5.

Search strategy #1 (Antimicrobial resistance)

Database: Ovid MEDLINE(R)

---

1 exp Drug Resistance, Microbial/

2 exp Drug Resistance, Multiple/

3 ((microb$ or antimicrob$ or anti-microb$ or "anti microb$") adj4 (resist$ or tolera$)).tw.

4 ((antiinfect$ or anti-infect$ or "anti infect$") adj4 (resist$ or tolera$)).tw.

5 ((bacter$ or antibacter$ or anti-bacter$ or "anti bacter$") adj4 (resist$ or tolera$)).tw.

6 ((antibiot$ or anti-biot$ or "anti biot$") adj4 (resist$ or tolera$)).tw.

7 ((viral$ or antiviral$ or anti-viral$ or "anti viral$") adj4 (resist$ or tolera$)).tw.

8 ((fung$ or antifung$ or anti-fung$ or "anti fung$") adj4 (resist$ or tolera$)).tw.

9 ((parasit$ or antiparasit$ or anti-parasit$ or "anti parasit$") adj4 (resist$ or tolera$)).tw.

10 (multi$ adj4 drug$ adj4 (resist$ or tolera$)).tw.

11 (multidrug$ adj4 (resist$ or tolera$)).tw.

12 (multiresist$ or multi-resist$ or "multi resist$").tw.

13 (superbug$ or super-bug$ or "super bug$").tw.

14 Superinfection/

15 (superinvasion$ or super-invasion$ or "super invasion$" or superinfection$ or super-infection$ or "super infection$").tw.

16 R Factors/

17 "r factor$".tw.

18 (resist$ factor$ or "r plasmid$" or resist$ plasmid$).tw.

19 or/1-18

Search strategy #2 (De-escalation)

Database: Ovid MEDLINE(R)

---

1 exp Drug Resistance, Microbial/

2 exp Drug Resistance, Multiple/

3 ((microb$ or antimicrob$ or anti-microb$ or "anti microb$") adj4 (resist$ or tolera$)).tw.

4 ((antiinfect$ or anti-infect$ or "anti infect$") adj4 (resist$ or tolera$)).tw.

5 ((bacter$ or antibacter$ or anti-bacter$ or "anti bacter$") adj4 (resist$ or tolera$)).tw.

6 ((antibiot$ or anti-biot$ or "anti biot$") adj4 (resist$ or tolera$)).tw.

7 ((viral$ or antiviral$ or anti-viral$ or "anti viral$") adj4 (resist$ or tolera$)).tw.

8 ((fung$ or antifung$ or anti-fung$ or "anti fung$") adj4 (resist$ or tolera$)).tw.

9 ((parasit$ or antiparasit$ or anti-parasit$ or "anti parasit$") adj4 (resist$ or tolera$)).tw.

10 (multi$ adj4 drug$ adj4 (resist$ or tolera$)).tw.

11 ((multidrug* or multipathogen*) adj4 (resist$ or tolera$)).tw.

12 (multiresist$ or multi-resist$ or "multi resist$").tw.

13 (superbug$ or super-bug$ or "super bug$").tw.

14 Superinfection/

15 (superinvasion$ or super-invasion$ or "super invasion$" or superinfection$ or super-infection$ or "super infection$").tw.

16 R Factors/

17 "r factor$".tw.

18 (resist$ factor$ or "r plasmid$" or resist$ plasmid$).tw.

19 or/1-18

20 (adequacy or adequate or extended-spectrum* or appropriate or empiric or empirical or broad-spectrum or "broad spectrum").tw.

21 (de-escalation or "de escalation" or deescalate or "narrow spectrum" or narrow-spectrum or "narrower spectrum" or narrower-spectrum or narrowered-spectrum or "narrowered spectrum" or narrowing or adjustment or adjust or tailoring or tailored or tailor or downgrading or discontinue* or stop or stopping or stopped).tw.

22 or/20-21

23 19 and 22

C.1.2.2 Decision making

The following search strategy was designed to identify the evidence-base for this review question. Study design filters to retrieve systematic reviews (lines 122-132), randomised controlled trials (lines 133-147), and qualitative studies (148-159) were added to the strategy.

The Medline randomised controlled trials filter was limited by date to retrieve results from 2005 to the present day in accordance with the process described in the Cochrane Handbook for running supplementary searches to identify trials that are not indexed in the CENTRAL database.

Search strategy

Database: Ovid MEDLINE(R)

---

1 *Anti-Infective Agents/

2 (antimicrob$ or anti-microb$ or "anti microb$").ti.

3 (antiinfect$ or anti-infect$ or "anti infect$").ti.

4 (antibacter$ or anti-bacter$ or "anti bacter$").ti.

5 (antibiot$ or anti-biot$ or "anti biot$").ti.

6 (antiviral$ or anti-viral$ or "anti viral$").ti.

7 (antifung$ or anti-fung$ or "anti fung$").ti.

8 (antiparasit$ or anti-parasit$ or "anti parasit$").ti.

9 or/1-8

10 ((inappropriat$ or irrational$ or imprudent$ or unnecessar$ or incorrect$ or irrespons$ or misus$ or improper$ or error$ or mistake$ or indiscriminat$ or suboptim$ or sub-optim$ or "sub optim$" or bad or badly or inefficient$ or uncontrol$ or overus$ or excess$ or vary$ or varia$ or poor$) adj4 (prescr$ or adminis$ or dispens$ or "use" or usag$ or utili$ or provi$ or distribut$ or therap$ or treatment$ or expos$ or consum$)).tw.

11 ((appropriat$ or rational$ or prudent$ or judicious$ or quality or optim$ or correct$ or proper$ or responsib$ or evidence-bas$ or improv$ or good$ or efficient$ or control$ or decreas$ or reduc$ or limit$ or curb$ or minim$ or lessen$ or curtail$ or abat$ or restrict$ or lower$ or discontinu$ or delay$) adj4 (prescr$ or adminis$ or dispens$ or "use" or usag$ or utili$ or provi$ or distribut$ or therap$ or treatment$ or expos$ or consum$)).tw.

12 exp *Medication Errors/

13 or/10-12

14 9 and 13

15 steward$.tw.

16 9 and 15

17 exp *Drug Resistance, Microbial/

18 exp *Drug Resistance, Multiple/

19 ((microb$ or antimicrob$ or anti-microb$ or "anti microb$") adj4 (resist$ or tolera$)).ti.

20 ((antiinfect$ or anti-infect$ or "anti infect$") adj4 (resist$ or tolera$)).ti.

21 ((bacter$ or antibacter$ or anti-bacter$ or "anti bacter$") adj4 (resist$ or tolera$)).ti.

22 ((antibiot$ or anti-biot$ or "anti biot$") adj4 (resist$ or tolera$)).ti.

23 ((viral$ or antiviral$ or anti-viral$ or "anti viral$") adj4 (resist$ or tolera$)).ti.

24 ((fung$ or antifung$ or anti-fung$ or "anti fung$") adj4 (resist$ or tolera$)).ti.

25 ((parasit$ or antiparasit$ or anti-parasit$ or "anti parasit$") adj4 (resist$ or tolera$)).ti.

26 (multi$ adj4 drug$ adj4 (resist$ or tolera$)).ti.

27 (multidrug$ adj4 (resist$ or tolera$)).ti.

28 (multiresist$ or multi-resist$ or "multi resist$").ti.

29 (superbug$ or super-bug$ or "super bug$").ti.

30 *Superinfection/

31 (superinvasion$ or super-invasion$ or "super invasion$" or superinfection$ or super-infection$ or "super infection$").ti.

32 *R Factors/

33 "r factor$".ti.

34 ("resist$ factor$" or "r plasmid$" or "resist$ plasmid$").ti.

35 or/17-34

36 14 or 35

37 *"Attitude of Health Personnel"/

38 exp *Health Personnel/px

39 *Health Knowledge, Attitudes, Practice/

40 (experience$ or belief$ or behav$ or view$ or opinion$ or perception$ or perspective$ or attitud$ or know$ or understand$ or aware$ or cultur$).ti.

41 ((chang$ or modif$ or alter or altera$ or alteri$ or altered) adj2 (experience$ or belief$ or behav$ or view$ or opinion$ or perception$ or perspective$ or attitud$ or know$ or understand$ or aware$ or cultur$)).ab.

42 *Decision Making/

43 *Choice behavior/

44 decision-mak$.tw.

45 ((decis$ or decid$ or choice$ or choos$ or determinant$ or predict$) adj2 (mak$ or prescr$ or adminis$ or dispens$ or "use" or usag$ or utili$ or provi$ or distribut$ or therap$ or treatment$)).tw.

46 ((chang$ or modif$ or alter or altera$ or alteri$ or altered) adj2 (decis$ or decid$ or choice$ or choos$ or prescr$ or adminis$ or dispens$ or "use" or usag$ or utili$ or provi$ or distribut$ or therap$ or treatment$)).tw.

47 *Physician's Practice Patterns/

48 *Nurse's Practice Patterns/

49 *Dentist's Practice Patterns/

50 ((practice$ or prescri$) adj2 pattern$).tw.

51 or/37-50

52 exp *Patient Care Team/

53 exp *Professional Role/

54 exp *Interprofessional Relations/

55 exp *"Delivery of Health Care, Integrated"/

56 (multidisciplin$ or multi-disciplin$ or mdt or multipartne$ or multi-partner$ or "multi partner" or multisector$ or multi-sector$ or "multi sector$" or multi-agenc$ or multiagenc$ or "multi agenc$" or multiprofession$ or multi-profession$ or "multi profession$" or intraprofression$ or intra-profession$ or "intra profession$" or interprofession$ or inter-profession$ or "inter profession$" or transdisciplin$ or trans-disciplin$ or "trans disciplin$" or interdisciplin$ or inter-disciplin$ or "inter disciplin$" or intradisciplin$ or intra-disciplin$ or "intra disciplin$").tw.

57 (crosssector$ or cross-sector$ or "cross sector$" or "across sector$" or intersector$ or inter-sector$ or "inter sector$" or interorgani$ or inter-organi$ or "inter organi$" or "cross organ$" or "across organi$" or "cross disciplin$" or "across disciplin$").tw.

58 (interagenc$ or inter-agenc$ or "inter agenc$").tw.

59 ((integrat$ or combined or collaborat$ or continuity) adj2 (care$ or team$ or service$ or network$ or system$)).tw.

60 (partner$ adj2 (work$ or training)).tw.

61 ("whole system$ approach$" or "whole system$ working").tw.

62 ("managed clinical network*" or "one-stop shop" or "chain of care" or "whole health economy" or "case conferencing").tw.

63 ((organi$ or care or work$) adj2 model$).tw.

64 ((pharmacy$ or pharmacist$) adj2 (interven$ or involv$ or collaborat$ or advi$ or support$ or guid$ or partner$ or integrat$ or role$ or input$ or contribut$ or led or aid$ or inclu$)).tw.

65 or/52-64

66 drug$ resistance ind$.tw.

67 statistical process control chart$.tw.

68 *Electronic Prescribing/

69 ((computer$ or electronic$) adj2 (prescrib$ or medicin$ or administ$ or surveillan$)).tw.

70 exp *Information Systems/

71 exp *Decision Making, Computer-Assisted/

72 exp *decision support techniques/

73 *Database Management Systems/

74 ((computer$ or clinical$) adj2 decision$ adj2 (support$ or system$)).tw.

75 (decision$ adj2 (rule$ or support$)).tw.

76 data$ warehous$.tw.

77 data$ system$.tw.

78 (CDSS or CCDS).tw.

79 exp *Microbial Sensitivity Tests/

80 ((microbial$ or bacter$ or virus$ or viral$ or fungal$ or fungus$ or parasit$) adj2 sensitiv$ adj2 test$).tw.

81 antibiogram$.tw.

82 exp guideline/

83 exp *Guidelines as Topic/

84 *Clinical Protocols/

85 exp consensus development conference/

86 *consensus/

87 exp *consensus development conferences as topic/

88 exp *Formularies as Topic/

89 *Pharmacopoeias as Topic/

90 (guid$ or protocol$ or consensus$ or polic$ or regulat$ or formular$ or pharmacop$).tw.

91 exp *Clinical Audit/

92 exp *Health Surveys/

93 (audit$ or survey$).tw.

94 exp *Management Audit/

95 benchmark$.tw.

96 exp *Feedback/

97 (feedback$ or "feed$ back" or "fed back").tw.

98 exp *education/

99 (educat$ or learn$ or teach$ or train$).tw.

100 (continu$ profession$ develop$ or cpd$).tw.

101 NICHE.tw.

102 (need adj5 investigation adj5 choice adj5 how adj5 evaluate).tw.

103 "start smart".tw.

104 (TARGET adj5 tool$).tw.

105 ((quality adj3 outcome$ adj3 framework$) or qof).

106 (pay adj3 performance$).tw.

107 qipp.tw.

108 (quality innovation productivity adj2 prevention$).tw.

109 *Motivation/

110 (incentive$ or motivat$).tw.

111 (academic adj2 (detail$ or workshop$)).tw.

112 ("4 r" or "four r" or "4 rs" or "four rs").tw.

113 (right adj5 dose$ adj5 drug).tw.

114 (point adj2 care).tw.

115 ((rapid$ or fast$) adj1 (diagn$ or test$)).tw.

116 or/66-115

117 (intervention$ or initiativ$ or project$ or strateg$ or program$ or scheme$).tw.

118 (barrier$ or obstacle$ or challeng$ or difficult$ or hurdle$ or impediment$ or obstruct$).tw.

119 116 or 117 or 118

120 51 or 65 or 119

121 36 and 120

122 Meta-Analysis.pt.

123 Meta-Analysis as Topic/

124 (metaanaly$ or metanaly$ or (meta adj2 analy$)).tw.

125 (systematic$ adj4 (review$ or overview$)).tw.

126 ((quantitative$ or qualitative$) adj4 (review$ or overview$)).tw.

127 (pool$ adj1 (analy$ or data)).tw.

128 (handsearch$ or (hand adj2 search$)).tw.

129 (manual$ adj2 search$).tw.

130 or/122-129

131 animals/ not humans/

132 130 not 131

133 Randomized Controlled Trial.pt.

134 Placebos/

135 Random Allocation/

136 clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/ or exp controlled clinical trials as topic/ or multicenter studies as topic/

137 Double-Blind Method/

138 Single-Blind Method/

139 Cross-Over Studies/

140 (random or randomi$ or randoml$).tw.

141 placebo$.tw.

142 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw.

143 (crossover$ or (cross adj over$)).tw.

144 or/133-143

145 animals/ not humans/

146 144 not 145

147 limit 146 to yr="2005 -Current"

148 Qualitative Research/

149 Nursing Methodology Research/

150 Interview.pt.

151 exp Interviews as Topic/

152 Questionnaires/

153 Narration/

154 Health Care Surveys/

155 (qualitative$ or interview$ or focus group$ or questionnaire$ or narrative$ or narration$ or survey$).tw.

156 (ethno$ or emic or etic or phenomenolog$ or grounded theory or constant compar$ or (thematic$ adj4 analys$) or theoretical sampl$ or purposive sampl$).tw.

157 (hermeneutic$ or heidegger$ or husser$ or colaizzi$ or van kaam$ or van manen$ or giorgi$ or glaser$ or strauss$ or ricoeur$ or spiegelberg$ or merleau$).tw.

158 (metasynthes$ or meta-synthes$ or metasummar$ or meta-summar$ or metastud$ or meta-stud$ or metathem$ or meta-them$).tw.

159 or/148-158

160 14 and 120

161 (16 or 160) and (132 or 147)

162 (16 or 121) and 159

163 limit 162 to yr="2000 -Current"

164 161 or 163

C.1.2.3 Barriers to decision making

The search strategy for the review question on decision making above was also used to retrieve evidence for this review question

C.1.2.4 Timely adoption and diffusion of a 'new' antimicrobial[d]

The following search strategy was designed to retrieve the evidence-base for review question D. No study design filters were added to the strategy.

Search strategy

Database: Ovid MEDLINE(R)

---

1 exp Anti-Infective Agents/

2 (antimicrob$ or anti-microb$ or "anti microb$").tw.

3 (antiinfect$ or anti-infect$ or "anti infect$").tw.

4 (antibacter$ or anti-bacter$ or "anti bacter$").tw.

5 (antibiot$ or anti-biot$ or "anti biot$").tw.

6 (antiviral$ or anti-viral$ or "anti viral$").tw.

7 (antifung$ or anti-fung$ or "anti fung$").tw.

8 (antiparasit$ or anti-parasit$ or "anti parasit$").tw.

9 or/1-8

10 exp Formularies as Topic/

11 Pharmacopoeias as Topic/

12 (formular$ or pharmacop$).tw.

13 (manag$ adj4 entry).tw.

14 ((adopt$ or diffus$ or uptak$ or implement$ or introduc$) adj4 (nhs or health or healthcare or care or system$ or practice$)).tw.

15 or/10-14

16 9 and 15

17 (new or newly or newer or novel or innovati$).tw.

18 16 and 17

C.1.2.5 Study design filters

The MEDLINE systematic reviews and randomised controlled trials search filters that were used for the review questions above are presented below. They were translated for use in MEDLINE In-Process and Embase

C.1.2.6 Systematic reviews filter

1. Meta-Analysis.pt.

[d]For the purpose of this protocol 'a new antimicrobial' includes:

- a new antimicrobial
- a newly marketed formulation of an existing antimicrobial and/or
- an antimicrobial that is licensed but not available on the NHS
- an older licensed antimicrobial that is not routinely prescribed by the NHS.

2. Meta-Analysis as Topic/
3. (metaanaly$ or metanaly$ or (meta adj2 analy$)).tw.
4. (systematic$ adj4 (review$ or overview$)).tw.
5. ((quantitative$ or qualitative$) adj4 (review$ or overview$)).tw.
6. (pool$ adj1 (analy$ or data)).tw.
7. (handsearch$ or (hand adj2 search$)).tw.
8. (manual$ adj2 search$).tw.
9. or/1-8
10. animals/ not humans/
11. 9 not 10

C.1.2.7 Randomised controlled trials filter

1. Randomized Controlled Trial.pt.

2. Controlled Clinical Trial.pt.

3. Clinical Trial.pt.

4. exp Clinical Trials as Topic/

5. Placebos/

6. Random Allocation/

7. Double-Blind Method/

8. Single-Blind Method/

9. Cross-Over Studies/

10. ((random$ or control$ or clinical$) adj2 (trial$ or stud$)).tw.

11. (random$ adj2 allocat$).tw.

12. placebo$.tw.

13. ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw.

14. (crossover$ or (cross adj over$)).tw.

15. or/1-14

16. animals/ not humans/

17. 15 not 16

The Medline randomised controlled trials filter was limited by date to retrieve results from 2005 to the present day in accordance with the process described in the Cochrane Handbook for running supplementary searches to identify trials that are not indexed in the CENTRAL database.

C.1.3 Economic evaluations and quality of life data

Sources searched to identify economic evaluations

- MEDLINE, MEDLINE in Process, Embase, NHS EED, HEED

Health economics studies

The following search strategy was designed to identify the health economics studies for all of the review questions. The searches were carried out within the same time period as the clinical searches, between JULY 2014 and OCTOBER 2014.

Search strategy

Database: Ovid MEDLINE(R)

---

1 *Anti-Infective Agents/

2 (antimicrob$ or anti-microb$ or "anti microb$").ti.

3 (antiinfect$ or anti-infect$ or "anti infect$").ti.

4 (antibacter$ or anti-bacter$ or "anti bacter$").ti.

5 (antibiot$ or anti-biot$ or "anti biot$").ti.

6 (antiviral$ or anti-viral$ or "anti viral$").ti.

7 (antifung$ or anti-fung$ or "anti fung$").ti.

8 (antiparasit$ or anti-parasit$ or "anti parasit$").ti.

9 or/1-8

10 ((inappropriat$ or irrational$ or imprudent$ or unnecessar$ or incorrect$ or irrespons$ or misus$ or improper$ or error$ or mistake$ or indiscriminat$ or suboptim$ or sub-optim$ or "sub optim$" or bad or badly or inefficient$ or uncontrol$ or overus$ or excess$ or vary$ or varia$ or poor$) adj4 (prescr$ or adminis$ or dispens$ or "use" or usag$ or utili$ or provi$ or distribut$ or therap$ or treatment$ or expos$ or consum$)).tw.

11 ((appropriat$ or rational$ or prudent$ or judicious$ or quality or optim$ or correct$ or proper$ or responsib$ or evidence-bas$ or improv$ or good$ or efficient$ or control$ or decreas$ or reduc$ or limit$ or curb$ or minim$ or lessen$ or curtail$ or abat$ or restrict$ or lower$ or discontinu$ or delay$) adj4 (prescr$ or adminis$ or dispens$ or "use" or usag$ or utili$ or provi$ or distribut$ or therap$ or treatment$ or expos$ or consum$)).tw.

12 exp *Medication Errors/

13 or/10-12

14 9 and 13

15 steward$.tw

16 9 and 15

17 exp *Drug Resistance, Microbial/

18 exp *Drug Resistance, Multiple/

19 ((microb$ or antimicrob$ or anti-microb$ or "anti microb$") adj4 (resist$ or tolera$)).ti.

20 ((antiinfect$ or anti-infect$ or "anti infect$") adj4 (resist$ or tolera$)).ti.

21 ((bacter$ or antibacter$ or anti-bacter$ or "anti bacter$") adj4 (resist$ or tolera$)).ti. (6213)

22 ((antibiot$ or anti-biot$ or "anti biot$") adj4 (resist$ or tolera$)).ti.

23 ((viral$ or antiviral$ or anti-viral$ or "anti viral$") adj4 (resist$ or tolera$)).ti.

24 ((fung$ or antifung$ or anti-fung$ or "anti fung$") adj4 (resist$ or tolera$)).ti.

25 ((parasit$ or antiparasit$ or anti-parasit$ or "anti parasit$") adj4 (resist$ or tolera$)).ti.

26 (multi$ adj4 drug$ adj4 (resist$ or tolera$)).ti.

27 (multidrug$ adj4 (resist$ or tolera$)).ti.

28 (multiresist$ or multi-resist$ or "multi resist$").ti.

29 (superbug$ or super-bug$ or "super bug$").ti.

30 *Superinfection/

31 (superinvasion$ or super-invasion$ or "super invasion$" or superinfection$ or super-infection$ or "super infection$").ti.

32 *R Factors/

33 "r factor$".ti.

34 ("resist$ factor$" or "r plasmid$" or "resist$ plasmid$").ti.

35 or/17-34

36 14 or 16 or 35

Health economics filters

The MEDLINE economic evaluations and quality of life search filters are presented below. They were translated for use in the MEDLINE In-Process and Embase databases.

Economic evaluations filter

1. Economics/
2. Economics, Dental/
3. exp Economics, Hospital/
4. exp Economics, Medical/
5. Economics, Nursing/
6. Economics, Pharmaceutical/
7. exp Models, Economic/
8. Markov Chains/
9. Monte Carlo Method/
10. Decision Trees/
11. econom$.tw.
12. cba.tw.
13. cea.tw.
14. cua.tw.
15. markov$.tw.
16. (monte adj carlo).tw.
17. (decision adj3 (tree$ or analys$)).tw.
18. (cost or costs or costing$ or costly or costed).tw.
19. (price$ or pricing$).tw.
20. budget$.tw.
21. expenditure$.tw.
22. (value adj3 (money or monetary)).tw.

23. (pharmacoeconomic$ or (pharmaco adj economic$)).tw.
24. or/1-24

Quality of life filter

1. "Quality of Life"/

2. quality of life.tw.

3. "Value of Life"/

4. Quality-Adjusted Life Years/

5. quality adjusted life.tw.

6. (qaly$ or qald$ or qale$ or qtime$).tw.

7. disability adjusted life.tw.

8. daly$.tw.

9. Health Status Indicators/

10. (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.

11. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.

12. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.

13. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.

14. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.

15. (euroqol or euro qol or eq5d or eq 5d).tw.

16. (qol or hql or hqol or hrqol).tw.

17. (hye or hyes).tw.

18. health$ year$ equivalent$.tw.

19. utilit$.tw.

20. (hui or hui1 or hui2 or hui3).tw.

21. disutili$.tw.

22. rosser.tw.

23. quality of wellbeing.tw.

24. quality of well-being.tw.

25. qwb.tw.

26. willingness to pay.tw.

27. standard gamble$.tw.

28. time trade off.tw.

29. time tradeoff.tw.

30. tto.tw.

31. or/1-30

C.2 Review questions and review protocols

C.2.1 Reducing antimicrobial resistance

	Details
Review question	What interventions, systems and processes are effective and cost-effective in reducing antimicrobial resistance without causing harm to patients?
Objectives	To determine the effectiveness and cost effectiveness of interventions, systems and processes to reduce the emergence of antimicrobial resistance whilst causing no additional harm to patients compared to usual care. In line with the three major goals of antimicrobial stewardship this includes interventions that lead prescribers to: • optimise therapy for individuals • reduce overuse, misuse or abuse of antimicrobials • minimise development of resistance at patient and community levels
Type of review	Interventional studies
Language	English only
Legislation	Such as the Section 20 regulations of the Health and Social Care Act 2008.
Regulation	Such as Regulation 12 of the Health and Social Care Act 2008 (Regulated Activities) Regulations 2010
Policy	Such as the UK 5 Year Antimicrobial Resistance Strategy 2013 to 2018
Study design	• NICE accredited guidance • Systematic review of randomised controlled trials (RCTs and prospective cohort studies) • RCTs If insufficient evidence is available progress to: • Other national guidance • Systematic reviews of non-randomised controlled trials • Non-randomised controlled trials • Prospective cohort studies
Status	Published papers only (full text). Papers back to 1985
Population	Adults, young people and children (including neonates) using antimicrobials in: • Hospital inpatients • Outpatients and all other community settings to include: ○ Primary care and general practice ○ Ambulatory settings (non inpatient care) ○ Dental ○ Select sub–groups and populations (for example those individuals

	Details
	with HIV, TB, Hepatitis)
Intervention	Any intervention related to reducing antimicrobial resistance such as: • Informatics, such as: ○ Data collection from urgent care ○ Drug Resistance Index ○ Statistical Process Control Charts ○ Electronic Prescribing and Medicines Administration [EPMA] ○ Electronic surveillance software ○ Impact of drug utilisation data systems ○ Use of Antibiograms and Reporting of Sensitivities ○ Impact of guidelines or formulary ○ Data warehousing ○ Decision-support • Quality and organisational governance processes and campaigns, such as: ○ Audit and/or benchmarking/CPD/education ○ Definition of appropriate antimicrobial use ○ British Society for Antimicrobial Chemotherapy – NICHE (Need (for antibiotic) Investigation (cultures for prescribing), Choice (spectrum of antibiotic), How Long (is your prescription for), Evaluate (your patient and prescription) ○ Infectious Diseases Society of America [IDSA] / Society for Healthcare Epidemiology of America [SHEA] - 7 strategies for antimicrobial stewardship (USA) – Australia (start smart) ○ Department of Health - Start smart then focus ○ Royal College of General Practitioners – TARGET antibiotic toolkit ○ QOF ○ QIPP ○ Incentives ○ Public campaigns ○ Academic detailing/workshops ○ Pharmaceutical industry • Clinical management interventions, such as: ○ Four R's (right dose, drug, duration, de-escalation) include right route of administration including frequency ○ Rapid diagnostics and point of care testing ○ Early hospital discharge ○ Decision rules (such as those found in Respiratory Tract Infection Clinical Guideline) ○ Safety net advice for patients / carers (non-drug prescriptions, minimum information sets, finish course of antibiotic advice etc.) ○ Antimicrobial chemoprophylaxis ○ Broad versus narrow spectrum treatment ○ Course length ○ Antimicrobial choice (allergy, dose frequency) ○ Minimum dosing for clinical effectiveness ○ Previous antimicrobial therapy ○ Medicine cost ○ Medicines adherence (except as stated in the exclusions) ○ Delayed prescribing ○ Ongoing monitoring / review/support

	Details
	○ Single intervention vs. ongoing/sustained intervention ○ Pledges ○ Prescription vs. OTC ○ Switching from systemic to oral ○ stewardship teams
Comparator	Any
Outcomes	• Clinical outcomes such as: ○ mortality and morbidity ○ infection cure rates or time to clinical cure ○ surgical infection rates ○ treatment failure ○ re-infection rates ○ recurrence rates (relapse rates) • Antimicrobial use as measured by reduction in the variation over time and movement of the mean over time. • Emergence of organisms resistant to antimicrobials. • Health and social care related quality of life. • Healthcare-associated infections. • Community-associated infections. • Hospitalisation and health and social care utilisation. • Planned and unplanned contacts with health professionals or services. • Patient-reported outcomes, such as medicines adherence, patient experience, patient satisfaction with decision making, patient information and patient expectations. • Professional belief systems and their attitude to the use of antimicrobials. • Adherence to antimicrobials (e.g. correct dose at the right time, completing the course) • Unintended consequences – harm
Other criteria for inclusion / exclusion of studies	Exclusions • Research for new antimicrobials. • Immunisation and vaccination. • Antimicrobial household cleaning products. • Antimicrobials use in animals. • Hand-hygiene, decolonisation and infection prevention and control measures. • Medicines adherence except where there are specific issues for health and social care practitioners to address for antimicrobials. The general principles of medicines adherence are covered by CG76 – Medicines adherence: Involving patients in decisions about prescribed medicines and supporting adherence, • Access to medicines, including local-decision making for drugs not included on local formularies. • Medicines shortages, including supply issues and discontinued medicines. • Prescription charges. • Waste medicines.
Search strategies	To be developed
Review strategies	Appraisal of evidence quality: • Legislation and national policy will not be appraised for quality.

	Details
	• For guidelines, these will be assessed for quality using the AGREE II criteria. • For studies, appropriate NICE methodology checklists will be used to appraise the quality of individual studies. All key outcomes from evidence will be presented in GRADE profiles, where possible. Synthesis of data: • Data on all included studies will be extracted into evidence tables. • Where possible, data may be pooled to give an overall summary effect. • Where data cannot be pooled, narrative summaries of the data will be presented.
Identified papers from scoping search and GDG experience for background, including relevant legislation (UK) or national policy	GDG identified that there is a Cochrane review ongoing – antimicrobial prescribing (including behaviour change of prescribers – GIS to use for search strategy if feasible). • Davey, P; Brown, E; Charani, E et al (2013) Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database of Systematic Reviews. 30th April • Falagas, ME; Bliziotis, IA; Rafailidis, PI (2007) Do high doses of quinolones decrease the emergence of antibacterial resistance: a systematic review of data from comparative clinical trials. Journal of Infection; 55(2); 97 – 105 • Malani, AN (2013) Clinical and economic outcomes from a community hospitals antimicrobial stewardship program. American Journal of Infection Control. 41(2): pp 145-148

C.2.2 Decision making

	Details
Review question	What interventions, systems and processes are effective and cost-effective in changing health and social care practitioners' decision making to ensure appropriate antimicrobial stewardship?
Objectives	To determine the effectiveness and cost effectiveness of interventions, systems and processes that change health and social care practitioners' decision making to ensure appropriate antimicrobial stewardship. In line with the three major goals of antimicrobial stewardship this includes interventions that lead prescribers to: • optimise therapy for individuals • reduce overuse, misuse or abuse of antimicrobials • minimise development of resistance at patient and community levels
Type of review	Interventional studies
Language	English only
Legislation	Such as the Section 20 regulations of the Health and Social Care Act 2008.
Regulation	Such as Regulation 12 of the Health and Social Care Act 2008 (Regulated Activities) Regulations 2010
Policy	Such as the UK 5 Year Antimicrobial Resistance Strategy 2013 to 2018
Study design	• NICE accredited guidance • Systematic review of randomised controlled trials (RCTs) • RCTs

	Details
	If insufficient evidence is available progress to: • Other national guidance • Systematic reviews of non-randomised controlled trials • Non-randomised controlled trials • Observational and cohort studies • Pre and post intervention studies (before and after) • Time series studies
Status	Published papers only (full text) Papers back to 1985
Population	Health and social care practitioners
Intervention	Any intervention, system or process related to changing health and social care staff decision making to ensure appropriate antimicrobial stewardship, including: • The effect of multi-disciplinary team (MDT) working and interprofessional collaboration • The effect of communication in reducing risk of infection / clinical risk • Interventions for health and social care staff attitudes, beliefs and culture • Interventions for specific sub-groups ○ Older people, ○ Children ○ Those individuals who are immune compromised • The effect of specialist roles such as the antimicrobial or antibiotic pharmacist • Informatics, such as: ○ Data collection from primary and secondary care sources including urgent care services such as out of hours, A&E or walk-in-centres ○ Drug Resistance Index ○ Statistical Process Control Charts ○ Electronic Prescribing and Medicines Administration [EPMA] ○ Electronic surveillance software ○ Impact of drug utilisation data systems ○ Use of Antibiograms and Reporting of sensitivities ○ Impact of guidelines or formulary ○ Data warehousing ○ Decision-support • Quality and organisational governance processes and campaigns, such as: ○ Audit and/or benchmarking/CPD/education ○ Definition of appropriate antimicrobial use ○ British Society for Antimicrobial Chemotherapy – NICHE (Need (for antibiotic) Investigation (cultures for prescribing), Choice (spectrum of antibiotic), How Long (is your prescription for), Evaluate (your patient and prescription) ○ Infectious Diseases Society of America [IDSA] / Society for Healthcare Epidemiology of America [SHEA] - 7 strategies for antimicrobial stewardship (USA) – Australia (start smart) ○ Department of Health - Start smart then focus ○ Royal College of General Practitioners – TARGET antibiotic toolkit

	Details
	○ QOF ○ QIPP ○ Incentives ○ Academic detailing/workshops ○ Pharmaceutical industry ○ Faculty of General Dental Practice (UK) Guidelines on Antimicrobial Prescribing for General Dental Practitioners ○ NICE guidance on infective endocarditis • Clinical management interventions, such as: ○ Four R's (right dose, drug, duration, de-escalation) include right route of administration including frequency ○ Rapid diagnostics and point of care testing ○ Early hospital discharge ○ Decision rules (such as those found in Respiratory Tract Infection Clinical Guideline) ○ Safety net advice for patients / carers (non-drug prescriptions, minimum information sets, finish course of antibiotic advice etc.) ○ Antimicrobial chemoprophylaxis ○ Broad versus narrow spectrum treatment ○ Course length ○ Antimicrobial choice (allergy, dose frequency) ○ Optimal dosing for clinical effectiveness ○ Previous antimicrobial therapy ○ Medicine cost ○ Medicines adherence (except as stated in the exclusions) ○ Delayed prescribing ○ Ongoing monitoring / review/support ○ Single intervention vs. ongoing/sustained intervention ○ Pledges ○ Prescription, over the counter and common/minor ailment schemes ○ Switching from systemic to oral ○ Stewardship teams • Point of care tests (RCTs only) ○ Procalcitonin ○ C-reactive protein
Comparator	Any
Outcomes	• Clinical outcomes such as: ○ mortality and morbidity ○ infection cure rates or time to clinical cure ○ surgical infection rates ○ treatment failure ○ re-infection rates. • Antimicrobial use by appropriate measures (may be a reduction) • Emergence of organisms resistant to antimicrobials. • Health and social care related quality of life. • Healthcare-associated infections. • Community-associated infections. • Hospitalisation and health and social care utilisation. • Planned and unplanned contacts with health professionals or services (re-consultations).

	Details
	• Patient-reported outcomes, such as medicines adherence, patient experience, patient satisfaction with decision making, patient information and patient expectations. • Professional belief systems and their attitude to the use of antimicrobials. • Adherence to antimicrobials (e.g. correct dose at the right time, completing the course) • No harm/unintended consequences
Other criteria for inclusion / exclusion of studies	Exclusions • Research for new antimicrobials. • Immunisation and vaccination. • Antimicrobial household cleaning products. • Antimicrobials use in animals. • Hand-hygiene, decolonisation and infection prevention and control measures. • Medicines adherence except where there are specific issues for health and social care practitioners to address for antimicrobials. The general principles of medicines adherence are covered by CG76 – Medicines adherence: Involving patients in decisions about prescribed medicines and supporting adherence, • Access to medicines, including local-decision making for drugs not included on local formularies. • Medicines shortages, including supply issues and discontinued medicines. • Prescription charges. • Waste medicines.
Search strategies	To be developed
Review strategies	Appraisal of evidence quality: • Legislation and national policy will not be appraised for quality. • For guidelines, these will be assessed for quality using the AGREE II criteria. • For studies, appropriate NICE methodology checklists will be used to appraise the quality of individual studies. All key outcomes from evidence will be presented in **GRADE profiles, where possible.** Synthesis of data: • Data on all included studies will be extracted into evidence tables. • Where possible, data may be pooled to give an overall summary effect. • Where data cannot be pooled, narrative summaries of the data will be presented.
Identified papers from scoping search and GDG experience for background, including relevant legislation (UK) or national policy	• Butler, C; Simpson, S; Dunstan, F et al (2012) Effectiveness of multifaceted educational programme to reduce antibiotic prescribing in primary care: practice based randomised controlled trial. BMJ 344 • Edeghere, O; Wilson, J; Hyde, C (2010) Interventions to improve the prescribing of antibiotics by health care professionals in ambulatory care settings. Birmingham: West Midlands Health Technology Assessment Collaboration (WMHTAC). DPHE Report No. 73. • Gross, R; Morgan, AS; Kinky, DE et al (2001) Impact of a Hospital-Based Antimicrobial Management Program on Clinical and Economic Outcomes. Clinical Infectious Diseases. Vol 33, Issue 3, pp289-295

C.2.3 Barriers to decision making

	Details
Review question	What interventions, systems and processes are effective and cost-effective in overcoming the barriers to decision making by health and social care practitioner's when ensuring appropriate antimicrobial stewardship?
Objectives	a) To determine the effectiveness and cost effectiveness of interventions, systems and processes that change health and social care practitioners' decision making to ensure appropriate antimicrobial stewardship. b) To determine what barriers exist for decision making in relation to antimicrobial stewardship by health and social care practitioners. In line with the three major goals of antimicrobial stewardship this includes interventions that lead prescribers to: • optimise therapy for individuals • reduce overuse, misuse or abuse of antimicrobials • minimise development of resistance at patient and community levels
Type of review	a) Interventional studies b) Descriptive studies
Language	English only
Legislation	Such as the Section 20 regulations of the Health and Social Care Act 2008.
Regulation	Such as Regulation 12 of the Health and Social Care Act 2008 (Regulated Activities) Regulations 2010
Policy	Such as the UK 5 Year Antimicrobial Resistance Strategy 2013 to 2018
Study design	Objective a) • NICE accredited guidance • Systematic review of randomised controlled trials (RCTs) • RCTs • Other national guidance • Systematic reviews of non-randomised controlled trials • Non-randomised controlled trials Objective b) (as this objective considers the identification of barriers RCT evidence will not be available – therefore the types of study deisgn below are the most appropriate to search for) • Observational studies • Descriptive studies • Qualitative studies
Status	Published papers only (full text) Papers back to 2000
Population	Health and social care practitioners
Intervention	Examples may include: • Audit/feedback and/or benchmarking/CPD/education • Access to computer systems/electronic prescribing • Funding • Collaborative working • Other schemes e.g. minor ailment schemes (management of infections through other mechanisms) • The effect of multi-disciplinary team (MDT) working and interprofessional collaboration

	Details
	• Communication • The effect of communication in reducing risk of infection / clinical risk • Interventions for health and social care staff attitudes, beliefs and culture • Decision-support • Impact of guidelines or formulary • the effect of specialist roles such as the antimicrobial or antibiotic pharmacist • QOF • QIPP • Incentives • Academic detailing/workshops • Ongoing monitoring / review/support • Single intervention vs. ongoing/sustained intervention • Pledges • Prescription vs. Over The Counter • Switching from systemic to oral • Stewardship programmes or teams • Decision rules (such as those found in Respiratory Tract Infection Clinical Guideline)
Comparator	Standard / usual care or no intervention
Outcomes	Objective a): Outcomes that measure changes in decision making by health and social care staff in relation to antimicrobial stewardship to antimicrobial medicine including: • clinical outcomes (mortality, morbidity, infection cure rates, time to clinical cure, surgical and reinfection rates) • Antimicrobial use as measured by change in the variation over time and movement of the mean over time. • Presence, emergence and incidence of organisms resistant to antimicrobials. • Health and social care related quality of life. • Healthcare-associated infections. • Community-associated infections. • Side effects, adverse events and critical incidents. • Hospitalisation and health and social care utilisation. • Planned and unplanned contacts with health professionals or services. • Patient-reported outcomes, such as medicines adherence related specifically to issues of antimicrobial stewardship, patient experience, patient satisfaction with decision making, patient information and patient expectations. • Professional belief systems and their attitude to the use of antimicrobials. • No harm/unintended consequences • Planned and unplanned contacts with health professionals or services (re-consultations). Objective b): To determine what barriers exist for decision making in relation to antimicrobial stewardship by health and social care practitioners
Other criteria for inclusion / exclusion of	Exclusions • Research for new antimicrobials.

	Details
studies	• Immunisation and vaccination. • Antimicrobial household cleaning products. • Antimicrobials use in animals. • Hand-hygiene, decolonisation and infection prevention and control measures. • Medicines adherence except where there are specific issues for health and social care practitioners to address for antimicrobials. The general principles of medicines adherence are covered by CG76 – Medicines adherence: Involving patients in decisions about prescribed medicines and supporting adherence, • Access to medicines, including local-decision making for drugs not included on local formularies. • Medicines shortages, including supply issues and discontinued medicines. • Prescription charges. • Waste medicines.
Search strategies	To be developed
Review strategies	Appraisal of evidence quality: • Legislation and national policy will not be appraised for quality. • For guidelines, these will be assessed for quality using the AGREE II criteria. • For studies, appropriate NICE methodology checklists will be used to appraise the quality of individual studies. All key outcomes from evidence will be presented in GRADE profiles, where possible. Synthesis of data: • Data on all included studies will be extracted into evidence tables. • Where possible, data may be pooled to give an overall summary effect. • Where data cannot be pooled, narrative summaries of the data will be presented**.**
Identified papers from scoping search and GDG experience for background, including relevant legislation (UK) or national policy	• Simpson, SA; Wood, F; Butler, CC (2007) General practitioners perceptions of antimicrobial resistance: a qualitative study. Journal of Antimicrobial Chemotherapy. Volume 59, Issue 2, pp292-296. • Hulscher, MEJL; Grol, RPTM; van der Meer, JWM (2010) Antibiotic prescribing in hospitals: a social and behavioural scientific approach. The Lancet Infectious Diseases, Volume 10, Issue 3, pp167-175 • Charani, E; Edwards, R; Sevdalis, N et al (2011) Behaviour Change Strategies to Influence Antimicrobial Prescribing in Acute Care: A Systematic Review. Clinical Infectious Diseases. Volume 53, Issue 7, pp 651-662

C.2.4 Timely adoption and diffusion of a new antimicrobial

	Details
Review question	What interventions, systems and processes are effective and cost-effective in the responsible and timely adoption and diffusion, , of a 'new' antimicrobial[e] into the National Health Service (NHS)?

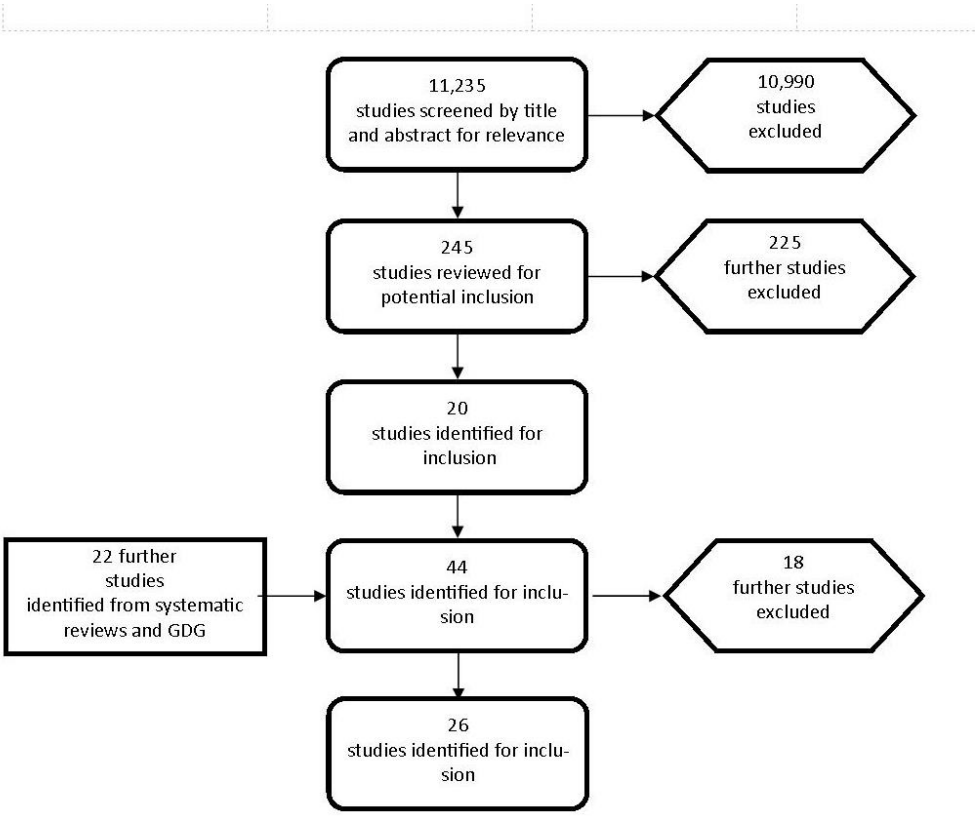
[e]For the purpose of this protocol 'a new antimicrobial' includes:
- a new antimicrobial
- a newly marketed formulation of an existing antimicrobial and/or
- an antimicrobial that is licensed but not available on the NHS
- an older licensed antimicrobial that is not routinely prescribed by the NHS.

	Details
Objectives	A) To determine the effectiveness and cost effectiveness of interventions, systems and processes that support the responsible, timely adoption and diffusion of new antimicrobials in the NHS. B) To determine if any specific barriers exist for the responsible, timely adoption and diffusion of new antimicrobial drugs within the NHS. In line with the three major goals of antimicrobial stewardship this includes interventions that lead prescribers to: • optimise therapy for individuals • reduce overuse, misuse or abuse of antimicrobials • minimise development of resistance at patient and community levels
Type of review	A) Any B) Any
Language	English only
Legislation	Such as the Section 20 regulations of the Health and Social Care Act 2008.
Regulation	Such as Regulation 12 of the Health and Social Care Act 2008 (Regulated Activities) Regulations 2010
Policy	• Department of Health, NHS Improvement & Efficiency Directorate, Innovation and Service Improvement (2011) Innovation, health and wealth • Department of Health (2013) NHS constitution
Study design	• NICE accredited guidance • Systematic review of randomised controlled trials (RCTs and prospective cohort studies) • RCTs If insufficient evidence is available progress to: • Other national guidance • Systematic reviews of non-randomised controlled trials • Non-randomised controlled trials • Prospective cohort studies
Status	Published papers only (full text) Papers back to 1999
Population	Health and social care practitioners
Intervention	• Antimicrobial stewardship type committees (examples include but not limited to: formulary committees, drug and therapeutics committees, medicines steering groups, individual funding request committees, area prescribing committees) • Multi-disciplinary team (MDT) working and inter-professional collaboration stewardship programmes or teams • Impact of guidelines or formulary, including the implementation • The effect of specialist roles such as the antimicrobial or antibiotic pharmacist • Funding processes to include commissioning • QOF • QIPP/national prescribing indicators • Incentives/engagement schemes • Pledges • Academic detailing/workshops

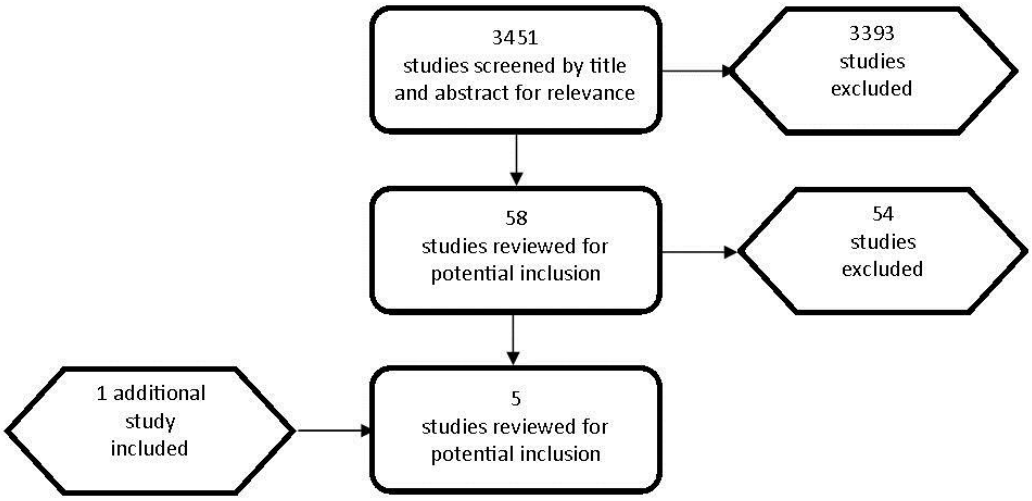
	Details
	• Ongoing monitoring / review/support • Single intervention vs. ongoing/sustained intervention
Comparator	Standard / usual care or no intervention.
Outcomes	a) Outcomes that measure changes in the adoption of new antimicrobials by NHS services (such as; monitoring the use of a new antimicrobial, post-prescription review, time taken from adoption to prescribing, rate of uptake of new antimicrobial) b) Antimicrobial use as measured by change in the variation over time and movement of the mean over time c) Any specific barriers that exist for the adoption of new antimicrobials by the NHS d) Side effects, adverse events and critical incidents relating to the use of 'new antimicrobials'
Other criteria for inclusion / exclusion of studies	Exclusions • Research for new antimicrobials • Immunisation and vaccination • Antimicrobial household cleaning products • Antimicrobials use in animals. • Hand-hygiene, decolonisation and infection prevention and control measures • Medicines adherence except where there are specific issues for health and social care practitioners to address for antimicrobials. The general principles of medicines adherence are covered by CG76 – Medicines adherence: Involving patients in decisions about prescribed medicines and supporting adherence • Prescription charges • Waste medicines
Search strategies	To be developed
Review strategies	Appraisal of evidence quality: • Legislation and national policy will not be appraised for quality. • For guidelines, these will be assessed for quality using the AGREE II criteria. • For studies and surveys, appropriate NICE methodology checklists will be used to appraise the quality of individual studies. Where possible, all key outcomes from evidence will be presented in GRADE profiles. Synthesis of data: • Data on all included studies will be extracted into evidence tables. • Where possible, data may be pooled to give an overall summary effect. • Where data cannot be pooled, narrative summaries of the data will be presented**.**
Identified papers from scoping search and GDG experience for background, including relevant legislation (UK) and national policy	NICE guidance on Developing and updating local formularies (MPG1) Infection prevention and control (QS61)

C.3 Clinical consort diagrams

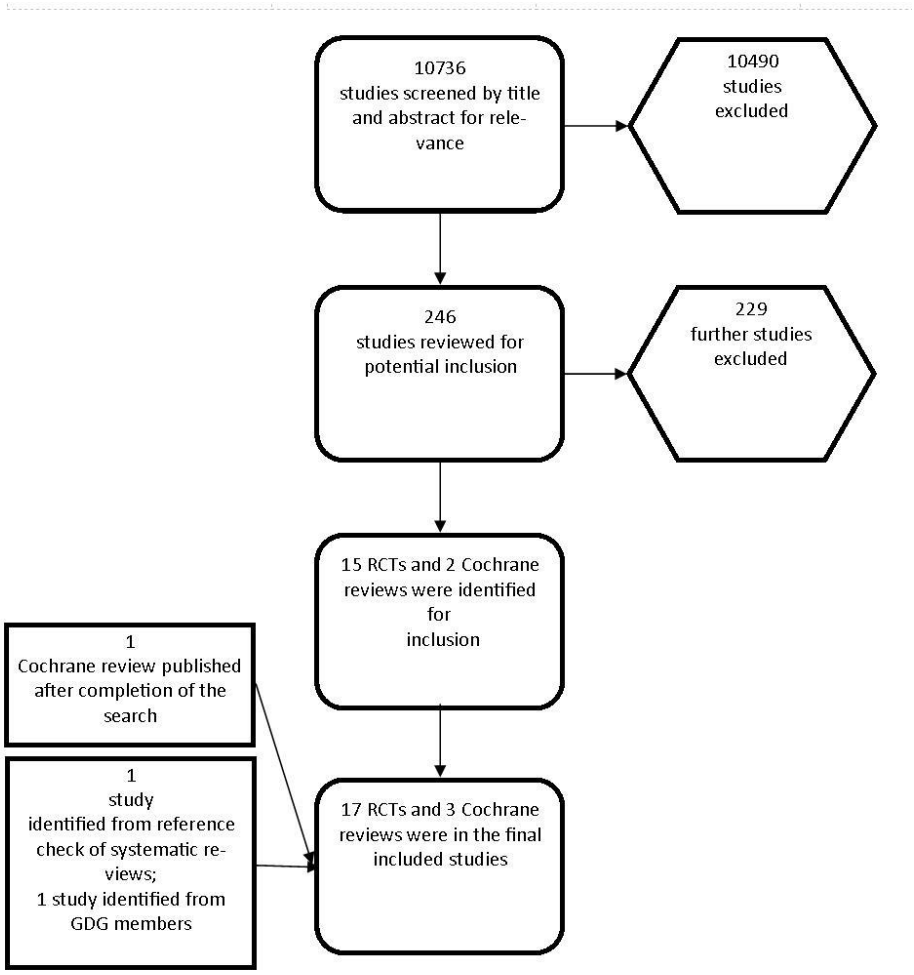
C.3.1 Reducing antimicrobial resistance



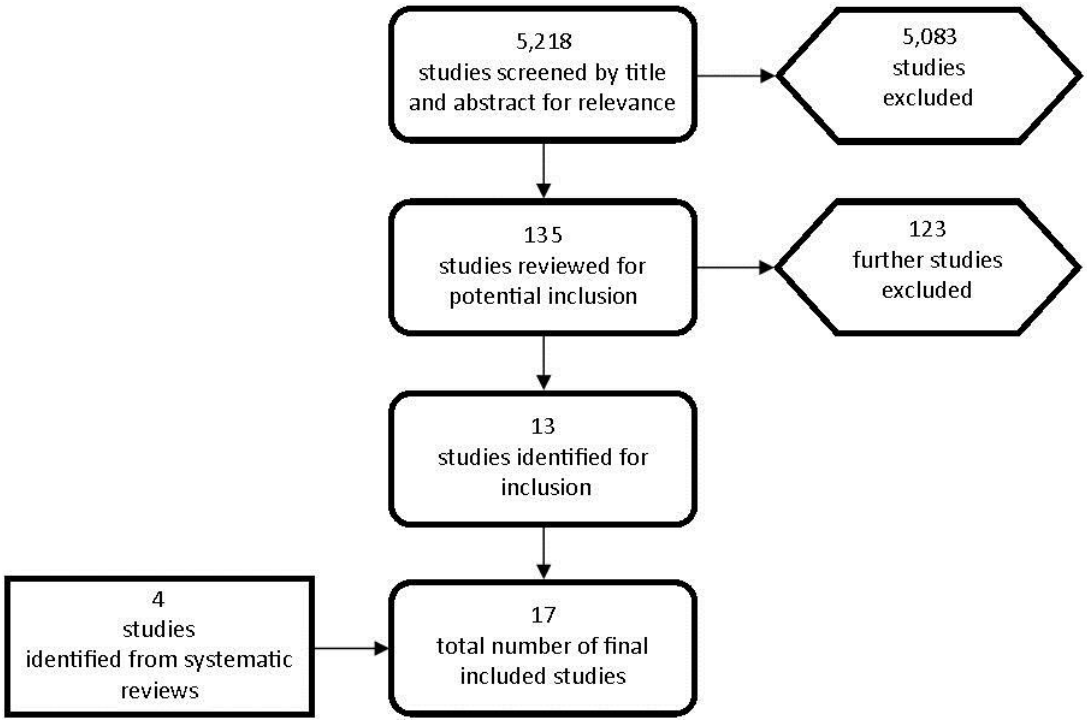
De-escalation studies



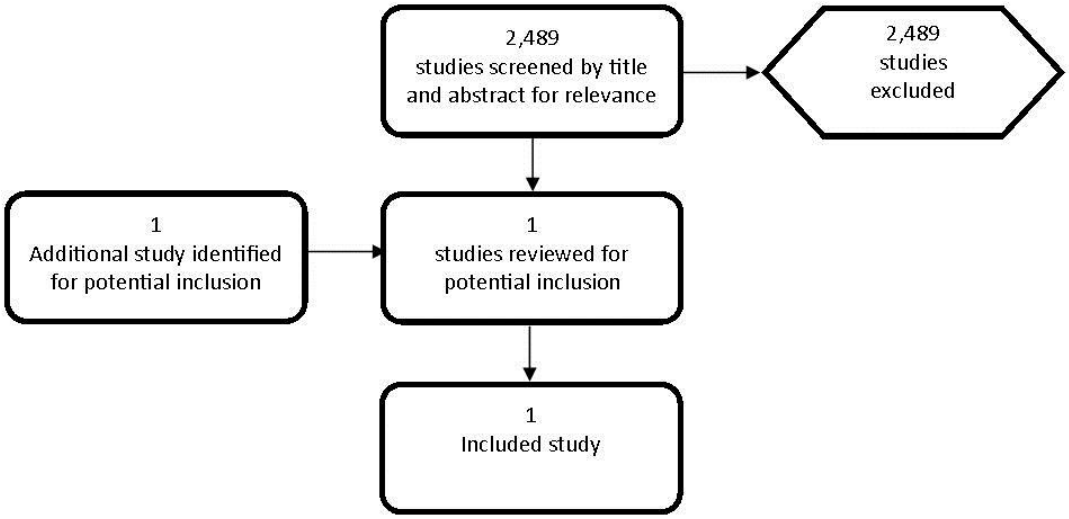
C.3.2 Decision making



C.3.3 Barriers to decision making

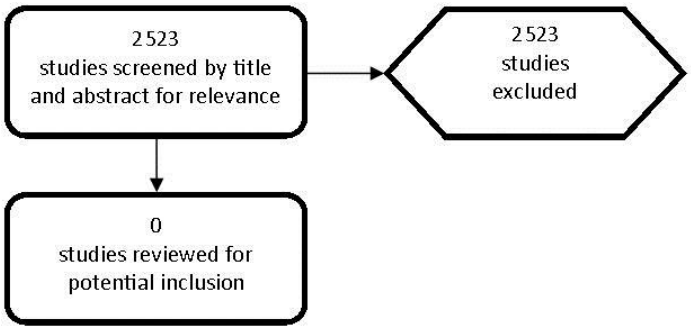


C.3.4 Timely adoption and diffusion of a new antimicrobial

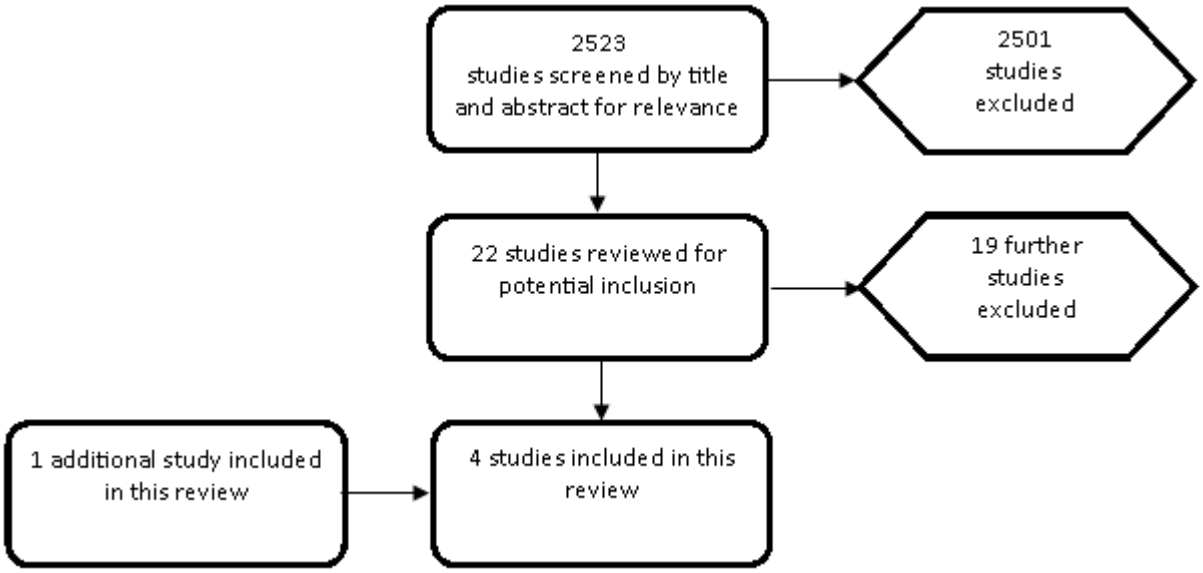


C.4 Economic consort diagrams

C.4.1 Reducing antimicrobial resistance



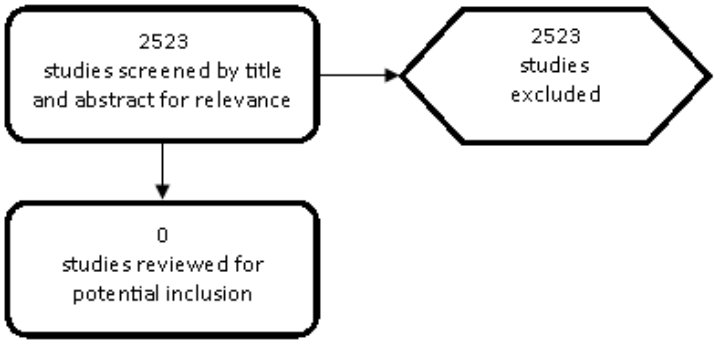
C.4.2 Decision making



C.4.3 Barriers to decision making

No health economic evidence

C.4.4 Timely adoption and diffusion of a new antimicrobial



C.5 Clinical excluded studies

C.5.1 Reducing antimicrobial resistance

Author	Reason for exclusion
Anon. (2012) Guide on the optimal use of antibiotics and the development of bacterial resistance (Project record) Health Technology Assessment Database (4)	Not English language
Adam D. (2000) Short-course antibiotic therapy for infections with a single causative pathogen. The Journal of international medical research 28 (Suppl 1): 13A-24A	Systematic review - literature search not sufficiently rigorous
Al Ansari NA, Foweraker J, Mackeown D, et al. (2006) Evaluation of once daily tobramycin versus the traditional three time daily for the treatment of acute pulmonary exacerbations in adult cystic fibrosis patients. Qatar Medical Journal 15(1): 34-8	Not relevant study
Amaya-Tapia G, Aguirre-Avalos G, Andrade-Villanueva J, et al. (1993) Once-daily azithromycin in the treatment of adult skin and skin-structure infections. Journal of Antimicrobial Chemotherapy 31 (Suppl E): 129-35	No relevant comparator
Andrews T, Thompson M, Buckley DI, et al. (2012) Interventions to influence consulting and antibiotic use for acute respiratory tract infections in children: a systematic review and meta-analysis. PloS One 7: e30334	No relevant outcomes
Apisarnthanarak A, Pinitchai U, Thongphubeth K, et al. (2008) A multifaceted intervention to reduce pandrug-resistant Acinetobacter baumannii colonization and infection in 3 intensive care units in a Thai tertiary care center: a 3-year study (Provisional abstract). Clinical Infectious Diseases 47: 760-7	Not an RCT or systematic review of RCTs
Arentz M, Sorensen B, Horne DJ, et al. (2013) Systematic review of the performance of rapid rifampicin resistance testing for drug-resistant tuberculosis. PloS One (8): e76533	No relevant outcomes
Arnold SR, Straus SE. (2005) Interventions to improve antibiotic prescribing practices in ambulatory care. The Cochrane database of systematic reviews: CD003539	Not an RCT or systematic review of RCTs
Askari R, Sawyer RG. (2005) New antibacterial administration treatment strategies. Surgical Infections 6 (Suppl 2): S-95	Not an RCT or systematic review of RCTs
Bago J, Majstorovic K, Belosic-Halle Z, et al. (2010) Antimicrobial resistance of H. pylori to the outcome of 10-days vs. 7-days Moxifloxacin based therapy for the eradication: a randomized controlled trial. Annals of Clinical Microbiology and Antimicrobials 9: 13.	Not relevant study
Baker SN, Acquisto NM, Ashley ED, et al. (2012) Pharmacist-managed antimicrobial stewardship program for patients discharged from the emergency department. Journal of Pharmacy Practice 25: 190-4	Not an RCT or a Systematic Review of RCTs.
Bazzoli F, Zagari M, Pozzato P, et al. (1998) Evaluation of short-term low-dose triple therapy for the eradication of Helicobacter pylori by factorial design in a randomized, double-blind, controlled study. Alimentary Pharmacology & Therapeutics 12: 439-45	Not relevant intervention
Beerepoot MAJ, ter Riet G, Nys S, et al. (2011) Cranberries vs antibiotics to prevent urinary tract infections: a randomized double-blind noninferiority trial in premenopausal women. Archives of Internal Medicine 171: 1270-8	Not relevant
Beerepoot MAJ, ter Riet G, Nys S, et al. (2012) Lactobacilli vs antibiotics to prevent urinary tract infections: a randomized, double-blind, noninferiority trial in postmenopausal women. Archives of Internal Medicine 172: 704-12	Not relevant

Author	Reason for exclusion
Bell BG, Schellevis F, Stobberingh E, et al. (2014) A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. BMC Infectious Diseases 14: 13	Not relevant
Bhutta ZA, Khan IA, Shadmani M. (2000) Failure of short-course ceftriaxone chemotherapy for multidrug-resistant typhoid fever in children: a randomized controlled trial in Pakistan. Antimicrobial Agents and Chemotherapy 44: 450-2	Unable to extrapolate to UK setting
Bodsworth N, Fife K, Koltun W, et al. (2009) Single-day famciclovir for the treatment of genital herpes: follow-up results of time to next recurrence and assessment of antiviral resistance. Current Medical Research and Opinion 25: 483-7	No relevant comparator
Boer WA, Haeck PW, Otten MH, et al. (1998) Optimal treatment of Helicobacter pylori with ranitidine bismuth citrate (RBC): a randomized comparison between two 7-day triple therapies and a 14-day dual therapy. American Journal of Gastroenterology 93: 1101-7	No relevant comparator
Bosso JA, Drew RH. (2011) Application of antimicrobial stewardship to optimise management of community acquired pneumonia. International Journal of Clinical Practice 65: 775-83	Not an RCT or systematic review of RCTs
Breen L, Aswani N. (2012) Elective versus symptomatic intravenous antibiotic therapy for cystic fibrosis. Cochrane Database Systematic Reviews 2: Art No: CD002767. DOI:10.1002/14651858.CD002767 pub 2	Not relevant study
Brown EM, Nathwani D. (2005) Antibiotic cycling or rotation: a systematic review of the evidence of efficacy. The Journal of Antimicrobial Chemotherapy 55: 6-9	Comment in: Journal of Antimicrobial Chemotherapy. Jan 55(1):1-5; PMID: 15574474
Brown JJ, Mutton TP, Wasilauskas BL, et al. (1982) Prospective, randomized, controlled trial of ticarcillin and cephalothin as prophylactic antibiotics for gastrointestinal operations. American Journal of Surgery 143: 343-8	No relevant comparator
Bröte L, Gillquist J, Höjer H. (1976) Prophylactic cephalothin in gastrointestinal surgery. Acta chirurgica Scandinavica 142: 238-45	No relevant comparator
Brumfitt W, Hamilton-Miller JM, Gargan RA, et al. (1983) Long-term prophylaxis of urinary infections in women: comparative trial of trimethoprim, methenamine hippurate and topical povidone-iodine. Journal of Urology 130: 1110-4	No relevant comparator
Buchanan P, Roos K, Tellier G, et al. (2005) Bacteriological efficacy of 5-day therapy with telithromycin in acute maxillary sinusitis. International Journal of Antimicrobial Agents 25: 237-46	Not an RCT or systematic review of RCTs
Burkhardt O, Ewig S, Haagen U, et al. (2010) Procalcitonin guidance and reduction of antibiotic use in acute respiratory tract infection. The European Respiratory Journal 36: 601-7	Not relevant study
Burkhardt O, Lehmann C, Madabushi R, et al. (2006) Once-daily tobramycin in cystic fibrosis: better for clinical outcome than thrice-daily tobramycin but more resistance development? The Journal of Antimicrobial Chemotherapy 58: 822-9	No relevant outcomes
Butler CC, Simpson SA, Dunstan F, et al. (2012) Effectiveness of multifaceted educational programme to reduce antibiotic dispensing in primary care: practice based randomised controlled trial. BMJ (Clinical research Edition) 344: d8173	Not relevant study
Cadieux PA, Chew BH, Nott L, et al. (2009) Use of triclosan-eluting ureteral stents in patients with long-term stents. Journal of Endourology / Endourological Society 23: 1187-94	Not an RCT or systematic review of RCTs
CADTH. (2013) Discontinuation of contact precautions for antibiotic resistant organisms: clinical evidence and guidelines (Structured	Not relevant study

Author	Reason for exclusion
abstract). Health Technology Assessment Database (4)	
Cammarota G, Branca G, Ardito F, et al. (2010) Biofilm demolition and antibiotic treatment to eradicate resistant Helicobacter pylori: a clinical trial. Clinical gastroenterology and hepatology: the Official Clinical Practice Journal of the American Gastroenterological Association 8: 817-20	No relevant outcomes
Casey JR, Pichichero ME.(2005) Metaanalysis of short course antibiotic treatment for group A streptococcal tonsillopharyngitis. Pediatric Infectious Disease Journal 24: 909-17	Not relevant study
Cavdar C, Saglam F, Sifil A et al. (2008) Effect of once-a-week vs thrice-a-week application of mupirocin on methicillin and mupirocin resistance in peritoneal dialysis patients: three years of experience. Renal Failure 30: 417-22	Not relevant study
Chang MT, Wu TH, Wang CY, et al. (2006) The impact of an intensive antimicrobial control program in a Taiwanese medical center. Pharmacy World & Science 28(4): 257-64	Not an RCT or systematic review of RCTs
Charani E, Edwards R, Sevdalis N, et al. (2011) Behavior change strategies to influence antimicrobial prescribing in acute care: a systematic review. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 53(7): 651-62	Not an RCT or systematic review of RCTs
Charbonneau P, Parienti JJ, Thibon P, et al. (2006) Fluoroquinolone use and methicillin-resistant Staphylococcus aureus isolation rates in hospitalized patients: a quasi-experimental study. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 42(6):778-84	Not an RCT or systematic review of RCTs
Chong Y, Shimoda S, Yakushiji H et al. (2013) Antibiotic rotation for febrile neutropenic patients with haematological malignancies: clinical significance of antibiotic heterogeneity. PloS One 8(1): e54190	Not an RCT or systematic review of RCTs
Costelloe C, Metcalfe C, Lovering A, et al. (2010) Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. BMJ (Clinical research Edition) 340: 2096	Duplicate of included population
Cremer J, Wallrauch C, Milatovic D, et al. (1998) Azithromycin versus cefaclor in the treatment of pediatric patients with acute group A beta-hemolytic streptococcal tonsillopharyngitis. European Journal of Clinical Microbiology & Infectious Diseases 17(4): 235-9	No relevant comparator
Danel C, Moh R, Chaix ML, et al. (2009) Two-months-off, four-months-on antiretroviral regimen increases the risk of resistance, compared with continuous therapy: a randomized trial involving West African adults. The Journal of Infectious Diseases 199(1): 66-76	Not relevant study
de Bruin MA, Riley LW. (2007) Does vancomycin prescribing intervention affect vancomycin-resistant enterococcus infection and colonization in hospitals? A systematic review. BMC Infectious Diseases 7: 24	Not an RCT or systematic review of RCTs
de Man P, Verhoeven BAN, Verbrugh HA, et al. (2000) An antibiotic policy to prevent emergence of resistant bacilli. The Lancet 355(9208): 973-78	Not an RCT or systematic review of RCTs
Depuydt P, Benoit D, Vogelaers D, et al. (2008) Systematic surveillance cultures as a tool to predict involvement of multidrug antibiotic resistant bacteria in ventilator-associated pneumonia. Intensive Care Medicine 34(4): 675-82	Not an RCT or systematic review of RCTs
Desrosiers M, Ferguson B, Klossek JM, et al. (2008) Clinical efficacy and time to symptom resolution of 5-day telithromycin versus 10-day amoxicillin-clavulanate in the treatment of acute bacterial sinusitis. Current Medical Research and Opinion 24(6): 1691-702	Not relevant

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Department of Health, Public Health England. (2014) European Antibiotic Awareness Day (EAAD) 2013 Evaluation Report.	Not relevant
Department of Health UK. (2014) UK 5 Year Antimicrobial Resistance (AMR) Strategy - Measuring Success.	Not relevant
Duffy L, Smith AD. (1982) Nitrofurantoin macrocrystals prevent bacteriuria in intermittent self-catheterization. Urology 20(1): 47-9	Not relevant
Dugan HA, MacLaren R, Jung R. (2003) Duration of antimicrobial therapy for nosocomial pneumonia: possible strategies for minimizing antimicrobial use in intensive care units. Journal of clinical pharmacy and therapeutics 28(2): 123-9	Not relevant
Durtschi MB, Orgain C, Counts GW, et al. (1982) A prospective study of prophylactic penicillin in acutely burned hospitalized patients. Journal of Trauma 22(1): 11-4	Not relevant
Eliakim-Raz N, Yahav D, Paul M, et al. (2013) Duration of antibiotic treatment for acute pyelonephritis and septic urinary tract infection-7 days or less versus longer treatment: Systematic review and meta-analysis of randomized controlled trials. Journal of Antimicrobial Chemotherapy 68(10): 2183-91	No relevant comparator
Eshleman SH, Guay LA, Mwatha A, et al. (2004) Comparison of nevirapine (NVP) resistance in Ugandan women 7 days vs. 6-8 weeks after single-dose nvp prophylaxis: HIVNET 012. AIDS Research and Human Retroviruses 20(6): 595-9	Not relevant
Esposito M, Grusovin MG, Worthington HV. (2013) Interventions for replacing missing teeth: antibiotics at dental implant placement to prevent complications. The Cochrane database of systematic reviews 7: CD004152	Not relevant
Fair WR, Crane DB, Peterson LJ, et al. (1980) Three-day treatment of urinary tract infections. Journal of Urology 123(5): 717-21	Not relevant
Falagas ME, Karageorgopoulos DE, Grammatikos AP, et al. (2009) Effectiveness and safety of short vs. long duration of antibiotic therapy for acute bacterial sinusitis: a meta-analysis of randomized trials. British Journal of Clinical pharmacology 67(2): 161-71	Not relevant
Fang Y-Q, Li T-C, Si T-J, et al. (2014) Antibiotic prophylaxis at time of catheter removal following laparoscopic radical prostatectomy: A prospective randomized study. Acta Medica Mediterranea 30: 161-5	Unable to extrapolate to UK setting
Feazel LM, Malhotra A, Perencevich EN et al. (2014) Effect of antibiotic stewardship programmes on Clostridium difficile incidence: a systematic review and meta-analysis. Journal of Antimicrobial Chemotherapy 69(7): 1748-54	Not an RCT or systematic review of RCTs
Fine JS, Jacobson MS. (1985) Single-dose versus conventional therapy of urinary tract infections in female adolescents. Pediatrics 75(5): 916-20	Not relevant
Fitzgerald A, Mori R, Lakhanpaul M, et al. (2012) Antibiotics for treating lower urinary tract infection in children. The Cochrane Database of Systematic Reviews: (8)	Duplicate of included population
Fox BC, Sollinger HW, Belzer FO, et al. (1990) A prospective, randomized, double-blind study of trimethoprim-sulfamethoxazole for prophylaxis of infection in renal transplantation: clinical efficacy, absorption of trimethoprim-sulfamethoxazole, effects on the microflora, and the cost-benefit of prophylaxis. American Journal of Medicine 89(3): 255-74	Not relevant
Gaudreault P BMG Jeal. (1992) Single daily doses of trimethoprim/sulphadiazine for three or 10 days in urinary tract infections. Acta Paediatric 81: 695-7	Not relevant
Gehanno P, Beauvillain C, Bobin S, et al. (2000) Short therapy with	Not relevant

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amoxicillin-clavulanate and costicosteroids in acute sinusitis: Results of a multicentre study in adults. Scandinavian Journal of Infectious Diseases 32(6): 679-84	
Geretti AM, Conibear T, Hill A, et al. (2014) Sensitive testing of plasma HIV-1 RNA and Sanger sequencing of cellular HIV-1 DNA for the detection of drug resistance prior to starting first-line antiretroviral therapy with etravirine or efavirenz. Journal of Antimicrobial Chemotherapy 69(4): 1090-7	Not relevant
Gilman RH, Spira W, Rabbani H, et al. (1981) Single-dose ampicillin therapy for severe shigellosis in Bangladesh. Journal of Infectious Diseases 143(2): 164-9	Unable to extrapolate to UK setting
Gjelstad S, Hoye S, Straand J, et al. (2013) Improving antibiotic prescribing in acute respiratory tract infections: cluster randomised trial from Norwegian general practice (prescription peer academic detailing (Rx-PAD study). BMJ (Clinical research Edition) 347: f4403	Not relevant
Glenny AM, Song F. (1999) Antimicrobial prophylaxis in total hip replacement: A systematic review. Health Technology Assessment 3 (21): iii-47	Not relevant
Goldman M, Cloud GA, Smedema M, et al. (2000) Does long-term itraconazole prophylaxis result in in vitro azole resistance in mucosal Candida albicans isolates from persons with advanced human immunodeficiency virus infection? The National Institute of Allergy and Infectious Diseases Mycoses study group. Antimicrobial Agents and Chemotherapy 44(6): 1585-7	Not relevant
Gonik B. (1985) Single- versus three-dose cefotaxime prophylaxis for cesarean section. Obstetrics and Gynaecology 65(2): 189-93	Not relevant
Gotuzzo E, Oberhelman RA, Maguiña C, et al. (1989) Comparison of single-dose treatment with norfloxacin and standard 5-day treatment with trimethoprim-sulfamethoxazole for acute shigellosis in adults. Antimicrobial Agents and Chemotherapy 33(7): 1101-4	Not relevant comparator
Gregoriou O, Bakas P, Grigoriadis C, et al. (2012) Antibiotic prophylaxis in diagnostic hysteroscopy: is it necessary or not? European Journal of Obstetrics, Gynaecology and Reproductive Biology 163(2): 190-2	Not relevant
Gribble MJ, Puterman ML. (1993) Prophylaxis of urinary tract infection in persons with recent spinal cord injury: a prospective, randomized, double-blind, placebo-controlled study of trimethoprim-sulfamethoxazole. American Journal of Medicine 95(2): 141-52	Not relevant
Grossman JH, Greco TP, Minkin MJ, et al. (1979) Prophylactic antibiotics in gynecologic surgery. Obstetrics and Gynecology 53(5): 537-44	Not relevant
Guibert J, Humbert G, Meyrier A, et al. (1995) Antibioprophylaxis of recurrent cystitis. A randomized double-blind trial with two pefloxacin regimens. Presse Medicale 24(4): 213-6	Not English language
Gupta K, Hooton TM, Roberts PL, et al. (2007) Short-course nitrofurantoin for the treatment of acute uncomplicated cystitis in women. Archives of Internal Medicine 167(20): 2207-12	Not relevant
Haider BA, Lassi ZS, Bhutta ZA. (2008) Short-course versus long-course antibiotic therapy for non-severe community-acquired pneumonia in children aged 2 months to 59 months. The Cochrane Database of Systematic Reviews (2)	Not relevant
Hallink SA. (2014) Recurrent uncomplicated cystitis in women: Allowing patients to self-initiate antibiotic therapy. Prescrire international 23(146): 47-9	Unable to source
Hamasuna R, Tanaka K, Hayami H, et al. (2014) Treatment of acute	Not relevant

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uncomplicated cystitis with faropenem for 3 days versus 7 days: multicentre, randomized, open-label, controlled trial. The Journal of Antimicrobial Chemotherapy 69(6): 1675-80	
Han T. (2006) Effectiveness of standard short-course chemotherapy for treating tuberculosis and the impact of drug resistance on its outcome (Structured abstract). International Journal of Evidence-Based Healthcare 4(4): 101-17	Not relevant
Handsfield HH, McCormack WM, Hook EW, et al. (1991) A comparison of single-dose cefixime with ceftriaxone as treatment for uncomplicated gonorrhea. The Gonorrhea Treatment Study Group. New England Journal of Medicine 325(19): 1337-41	Not relevant
Harbarth S, Fankhauser C, Schrenzel J, et al. (2008) Universal screening for methicillin-resistant Staphylococcus aureus at hospital admission and nosocomial infection in surgical patients. Journal of the American Medical Association 299(10): 1149-57	Not an RCT or systematic review of RCTs
Hargreave TB, Gould JC, Kinninmonth AW, et al. (1984) A randomized trial of 48 hours of prophylactic cefotaxime versus single dose in transurethral prostatic surgery. Journal of Antimicrobial Chemotherapy 14(Suppl B): 263-9	Not relevant
Harris DJ. (2013) Initiatives to improve appropriate antibiotic prescribing in primary care. The Journal of Antimicrobial Chemotherapy 68(11): 2424-7	Not an RCT or systematic review of RCTs
Harris M, Clark J, Coote N, et al. (2011) British Thoracic Society guidelines for the management of community acquired pneumonia in children: Update 2011. Thorax 66(Suppl 2): ii1-ii23	Not relevant
Hashizume T, Nishizawa R, Aizawa S, et al. (2004) Clinical Study of Using Prophylactic Antibiotics and Chemical Preparation for Elective Operation of Colorectal Cancer. Japanese Journal of Gastroenterological Surgery 37(4): 375-83	Not English language
Havey TC, Fowler RA, Daneman N. (2011) Duration of antibiotic therapy for bacteremia: a systematic review and meta-analysis. Critical care 15(6): R267	Not relevant
Havlir DV, Dubé MP, Sattler FR, et al. (1996) Prophylaxis against disseminated Mycobacterium avium complex with weekly azithromycin, daily rifabutin, or both. California Collaborative Treatment Group. New England Journal of Medicine 335(6): 392-8	No relevant comparator
Heikkinen T, Saeed KA, McCormick DP, et al. (2000) A single intramuscular dose of ceftriaxone changes nasopharyngeal bacterial flora in children with acute otitis media. Acta paediatrica 89(11): 1316-21	Not relevant
Hill RL, Fisher AP, Ware RJ, et al. (1990) Mupirocin for the reduction of colonization of internal jugular cannulae--a randomized controlled trial. Journal of Hospital Infection 15(4): 311-21	Not relevant
Hochreiter M, Kohler T, Schweiger AM, et al. (2009) Procalcitonin to guide duration of antibiotic therapy in intensive care patients: a randomized prospective controlled trial. Critical Care 13(3): R83	Not relevant
Hodge WG, Bui DP, Cevallos V, et al. (1995) Frequency of recovery of ciprofloxacin-resistant ocular isolates following topical ciprofloxacin therapy. IOVS 36: ARVO	Abstract only
Hoffken G, Pasold R, Pfluger KH, et al. (1999) An open, randomized, multicentre study comparing the use of low-dose ceftazidime or cefotaxime, both in combination with netilmicin, in febrile neutropenic patients. Journal of Antimicrobial Chemotherapy 44(3): 367-76	Not relevant
Hooton TM, Latham RH, Wong ES, et al. (1989) Ofloxacin versus trimethoprim-sulfamethoxazole for treatment of acute cystitis.	No relevant comparator

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Antimicrobial agents and Chemotherapy 33(8): 1308-12	
Huebner J, Rack-Hoch AL, Pecar A, et al. (2013) Pilot project of a pediatric Antibiotic Stewardship initiative at the Hauner Children's Hospital (Provisional abstract). Klinische Padiatrie 225(4): 223-9	Article in German with only Abstract in English.
Hurenkamp GJ, Ende A, Grundmeijer HG, et al. (2000) Equally high efficacy of 4, 7 and 10-day triple therapies to eradicate Helicobacter pylori infection in patients with ulcer disease. Alimentary Pharmacology & Therapeutics 14(8): 1065-70	Not relevant
Huskins WC, Huckabee CM, O'Grady NP, et al. (2011) Intervention to reduce transmission of resistant bacteria in intensive care. The New England Journal of Medicine 364(15): 1407-18	Not relevant
Ivanovska V, Holloway KA. (2013) Interventions to improve antibiotic prescribing in upper middle income countries: A systematic review of the literature 1990-2009. Macedonian Journal of Medical Sciences 6(1): 84-91	Not relevant
Jafri NS, Hornung CA, Howden CW. (2008) Meta-analysis: Sequential therapy appears superior to standard therapy for Helicobacter pylori infection in patients naive to treatment. Annals of Internal Medicine 148(12): 923-31	Not relevant
Jeyaratnam D, Whitty CJM, Phillips K et al. (2008) Impact of rapid screening tests on acquisition of meticillin resistant Staphylococcus aureus: cluster randomised crossover trial. BMJ (Clinical Research Edition) 336: 927-30	Not relevant
Johnson CE, Maslow JN, Fattler RN, et al. (1993) The role of bacterial adhesins in the outcome of childhood urinary tract infections. Am J Dis Child 147: 1090-3	No results given
Joyce FS, Szczepanski KP. (1986) A double-blind comparative study of prophylactic antibiotic therapy in open heart surgery: penicillin G versus vancomycin. Thoracic and Cardiovascular Surgeon 34(2): 100-3	Not relevant
Kaki R, Elligsen M, Walker S, et al. (2011) Impact of antimicrobial stewardship in critical care: a systematic review. The Journal of Antimicrobial Chemotherapy 669(6): 1223-30	Not an RCT or systematic review of RCTs
Karp JE, Merz WG, Hendricksen C, et al. (1987) Oral norfloxacin for prevention of gram-negative bacterial infections in patients with acute leukemia and granulocytopenia. A randomized, double-blind, placebo-controlled trial. Annals of Internal Medicine 106(1): 1-7	No relevant comparator
Kato D, Maezawa K, Yonezawa I, et al. (2006) Randomized prospective study on prophylactic antibiotics in clean orthopedic surgery in one ward for 1 year. Journal of orthopaedic science : official journal of the Japanese Orthopaedic Association 11(1): 20-7	Not an RCT or systematic review of RCTs
Kato Y, Shime N, Hashimoto S, et al. (2007) Effects of controlled perioperative antimicrobial prophylaxis on infectious outcomes in pediatric cardiac surgery. Critical care medicine 35(7): 1763-8	Not an RCT or systematic review of RCTs
Katsios CM, Burry L, Nelson S, et al. (2012) An antimicrobial stewardship program improves antimicrobial treatment by culture site and the quality of antimicrobial prescribing in critically ill patients (Provisional abstract). Critical Care 16(6)	Not an RCT or systematic review of RCTs
Katz S, Glicksman A, Levy Y, et al. (1993) Cefuroxime prophylaxis in biliary surgery: single versus triple dose. Israel journal of medical sciences 29(11): 673-6	Not relevant
Kaufman D, Boyle R, Hazen KC, et al. (2005) Twice weekly fluconazole prophylaxis for prevention of invasive Candida infection in high-risk infants of <1000 grams birth weight. The Journal of Pediatrics 147(2): 172-9	Not relevant study

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Keighley MR, Arabi Y, Alexander-Williams J, et al. (1979) Comparison between systemic and oral antimicrobial prophylaxis in colorectal surgery. Lancet 1(8122): 894-7	Not relevant
Kellum JM, Gargano S, Gorbach SL, et al. (1984) Antibiotic prophylaxis in high-risk biliary operations: multicenter trial of single preoperative ceftriaxone versus multidose cefazolin. American Journal of Surgery 148(4A): 15-8	Not relevant
Kerremans JJ, Verboom P, Stijnen T, et al. (2008) Rapid identification and antimicrobial susceptibility testing reduce antibiotic use and accelerate pathogen-directed antibiotic use. The Journal of Antimicrobial Chemotherapy 61(2): 428-35	Not relevant
Kim SJ, Toma HS. (2011) Antimicrobial resistance and ophthalmic antibiotics: 1-year results of a longitudinal controlled study of patients undergoing intravitreal injections. Archives of Ophthalmology 129: 1180-8	Not relevant
Kim SJ, Toma HS. (2011) Ophthalmic antibiotics and antimicrobial resistance a randomized, controlled study of patients undergoing intravitreal injections. Ophthalmology 118(7): 1358-63	Not relevant
Kondell PA, Nord CE. (1984) Influence on oropharyngeal and nasal carriage of Staphylococcus aureus by dicloxacillin therapy in patients undergoing oral surgery. International Journal of Oral Surgery 13(3)	Not relevant
Kopterides P, Siempos II, Tsangaris I et al. (2010) Procalcitonin-guided algorithms of antibiotic therapy in the intensive care unit: a systematic review and meta-analysis of randomized controlled trials. Critical care medicine 38: 2229-41.	Duplicate of included population
Korbila IP, Tansarli GS, Karageorgopoulos DE, et al. (2013) Extended or continuous versus short-term intravenous infusion of cephalosporins: A meta-analysis. Expert review of Anti-infective Therapy 11(6): 585-95	Not relevant
Kullar R, Davis SL, Kaye KS, et al. (2013) Implementation of an antimicrobial stewardship pathway with daptomycin for optimal treatment of methicillin-resistant Staphylococcus aureus bacteremia (Provisional abstract). Pharmacotherapy 33(1): 3-10	Not relevant
Kusachi S, Sumiyama Y, Nagao J, et al. (2008) Prophylactic antibiotics given within 24 hours of surgery, compared with antibiotics given for 72 hours perioperatively, increased the rate of methicillin-resistant Staphylococcus aureus isolated from surgical site infections. Journal of Infection and Chemotherapy: Official Journal of the Japan Society of Chemotherapy 14(1): 44-50	Not an RCT or systematic review of RCTs
Kyriakidou KG, Rafailidis P, Matthaiou DK, et al. (2008) Short- versus long-course antibiotic therapy for acute pyelonephritis in adolescents and adults: a meta-analysis of randomized controlled trials. Clinical Therapeutics 30(10): 1859-68	Not relevant
Lacey RW, Simpson MH, Lord VL, et al. (1981) Comparison of single-dose trimethoprim with a five-day course for the treatment of urinary tract infections in the elderly. Age and ageing 10(3): 179-85	Not an RCT or systematic review of RCTs
Latha K, Ruckmani A (2010) The effect of verapamil in malaria - a prospective randomized double blind control clinical study. Journal of Clinical and Diagnostic Research 4(4): 2707-13.	Not relevant
Le Corvoisier P, Renard V, Roudot-Thoraval F, et al. (2013) Long-term effects of an educational seminar on antibiotic prescribing by GPs: a randomised controlled trial. The British Journal of General Practice: Journal of the Royal College of General Practitioners 63(612): e455-e464	No relevant outcomes
Leach A, Morris P.(2003) Pneumococcal resistance of long-term	Unable to source

Author	Reason for exclusion
antibiotics for prevention of otitis media: a randomized placebo controlled trial ina high-risk population. 8th International Symposium on Recent Advances in Otitis Media 3-7 June, Fort Lauderdale USA: 250 Abstract	
Lee TA, Hacek DM, Stroupe KT, et al. (2005) Three surveillance strategies for vancomycin-resistant enterococci in hospitalized patients: detection of colonization efficiency and a cost-effectiveness model (Structured abstract). Infection Control and Hospital Epidemiology 26(1): 39-46	Not relevant
Lehman DA, Chung MH, Mabuka JM, et al. (2009) Lower risk of resistance after short-course HAART compared with zidovudine/single-dose nevirapine used for prevention of HIV-1 mother-to-child transmission. Journal of acquired immune deficiency syndromes (1999) 51(5): 522-9	Unable to extrapolate to UK setting
Leibovitz E, Piglansky L, Raiz S, et al. (2000) Bacteriologic and clinical efficacy of one day vs. three day intramuscular ceftriaxone for treatment of nonresponsive acute otitis media in children. Pediatric Infectious Disease Journal 19(11): 1040-5	Not relevant
Li JZ, Winston LG, Moore DH, et al. (2007) Efficacy of short-course antibiotic regimens for community-acquired pneumonia: a meta-analysis. The American journal of medicine 120(9): 783-90	Not relevant
Linner A, Sunden-Cullberg J, Johansson L, et al. (2013) Short- and long-term mortality in severe sepsis/septic shock in a setting with low antibiotic resistance: a prospective observational study in a Swedish university hospital. Frontiers in Public Health 1: 51	Not an RCT or systematic review of RCTs
Lipsky BA, Holroyd KJ, Zasloff M. (2008) Topical versus systemic antimicrobial therapy for treating mildly infected diabetic foot ulcers: a randomized, controlled, double-blinded, multicenter trial of pexiganan cream. Clinical Infectious Diseases: an official publication of the Infectious Diseases Society of America 47: 1537-45	Not relevant
Little P, Stuart B, Francis N, et al. (2013) Effects of internet-based training on antibiotic prescribing rates for acute respiratory-tract infections: a multinational, cluster, randomised, factorial, controlled trial. Lancet 382(9899): 1175-82	Not relevant
Lord RW. (2000) Is a 5-day course of antibiotics as effective as a 10-day course for the treatment of streptococcal pharyngitis and the prevention of poststreptococcal sequelae? Journal of Family Practice 49(12): 1147	No relevant comparator
Mandel EM, Casselbrant ML, Rockette HE, et al. (1996) Efficacy of antimicrobial prophylaxis for recurrent middle ear effusion. Pediatric Infectious Disease Journal 15(12): 1074-82	No relevant comparator
Martinez J-A, Nicolas J-M, Marco F, et al. (2006) Comparison of antimicrobial cycling and mixing strategies in two medical intensive care units. Critical care medicine 34(2): 329-36	Not an RCT or systematic review of RCTs
Mathew R, Rehman F, Santha T, et al. (1997) A controlled clinical trial of oral short-course regimens in the treatment of sputum-positive pulmonary tuberculosis. Tuberculosis Research Centre. International Journal of Tuberculosis and Lung Disease 1(6): 509-17	Unable to extrapolate to UK setting
Mathur P, Trikha V, Farooque K ,et al. (2013) Implementation of a short course of prophylactic antibiotic treatment for prevention of postoperative infections in clean orthopaedic surgeries. The Indian Journal of Medical Research 137(1): 111-6	No relevant comparator
Matthaiou DK, Ntani G, Kontogiorgi M, et al. (2012) An ESICM systematic review and meta-analysis of procalcitonin-guided antibiotic therapy algorithms in adult critically ill patients. Intensive Care Medicine 38(6): 940-9	Not relevant

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McIntyre JA, Hopley M, Moodley D, et al. (2009) Efficacy of short-course AZT plus 3TC to reduce nevirapine resistance in the prevention of mother-to-child HIV transmission: a randomized clinical trial. PLoS medicine 6(10): e1000172	Unable to extrapolate to UK setting
Mehra S, Moerkerke M, Welck J, et al. (1998) Short course therapy with cefuroxime axetil for group A streptococcal tonsillopharyngitis in children. Pediatric Infectious Disease Journal 17(6): 452-7	Not relevant
Menzies D, Benedetti A, Paydar A, et al. (2009) Effect of duration and intermittency of rifampin on tuberculosis treatment outcomes: a systematic review and meta-analysis. PLoS medicine 6(9): e1000146	Unable to extrapolate to UK setting
Meyer E, Buttler J, Schneider C, et al. (2007) Modified guidelines impact on antibiotic use and costs: duration of treatment for pneumonia in a neurosurgical ICU is reduced (Provisional abstract). Journal of Antimicrobial Chemotherapy 59(6): 1148-54	Not an RCT or systematic review of RCTs
Michael M, Hodson EM, Craig JC, et al. (2002) Short compared with standard duration of antibiotic treatment for urinary tract infection: a systematic review of randomised controlled trials. Archives of disease in childhood 87(2): 118-23	Systematic review, not all studies relevant. Relevant studies extracted and included in analysis
Michael M, Hodson EM, Craig JC, et al. (2003) Short versus standard duration oral antibiotic therapy for acute urinary tract infection in children. The Cochrane database of systematic reviews(1)	Duplicate article
Michaelidis CI, Zimmerman RK, Nowalk MP, et al. (2014) Cost-effectiveness of procalcitonin-guided antibiotic therapy for outpatient management of acute respiratory tract infections in adults. Journal of General Internal Medicine 29(4): 579-86	Not relevant
Milos V, Jakobsson U, Westerlund T, et al. (2013) Theory-based interventions to reduce prescription of antibiotics--a randomized controlled trial in Sweden. Family Practice 30(6): 634-40	Not relevant
Moore M, Stuart B, Coenen S, et al. (2014) Amoxicillin for acute lower respiratory tract infection in primary care: subgroup analysis of potential high-risk groups. The British Journal of General Practice : the Journal of the Royal College of General Practitioners 64: e75-e80	Not relevant
Morris DL, Young D, Burdon DW, et al. (1984) Prospective randomized trial of single dose cefuroxime against mezlocillin in elective gastric surgery. Journal of Hospital Infection 5(2): 200-4	Not relevant
Neuman M, Langer R, Bachar R, et al. (2012) Penicillin-tetracycline prophylaxis in cesarean delivery: prospective and randomized comparison of short and long term therapy. Journal of Perinatal Medicine 18(2): 145-8	No relevant comparator
Nicolle LE. (2014) Antimicrobial stewardship in long term care facilities: What is effective? Antimicrobial resistance and Infection Control 3(1)	Not relevant
Niel-Weise BS, van den Broek PJ, da Silva EMK, et al. (2012) Urinary catheter policies for long-term bladder drainage. The Cochrane Database of Systematic Reviews 8: CD004201	Not relevant
Nijssen S, Fluit A, van de Vijver D, et al. (2010) Effects of reducing beta-lactam antibiotic pressure on intestinal colonization of antibiotic-resistant gram-negative bacteria. Intensive Care Medicine 36(3): 512-9	Not an RCT or systematic review of RCTs
Notowicz A, Stolz E, Klingeren B. (1984) A double blind study comparing two dosages of enoxacin for the treatment of uncomplicated urogenital gonorrhoea. Journal of Antimicrobial Chemotherapy 14 (Suppl C): 91-4	Not relevant
Nseir S, Ader F, Marquette CH. (2009) Nosocomial tracheobronchitis. Current opinion in infectious diseases 22(2): 148-53	Not an RCT or systematic review of RCTs

Author	Reason for exclusion
Oguz F, Unüvar E, Lu Y, et al. (2003) Etiology of acute otitis media in childhood and evaluation of two different protocols of antibiotic therapy: 10 days cefaclor vs. 3 days azitromycin. International Journal of Pediatric Otorhinolaryngology 67(1): 43-51	Not relevant
Ohm MJ, Galask RP. (1975) The effect of antibiotic prophylaxis on patients undergoing vaginal operations. I. The effect on morbidity. American Journal of Obstetrics and Gynecology 123(6): 590-6.	No relevant comparator
Pakistan Multicentre Amoxicillin Short Course Therapy (MASCOT) pneumonia study group. (2002) Clinical efficacy of 3 days versus 5 days of oral amoxicillin for treatment of childhood pneumonia: a multicentre double-blind trial. Lancet 360(9336): 835-41	Unable to extrapolate to UK setting
Palmer S, Boltz VF, Chow JY et al. (2012) Short-course Combivir after single-dose nevirapine reduces but does not eliminate the emergence of nevirapine resistance in women. Antiviral therapy 17(2): 327-36	Unable to extrapolate to UK setting
Pankhurst CL (2012) Candidiasis (oropharyngeal). Clinical evidence 2012	Systematic review, not all studies relevant. Relevant studies extracted and included in analysis
Parthasarathy R, Prabhakar R, Somasundaram PR. (1986) A controlled clinical trial of 3- and 5-month regimens in the treatment of sputum-positive pulmonary tuberculosis in South India. American review of respiratory disease 134(1): 27-33	Not an RCT or systematic review of RCTs
Pasipanodya JG, Gumbo T. (2013) A meta-analysis of self-administered vs directly observed therapy effect on microbiologic failure, relapse, and acquired drug resistance in tuberculosis patients. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 57(1): 21-31	Not an RCT or systematic review of RCTs
Patacchiola F, Paolantonio L, Palermo P, et al. (2000) Antibiotic prophylaxis of postcesarean infections. Personal experience. Minerva Ginecologica 52(10): 385-9	Not English language
Patel SJ, Oshodi A, Prasad P et al. (2009) Antibiotic use in neonatal intensive care units and adherence with Centers for Disease Control and Prevention 12 Step Campaign to Prevent Antimicrobial Resistance. Pediatric Infectious Disease Journal 28: 1047-51.	Not an RCT or systematic review of RCTs
Pessey JJ, Gehanno P, Thoroddsen E, et al. (1999) Short course therapy with cefuroxime axetil for acute otitis media: results of a randomized multicenter comparison with amoxicillin/clavulanate. Pediatric Infectious Disease Journal 18(10): 854-9	Not relevant
Phuong CXT, Kneen R, Anh NT, et al. (1999) A comparative study of ofloxacin and cefixime for treatment of typhoid fever in children. Pediatric Infectious Disease Journal 18(3): 245-8	Not relevant
Plummer A, Wildman M (2013) Duration of intravenous antibiotic therapy in people with cystic fibrosis. The Cochrane database of systematic reviews (5): CD006682	Not relevant
Pontzer RE, Krieger RE, Boscia JA, et al. (1983) Single-dose cefonicid therapy for urinary tract infections. Antimicrobial Agents and Chemotherapy 23(6): 814-6	No relevant comparator
Prentice HG, Hann IM, Nazareth B, et al. (2001) Oral ciprofloxacin plus colistin: prophylaxis against bacterial infection in neutropenic patients. A strategy for the prevention of emergence of antimicrobial resistance. British Journal of Haematology 115(1): 46-52	No relevant comparator
Pugh R, Grant C, Cooke RP, et al. (2011) Short-course versus prolonged-course antibiotic therapy for hospital-acquired pneumonia in critically ill adults. The Cochrane Database of Systematic	Systematic review, not all studies relevant. Relevant studies extracted and

Author	Reason for exclusion
Reviews(10): CD007577	included in analysis
Rajabi-Mashhadi MT, Mousavi SH, Mh K-M, et al. (2012) Optimum duration of perioperative antibiotic therapy in patients with acute non-perforated appendicitis: A prospective randomized trial. Asian Biomedicine 6(6): 891-4	Not relevant
Rajan GP, Fergie N, Fischer U, et al. (2005) Antibiotic prophylaxis in septorhinoplasty? A prospective, randomized study. Plastic and Reconstructive Surgery 116(7): 1995-8	Not relevant
Rapp RP, Connors JE, Hager WD et al. (1986) Comparison of single-dose moxalactam and a three-dose regimen of cefoxitin for prophylaxis in vaginal hysterectomy. Clinical pharmacy 5(12): 988-93	No relevant comparator
Roberts JA, Kruger P, Paterson DL, et al. (2008) Antibiotic resistance--what's dosing got to do with it? Critical Care Medicine 36: 2433-40	Not an RCT or systematic review of RCTs
Roos K, Tellier G, Baz M, et al. (2005) Clinical and bacteriological efficacy of 5-day telithromycin in acute maxillary sinusitis: a pooled analysis. The Journal of Infection 50(3): 210-20	Not an RCT or systematic review of RCTs
Sack DA, Kaminsky DC, Sack RB, et al. (1978) Prophylactic doxycycline for travelers' diarrhea. Results of a prospective double-blind study of Peace Corps volunteers in Kenya. New England Journal of Medicine 298(14): 758-63	Not relevant
Saginur R, Croteau D, Bergeron MG. (2000) Comparative efficacy of teicoplanin and cefazolin for cardiac operation prophylaxis in 3027 patients. The ESPRIT Group. Journal of Thoracic and Cardiovascular Surgery 120(6): 1120-30	No relevant comparator
Sandock DS, Gothe BG, Bodner DR. (1995) Trimethoprim-sulfamethoxazole prophylaxis against urinary tract infection in the chronic spinal cord injury patient. Paraplegia 33(3): 156-60	No relevant comparator
Schrag SJ, Peña C, Fernández J, et al. (2001) Effect of short-course, high-dose amoxicillin therapy on resistant pneumococcal carriage: a randomized trial. JAMA : the journal of the American Medical Association 286(1): 49-56	Not relevant
Schroeder S, Hochreiter M, Koehler T, et al. (2009) Procalcitonin (PCT)-guided algorithm reduces length of antibiotic treatment in surgical intensive care patients with severe sepsis: results of a prospective randomized study. Langenbeck's Archives of Surgery / Deutsche Gesellschaft fur Chirurgie 394(2): 221-6	Not relevant
Schuetz P, Briel M, Mueller B. (2013) Clinical outcomes associated with procalcitonin algorithms to guide antibiotic therapy in respiratory tract infections. JAMA - Journal of the American Medical Association 309(7): 717-8	Not an RCT or systematic review of RCTs
Schuetz P, Muller B, Christ-Crain M, et al. (2013) Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. Evidence-Based Child Health 8: 1297-371	No relevant outcomes
Schütze K, Hentschel E, Hirschl AM. (1996) Clarithromycin or amoxycillin plus high-dose ranitidine in the treatment of Helicobacter pylori-positive functional dyspepsia. European Journal of Gastroenterology & Hepatology 8: 41-6	Not relevant
Shaikh ZH, Osting CA, Hanna HA, et al. (2002) Effectiveness of a multifaceted infection control policy in reducing vancomycin usage and vancomycin-resistant enterococci at a tertiary care cancer centre (Structured abstract). Journal of Hospital Infection 51: 52-8	Not an RCT or systematic review of RCTs
Shigemura K, Tanaka K, Yasuda M et al. (2005) Efficacy of 1-day prophylaxis medication with fluoroquinolone for prostate biopsy. World journal of urology 23: 356-60	Not relevant

Author	Reason for exclusion
Shiu J, Wang E, Tejani AM, et al. (2013) Continuous versus intermittent infusions of antibiotics for the treatment of severe acute infections. The Cochrane Database of Systematic Reviews 3: CD008481	Not relevant
Siegel JD, McCracken GH, Threlkeld N, et al. (1982) Single-dose penicillin prophylaxis of neonatal group-B-streptococcal disease. Lancet 1(8287):1426-30	Not relevant
Silva-Brenda NG, Andriolo RB, Atallah ÁN et al. (2013) De-escalation of antimicrobial treatment for adults with sepsis, severe sepsis or septic shock. The Cochrane Database of Systematic Reviews(3)	Not relevant
Singh N. (1998) Short-Course Empiric Antibiotic Therapy for Suspected Nosocomial Pneumonia: a Proposed Solution for Indiscriminate Antibiotic Prescription for Pulmonary Infiltrates in the ICU (abstract). Infectious Diseases Society of America	Abstract only
Sinha LM, Yunus A, Hussain S, et al. (2012) Antibiotic prophylaxis for preventing surgical site infection after coronary artery bypass graft: Prospective randomized comparative study. Pakistan Journal of Medical and Health Sciences 6: 742-5	Not relevant
Smith SR, Montgomery LG, Williams JWJ. (2012) Treatment of mild to moderate sinusitis. Archives of internal medicine 172: 510-3	Not an RCT or systematic review of RCTs
Smyth AR, Walters S. (2012) Prophylactic anti-staphylococcal antibiotics for cystic fibrosis. The Cochrane database of systematic reviews 12: CD001912	Not an RCT or systematic review of RCTs
Song F, Glenny A-M. (1998) Antimicrobial prophylaxis in colorectal surgery: a systematic review of randomised controlled trials. Health Technology Assessment 2(7): 1-IV	Not relevant
Southern KW, Barker PM, Solis MA, et al. (2012) Macrolide antibiotics for cystic fibrosis. The Cochrane Database of Systematic Reviews	Not relevant
Spurling-Geoffrey KP, Del-Mar CB, Dooley L, et al. (2013) Delayed antibiotics for respiratory infections. The Cochrane Database of Systematic Reviews (11)	Not relevant
Stage AH, Glover DD, Vaughan JE. (1982) Low-dose cephradine prophylaxis in obstetric and gynecologic surgery. Journal of Reproductive Medicine 27: 113-9	Unable to extrapolate to UK setting
Steingart KR, Sohn H, Schiller I, et al. (2013) Xpert MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane database of systematic reviews 1: CD009593	Not relevant
Stewart A, Inglis-Garry DT, Jardine LA, et al. (2012) Prophylactic antibiotics to reduce morbidity and mortality in newborn infants with intercostal catheters. Cochrane Database of Systematic Reviews(4)	Not an RCT or systematic review of RCTs
Stiver HG, Forward KR, Tyrrell DL. (1984) Comparative cervical microflora shifts after cefoxitin of cefazolin prophylaxis against infection following cesarean section. American Journal of Obstetrics and Gynecology 149: 718-21	Not relevant
Syrogiannopoulos GA, Bozdogan B, Grivea IN, et al. (2004) Two dosages of clarithromycin for five days, amoxicillin/clavulanate for five days or penicillin V for ten days in acute group A streptococcal tonsillopharyngitis. Pediatric Infectious Disease Journal 23: 857-65	No relevant comparator
T P, Miller LG. (2001) Empirical therapy for uncomplicated urinary tract infections in an era of increasing antimicrobial resistance: a decision and cost analysis (Structured abstract). Clinical Infectious Diseases 33: 615-21	Not relevant
Ta CN, He L, Nguyen E, et al. (2006) Does not answer the question of resistance.Prospective randomized study determining whether a 3-	Not relevant

Author	Reason for exclusion
day application of ofloxacin results in the selection of fluoroquinolone-resistant coagulase-negative Staphylococcus. European Journal of Ophthalmology 16: 359-64	
Tacconelli E, De Angelis G, Cataldo MA, et al. (2008) Does antibiotic exposure increase the risk of methicillin-resistant Staphylococcus aureus (MRSA) isolation? A systematic review and meta-analysis. The Journal of Antimicrobial Chemotherapy 61: 26-38	Not relevant
Talan DA, Stamm WE, Hooton TM, et al. (2000) Comparison of ciprofloxacin (7 days) and trimethoprim-sulfamethoxazole (14 days) for acute uncomplicated pyelonephritis pyelonephritis in women: a randomized trial. JAMA : the journal of the American Medical Association 283: 1583-90	No relevant comparator
Tamayo E, Gualis J, Florez S, et al. (2008) Comparative study of single-dose and 24-hour multiple-dose antibiotic prophylaxis for cardiac surgery. The Journal of Thoracic and Cardiovascular Surgery 136: 1522-7	Not relevant
Tellier G, Niederman MS, Nusrat R, et al. (2004) Clinical and bacteriological efficacy and safety of 5 and 7 day regimens of telithromycin once daily compared with a 10 day regimen of clarithromycin twice daily in patients with mild to moderate community-acquired pneumonia. Journal of Antimicrobial Chemotherapy 54: 515-23	Not relevant
Toltzis P, Yamashita T, Vilt L, et al. (1998) Antibiotic restriction does not alter endemic colonization with resistant gram-negative rods in a pediatric intensive care unit. Critical Care Medicine 26: 1893-9.	Not an RCT or systematic review of RCTs
Toltzis P, Dul MJ, Hoyen C, et al. (2002) The effect of antibiotic rotation on colonization with antibiotic-resistant bacilli in a neonatal intensive care unit. Pediatrics 110: 707-11.	Not an RCT or systematic review of RCTs
Tramper-Stranders GA, Wolfs TFW, van Haren Noman S et al. (2010) Controlled trial of cycled antibiotic prophylaxis to prevent initial Pseudomonas aeruginosa infection in children with cystic fibrosis. Thorax 65: 915-20	No relevant comparator
Troitino AX, Porhomayon J, El-Solh AA. (2013) Guideline-concordant antimicrobial therapy for healthcare-associated pneumonia: a systematic review and meta-analysis. Lung 191: 229-37	No relevant outcomes
van Buul LW, van der Steen JT, Veenhuizen RB, et al. (2012) Antibiotic Use and Resistance in Long Term Care Facilities. Journal of the American Medical Directors Association 13: 568	Not an RCT or systematic review of RCTs
van den Brand IC, Castelein RM. (2001) Total joint arthroplasty and incidence of postoperative bacteriuria with an indwelling catheter or intermittent catheterization with one-dose antibiotic prophylaxis: a prospective randomized trial. Journal of Arthroplasty 16: 850-5	Not relevant
Van Dyke RB, Ngo-Giang-Huong N, Shapiro DE, et al. (2012) A comparison of 3 regimens to prevent nevirapine resistance mutations in HIV-infected pregnant women receiving a single intrapartum dose of nevirapine. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 54: 285-93	Unable to extrapolate to UK setting
Van Poppel H, Willemen P, Wegge M, et al. (1990) Antibiotic cover of transurethral maneuvers with ciprofloxacin and susceptibility behavior of pathogens in patients with neurogenic bladder. Urologia Internationalis 45: 342-5	No relevant outcomes
van Zon A, van der Heijden GJ, van Dongen TMA, et al. (2012) Antibiotics for otitis media with effusion in children. The Cochrane Database of Systematic Reviews(9): CD009163	Not relevant
Vettese N, Hendershot J, Irvine M, et al. (2013) Outcomes associated with a thrice-weekly antimicrobial stewardship programme in a 253-	No relevant outcomes

Author	Reason for exclusion
bed community hospital (Provisional abstract). Journal of clinical Pharmacy and Therapeutics 38: 401-4	
Vodicka TA, Thompson M, Lucas P, et al. (2013) Reducing antibiotic prescribing for children with respiratory tract infections in primary care: a systematic review. The British Journal of General Practice: the Journal of the Royal College of General Practitioners 63: e445-e454	No relevant outcomes
Vollenweider DJ, Jarrett H, Steurer-Stey CA, et al. (2012) Antibiotics for exacerbations of chronic obstructive pulmonary disease. The Cochrane Database of Systematic Reviews (12): CD010257	No relevant outcomes
Weaver M, Burdon DW, Youngs DJ, et al. (1986) Oral neomycin and erythromycin compared with single-dose systemic metronidazole and ceftriaxone prophylaxis in elective colorectal surgery. American Journal of Surgery 151: 437-42	No relevant comparator
Wenzhen Y, Yumin L, Quanlin G, et al. (2010) Is antimicrobial susceptibility testing necessary before first-line treatment for Helicobacter pylori infection? Meta-analysis of randomized controlled trials. Internal Medicine 49: 1103-9	Not relevant
West TE, Guerry C, Hiott M, et al. (2006) Effect of targeted surveillance for control of methicillin-resistant Staphylococcus aureus in a community hospital system (Structured abstract). Infection Control and Hospital Epidemiology 27: 233-8	Not an RCT or systematic review of RCTs
Wilton P, Smith R, Coast J, et al. (2002) Strategies to contain the emergence of antimicrobial resistance: a systematic review of effectiveness and cost-effectiveness. Journal of Health Services Research & Policy 7: 111-7	Systematic review, not all studies relevant. Relevant studies extracted and included in analysis
Wong RLM, Gangwani RA, Yu LWH, et al. (2012) New treatments for bacterial keratitis. Journal of Ophthalmology 2012: 831502	Not relevant
Wurzer H, Rodrigo L, Stamler D et al. (1997) Short-course therapy with amoxycillin-clarithromycin triple therapy for 10 days (ACT-10) eradicates Helicobacter pylori and heals duodenal ulcer. ACT-10 Study Group. Alimentary pharmacology & therapeutics 11: 943-52	No relevant comparator
Yardley L, Douglas E, Anthierens S et al. (2013) Evaluation of a web-based intervention to reduce antibiotic prescribing for LRTI in six European countries: quantitative process analysis of the GRACE/INTRO randomised controlled trial. Implementation Science 8:134	No relevant outcomes
Young SW, Zhang M, Freeman JT, et al. (2014) The Mark Coventry Award: Higher tissue concentrations of vancomycin with low-dose intraosseous regional versus systemic prophylaxis in TKA: a randomized trial. Clinical Orthopaedics and Related Research 472: 57-65	Not relevant
Zalmanovici TA, Green H, Paul M, et al. (2010) Antimicrobial agents for treating uncomplicated urinary tract infection in women. The Cochrane Database of Systematic Reviews (10)	Not relevant
Zhang ZM, Zhang ZJ, Li PJ, et al. (2010) Value of diagnostic tests for the ethambutol resistance in Mycobacterium tuberculosis: a systematic review (Provisional abstract). Chinese Journal of Evidence-Based Medicine 10: 1456-60	Not relevant
Zhou YQ, Xu L, Wang BF, et al. (2012) Modified Sequential Therapy Regimen versus Conventional Triple Therapy for Helicobacter Pylori Eradication in Duodenal Ulcer Patients in China: A Multicenter Clinical Comparative Study. Gastroenterology Research and Practice 2012: 405425	No relevant comparator
Zhu H, Lei X, Zhang F, et al. (2012) Effectiveness and safety of levofloxacin for multidrug resistant pulmonary tuberculosis: a	Not relevant

Author	Reason for exclusion
systematic review (Provisional abstract). Chinese Journal of Evidence-Based Medicine 12: 201-8	

Excluded de-escalation studies

Author	Reason for exclusion
Anon. (2011) Early intervention with empirical antibacterials is essential in the treatment of ventilator-associated pneumonia. Drugs Therapy Perspectives 27(6):9-12	Not an RCT or a systematic review of RCTs
Anon. (2007) Second-line antibiotics more effective than first line in acute exacerbation of chronic bronchitis. Journal of the National Medical Association 99(12):1421-1422	Not relevant
Alvarez-Lerma F. (1996) Modification of empiric antibiotic treatment in patients with pneumonia acquired in the intensive care unit. ICU-Acquired Pneumonia Study Group. Intensive Care Medicine 22(5): 387-394	Not an RCT or a systematic review of RCTs
Alvarez-Lerma F, Alvarez, B, Luque, P. et al. (2006) Empiric broad-spectrum antibiotic therapy of nosocomial pneumonia in the intensive care unit: a prospective observational study. Critical Care 10(3): R78	Not an RCT or a systematic review of RCTs
Alvarez-Lerma F, Grau S. (2012) Management of antimicrobial use in the intensive care unit. Drugs 72(4):447-470	Not an RCT or a systematic review of RCTs
Antonelli M, Mercurio G, Di Nunno S, et al. (2001) De-escalation antimicrobial chemotherapy in critically III patients: pros and cons. Journal of Chemotherapy 13(1):218-23	Not an RCT or a systematic review of RCTs
Arnold HM, Micek ST, Skrupky LP, Kollef MH. (2011) Antibiotic stewardship in the intensive care unit. Seminars in Respiratory and Critical Care Medicine 32(2):215-227	Not an RCT or a systematic review of RCTs
Au E, Ang PT. (1993) Management of chemotherapy-induced neutropenic sepsis--combination of cephalosporin and aminoglycoside. Annals of the Academy of Medicine Singapore 22(3):319-22	Not an RCT or a systematic review of RCTs
Averbuch D, Orasch C, Cordonnier C, et al. (2013) European guidelines for empirical antibacterial therapy for febrile neutropenic patients in the era of growing resistance: Summary of the 2011 4th European Conference on Infections in Leukemia. Haematologica 98(12):1826-35	Not relevant
Badawy AA, Zaher TI, Sharaf SM, et al.(2013) Effect of alternative antibiotics in treatment of cefotaxime resistant spontaneous bacterial peritonitis. World Journal of Gastroenterology 19(8):1271-77	Not relevant
Camargo LFA. (2013) The "de-escalation Concept" and Antibiotic De-escalation: A Missed Opportunity? Shock 39: 29-31	Not an RCT or a systematic review of RCTs
Chastre J. (2006) Ventilator-associated pneumonia: what is new? Surgical Infections (7)Suppl 2: 81-85	Not an RCT or a systematic review of RCTs
Chastre J, Blasi F, Masterton RG, et al. (2014) European perspective and update on the management of nosocomial pneumonia due to methicillin-resistant Staphylococcus aureus after more than 10 years of experience with linezolid. Clinical Microbiology and Infection (20) Suppl 4:19-36	Not an RCT or a systematic review of RCTs
Cotta MO, Roberts JA, Tabah A, et al. (2014) Antimicrobial stewardship of beta-lactams in intensive care units. Expert Review of Anti Infectious Therapy 12(5):581-595	Not an RCT or a systematic review of RCTs
Craven D, Vella S. (1999) A case for proactive switching? AIDS Clinical Care 11(8):66-7	Not relevant
Craven DE, Palladino R, McQuillen DP. (2004) Healthcare-associated pneumonia in adults: management principles to improve outcomes. Infect Disease Clinics of North America 18(4):939-62	Not an RCT or a systematic review of RCTs

Author	Reason for exclusion
Dalhoff K, Ewig S.(2013) Adult patients with nosocomial pneumonia: epidemiology, diagnosis, and treatment. Deutsches Arzteblatt International 110 (38): 634-40	Not an RCT or a systematic review of RCTs
Dellit TH, Chan JD, Skerrett SJ, et al. (2008) Development of a guideline for the management of ventilator-associated pneumonia based on local microbiologic findings and impact of the guideline on antimicrobial use practices. Infect Control and Hospital Epidemiology 29(6): 525-33	Not an RCT or a systematic review of RCTs
Depuydt, P, Myny, D, Blot S. (2006) Nosocomial pneumonia: Aetiology, diagnosis and treatment. Current Opinion in Pulmonary Medicine 2006; 12(3):192-97	Not an RCT or a systematic review of RCTs
Dennesen PJ, van der Ven AJ, Kessels AG, et al. (2001) Resolution of infectious parameters after antimicrobial therapy in patients with ventilator-associated pneumonia. American Journal Respiratory Critical Care Medicine 163(6):1371-5	Not an RCT or a systematic review of RCTs
DeRyke CA, Maglio D, Nicolau DP. (2005) Defining the need for new antimicrobials: clinical and economic implications of resistance in the hospitalised patient. Expert Opinion in Pharmacotherapy 6(6):873-89	Not an RCT or a systematic review of RCTs
Driscoll JA, Brody SL, Kollef MH. (2007) The epidemiology, pathogenesis and treatment of Pseudomonas aeruginosa infections. Drugs 67(3):351-68	Not an RCT or a systematic review of RCTs
Eachempati,SR, Hydo LJ. et al.(2014) Does De-Escalation of Antibiotic Therapy for Ventilator-Associated Pneumonia Affect the Likelihood of Recurrent Pneumonia or Mortality in Critically Ill Surgical Patients? Journal of Trauma-Injury Infection & Critical Care 66(5):1343-48	Not an RCT or a systematic review of RCTs
File TMJ. (2012) Duration and cessation of antimicrobial treatment. Journal of Hospital Medicine 7(Suppl 1):S22-33	Not an RCT or a systematic review of RCTs
Franzetti F, Antonelli M, et al. (2010) Consensus document on controversial issues for the treatment of hospital-associated pneumonia. International Journal of Infectious Diseases 14 (Suppl 4) S55-65	Reference checked, no additional studies identified
Giamarellou H.(2010) Multidrug-resistant gram-negative bacteria: how to treat and for how long. International Journal of Antimicrobial Agents 36 (Suppl 2):S50-4	Not an RCT or a systematic review of RCTs
Hoffken G, Niederman MS. (2002) Nosocomial pneumonia: The importance of a de-escalating strategy for antibiotic treatment of pneumonia in the ICU. Chest 122(6):2183-96	Not an RCT or a systematic review of RCTs
Ibrahim EH, Ward S, Sherman G, et al. (2001) Experience with a clinical guideline for the treatment of ventilator-associated pneumonia. Critical Care Medicine 29(6):1109-15	Not an RCT or a systematic review of RCTs
Jackson WL, Shorr AF. (2006) Update in ventilator-associated pneumonia Current Opinion in Anaesthesiology 19(2): 117-21	Not an RCT or a systematic review of RCTs
Joffe AR, Muscedere J, Marshall JC, et al. (2008) Canadian Critical Care Trials Group. The safety of targeted antibiotic therapy for ventilator-associated pneumonia: a multicenter observational study. Journal Critical Care 23(1): 82-90	Not an RCT or a systematic review of RCTs
Kaki R, Elligsen, Marion, et al. (2011) Impact of antimicrobial stewardship in critical care: a systematic review. The Journal of Antimicrobial Chemotherapy 66(6): 1223-30	Systematic review two RCTs included already included in review
Ko WT. (2007) Management of ventilator-associated pneumonia in paediatric setting. Hong Kong Journal of Paediatrics 12(1):27	Not an RCT or a systematic review of RCTs
Kollef MH.(2004) Appropriate empiric antimicrobial therapy of nosocomial pneumonia: the role of the carbapenems. Respiratory	Not an RCT or a systematic review of RCTs

Author	Reason for exclusion
Care 49(12):1530-41	
Kollef MH, Kollef KE. (2005) Antibiotic utilization and outcomes for patients with clinically suspected ventilator-associated pneumonia and negative quantitative BAL culture results. Chest 128(4): 2706-13	Not an RCT or a systematic review of RCTs
Lancaster JW, Lawrence KR, Fong JJ, et al. (2008) Impact of an institution-specific hospital-acquired pneumonia protocol on the appropriateness of antibiotic therapy and patient outcomes. Pharmacotherapy 28(7): 852-62	Not an RCT or a systematic review of RCTs
Lisboa T, Rello J.(2006) De-escalation in lower respiratory tract infections. Current Opinion in Pulmonary Medicine 12 364-8	Not an RCT or a systematic review of RCTs
Luna CM, Blanzaco D, Niederman MS, et al. (2003) Resolution of ventilator-associated pneumonia: prospective evaluation of the clinical pulmonary infection score as an early clinical predictor of outcome. Critical Care Medicine. 31(3):676-82	Not an RCT or a systematic review of RCTs
Masterton RG.(2011) Antibiotic De-Escalation. Critical Care Clinics 27(1): 149-162	Not an RCT or a systematic review of RCTs
McConeghy KW, Bleasdale SC, Rodvold KA. (2013) The empirical combination of vancomycin and a beta-lactam for Staphylococcal bacteremia. Clinical Infectious Diseases 57(12):1760-65	Comment in: Clin Infect Dis. 2014 Apr;58(7):1041-2; PMID: 24429429
Micek ST, Skrupky LP. (2010) Current concepts in the prevention and treatment of ventilator-associated pneumonia. Journal Pharmacy Practice 23(1):25-32	Not an RCT or a systematic review of RCTs
Muscedere JM (2008). Comprehensive evidence-based clinical practice guidelines for ventilator-associated pneumonia: Diagnosis and Treatment. Journal of Critical Care 23(1): 138-147	Not relevant
Niederman MS. (2006) Use of broad-spectrum antimicrobials for the treatment of pneumonia in seriously ill patients: Maximizing clinical outcomes and minimizing selection of resistant organisms. Clinical Infectious Diseases 42(SUPPL. 2):S72-81	Not an RCT or a systematic review of RCTs
Niederman MS. (2010) Hospital-acquired pneumonia, health care-associated pneumonia, ventilator-associated pneumonia, and ventilator-associated tracheobronchitis: definitions and challenges in trial design. Clinical Infectious Diseases 51 (Suppl 1):S12-17	Not an RCT or a systematic review of RCTs
Neiderman, MS, Craven DE, et al. (2005) Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. American Journal of Respiratory and Critical Care Medicine 171(4): 388-416	Reference checked, no additional studies identified
Nijssen S, Bootsma M, Bonten M. (2006) Potential confounding in evaluating infection-control interventions in hospital settings: changing antibiotic prescription. Clinical Infectious Diseases 43(5):616-23	Not relevant
Paterson DL. (2008) Impact of antibiotic resistance in gram-negative bacilli on empirical and definitive antibiotic therapy. Clinical Infectious Diseases 47 (Suppl 1):S14-20	Not an RCT or a systematic review of RCTs
Santolaya ME, Villarroel M, Avendano LF, et al. (1997) Discontinuation of antimicrobial therapy for febrile, neutropenic children with cancer: a prospective study. Clinical Infectious Disease 25(1):92-97	Not relevant
Sartelli MA. (2010) Focus on intra-abdominal infections. World Journal of Emergency Surgery (5): 9	Not an RCT or a systematic review of RCTs
Shime N, Kosaka T, Fujita N, et al.(2013) De-escalation of antimicrobial therapy for bacteraemia due to difficult-to-treat gram-negative bacilli. Infection 41(1): 203-10	Not an RCT or a systematic review of RCTs
Silva, BN, Andriolo RB, Atallah AN, et al. (2013) De-escalation of antimicrobial treatment for adults with sepsis, severe sepsis or septic	Systematic review no RCT identified for inclusion,

Author	Reason for exclusion
shock. Cochrane Database of Systematic Reviews. Art No. CD007934. DOI:10.1002/14651858	reference checked for additional studies.
Singh N. (1998) Short-Course Empiric Antibiotic Therapy for Suspected Nosocomial Pneumonia: a Proposed Solution for Indiscriminate Antibiotic Prescription for Pulmonary Infiltrates in the ICU Infectious Diseases Society of America	Abstract only
Soo Hoo GW, Wen YE, Nguyen TV, et al. (2005)Impact of clinical guidelines in the management of severe hospital-acquired pneumonia. Chest. 128(4): 2778-87	Not an RCT or a systematic review of RCTs
Valencia M, Torres A. (2009) Ventilator-associated pneumonia. Current Opinion in Critical Care 15(1):30-35	Not an RCT or a systematic review of RCTs
van den Bosch CM, Hulscher ME, Natsch S, et al. (2014) Development of quality indicators for antimicrobial treatment in adults with sepsis. BMC Infectious Disease 14(1)	Not an RCT or a systematic review of RCTs
Wang JS, Bearman G, Edmond M, et al. (2012) Guarding the Goods: An Introduction to Antimicrobial Stewardship. Clinical Microbiology Newsletter 34(12):93-97	Not an RCT or a systematic review of RCTs
Kollef MH, Kollef KE. (2005) Antibiotic utilization and outcomes for patients with clinically suspected ventilator-associated pneumonia and negative quantitative BAL culture results. Chest 128(4): 2706-13	Not an RCT or a systematic review of RCTs

C.5.2 Decision making

Author	Reason for exclusion
Aagaard EM, Gonzales R, Camargo CAJ, et al. (2010) Physician champions are key to improving antibiotic prescribing quality. Joint Commission Journal on Quality and Patient Safety 36(3):109-116	Not an RCT
Abbo L, Sinkowitz-Cochran R, Smith L, et al. (2011) Faculty and resident physicians' attitudes, perceptions, and knowledge about antimicrobial use and resistance. Infection Control and Hospital Epidemiology 32(7):714-718	Not an RCT
Abbo L, Lo K, Sinkowitz-Cochran R, et al. (2013) Antimicrobial stewardship programs in Florida's acute care facilities. Infection Control and Hospital Epidemiology 34(6):634-637	Not an RCT
Ackerman SL, Gonzales R, Stahl MS, et al. (2013) One size does not fit all: evaluating an intervention to reduce antibiotic prescribing for acute bronchitis. BMC health services research 13:462	Not an RCT
Agwu AL, Lee CKK, Jain SK, et al. (2008) A world wide web-based antimicrobial stewardship program improves efficiency, communication, and user satisfaction and cost in a tertiary care pediatric medical centre. Clinical Infectious Diseases	Localised intervention, lack of detail on intervention
Akter SFU, Heller RD, Smith AJ, et al. (2009) Impact of a training intervention on use of antimicrobials in teaching hospitals. Journal of Infection in Developing Countries 3(6):447-451	Localised intervention, lack of detail on intervention
Albrich WC, Dusemund F, Bucher B, et al (2012) Effectiveness and safety of procalcitonin-guided antibiotic therapy in lower respiratory tract infections in "real life". Archives of Internal Medicine 172(9):715-723	Not an RCT
Alden DL, Tice AD and Berthiaume JT. (2010) Investigating approaches to improving appropriate antibiotic use among higher risk ethnic groups. Hawaii Medical Journal 69(11):260-263	Cold packs with education compared with education alone
Alder SC, Trunnell EP, White GL, et al. (2005) Reducing parental demand for antibiotics by promoting communication skills. American Journal of Health Education	Intervention with parents
Aldeyab MA, Kearney MP, McElnay JC, et al. (2012) A point	Not an RCT

Author	Reason for exclusion
prevalence survey of antibiotic use in four acute-care teaching hospitals utilizing the European surveillance of antimicrobial consumption (ESAC) tool. Epidemiology and Infection	
Al-Harthi SE, Khan LM, Abed HH, et al. (2013) Appraisal of antimicrobial prescribing practices of governmental and non-governmental dentists for hospitals in the western region of Saudi Arabia. Saudi Medical Journal 34(12):1262-1269	Not an RCT
Ali MH, Kalima P, and Maxwell SRJ. (2006) Failure to implement hospital antimicrobial prescribing guidelines: a comparison of two UK academic centres. Journal of Antimicrobial Chemotherapy 57(5):959-962	Not an RCT
Altiner A, Berner R, Diener A, et al. (2012) Converting habits of antibiotic prescribing for respiratory tract infections in German primary care – the cluster-randomized controlled CHANGE-2 trial. BMC family practice 13:124	Not an RCT
Andre M, Hedin K, Hakansson H, et al. (2007) More physician consultations and antibiotics prescriptions in families with high concern about infectious illness – adequate response to infection-prone child or self-fulfilling prophecy? Family Practice	Not an RCT
Andreeva E and Melbye H. (2014) Usefulness of C-reactive protein testing in acute cough/respiratory tract infection: an open cluster-randomised clinical trial with C-reactive protein testing in the intervention group. BMC Family Practice 15:80	Included in Aabenhus Cochrane review
Ansari F, Gray K, Nathwani D, et al. (2003) Outcomes of an intervention to improve hospital antibiotic prescribing: interrupted time series with segmented regression analysis. Journal of Antimicrobial Chemotherapy 52(5):842-848	Not an RCT
Anthierens S, Tonkin-Crine S, Douglas E, et al. (2012) General practitioners' views on the acceptability and applicability of a web-based intervention to reduce antibiotic prescribing for acute cough in multiple European countries: a qualitative study prior to a randomised trial. BMC family practice 13:101	Not an RCT
Arnold SR and Straus SE. (2005) Interventions to improve antibiotic prescribing practices in ambulatory care. Cochrane Database of Systematic Reviews	Superseded by 2010 HTA group report
Arnold SR and Bush AJ. (2006) Decline in inappropriate antibiotic use over a decade by paediatricians in a Tennessee community. Ambulatory Pediatrics 6(4):225-229	Not an RCT
Arroll B and Goodyear-Smith F. (2000) General practitioner management of upper respiratory tract infections: when are antibiotics prescribed? The New Zealand Medical Journal 113(1122):493-496	Not an RCT
Arroll B, Goodyear-Smith F, Thomas DR, et al. (2002) Delayed antibiotic prescriptions: what are the experiences and attitudes of physicians and patients? The Journal of Family Practice 51(11):954-959	Not an RCT
Arroll B, Kenealy T and Kerse N. (2002) Do delayed prescriptions reduce the use of antibiotics for the common cold? The Journal of Family Practice 51(4):324-328	Included in the Spurling Cochrane review
Arroll B, Kenealy T and Kerse N. (2003) Do delayed prescriptions reduce antibiotic use in respiratory tract infections? A systematic review. Journal of Family Practice	Insufficient detail, narrative, references checked
Ashe D, Patrick PA, Stempel MM, et al. (2006) Educational posters to reduce antibiotic use. Journal of Pediatric Health Care 20(3):192-197	Trial of poster aimed at parents
Ashiru-Oredope D, Sharland M, Charani E, et al. (2012) Improving	Development of

Author	Reason for exclusion
the quality of antibiotic prescribing in the NHS by developing a new antimicrobial stewardship programme: Start Smart – Then Focus. Journal of Antimicrobial Chemotherapy 67(suppl 1):i57-i63	antimicrobial stewardship programmes for primary care and hospitals
Atlas SJ, McDermott SM, Mannone C, et al. (2005) The role of point of care testing for patients with acute pharyngitis. Journal of General Internal medicine 20:759-761	Brief report
Author unknown (2005) Guidance meetings plus education of assistants and patients reduces antibiotic prescribing for respiratory tract infections by general practitioners. Evidence-Based Healthcare and Public Health 9(1):52-52	Brief report
Author unknown (2012) Antibiotics reduced the time to resolution of symptoms in otitis media. Archives of Disease in Childhood	Abstract
Author unknown (2013) Education and feedback improve antibiotic prescribing for children. BMJ 346:f3794	Brief report
Author unknown (2012) Guide on the optimal use of antibiotics and development of bacterial resistance. HTA Database HTA Database 4	Project record, not a study
Author unknown (2006) Implementation of a multiple intervention aimed at optimising prescription of antibiotics for respiratory tract infections, embedded within the new practice accreditation of the Dutch College of General Practitioners; a randomized controlled trial. HTA Database 4	Not in English
Avdic E and Carroll KC. (2014) The role of the microbiology laboratory in antimicrobial stewardship programs. Infectious Disease Clinics of North America 28(2):215-235	Role of the lab
Avorn J, Soumerai SB, Taylor W, et al. (1988) Reduction of incorrect antibiotic dosing through a structured educational order form. Archives of Internal Medicine 148(8):1720-4	Localised intervention, lack of detail on intervention
Bannan A, Buono E, McLaws ML, et al. (2009) A survey of medical staff attitudes to an antibiotic approval and stewardship programme. Internal Medicine Journal 39(10):662-668	Not an RCT
Barenfanger J, Short MA and Groesch AA.(2001) Improved antimicrobial interventions have benefits, Journal of Clinical Microbiology 39(8):2823-2828	USA based, software intervention not in interventions
Barlam TF and DiVall M. (2006) Antibiotic-stewardship practices at top academic centers throughout the united states and at hospitals throughout Massachusetts. Infection Control and Hospital Epidemiology 27(7):695-703	Not an RCT
Bauchner H, Osganian S, Smith K, et al. (2001) Improving parent knowledge about antibiotics: a video intervention. Pediatrics 108(4):845-850	Parent study
Bauer S and Lamy O. (2010) C-reactive protein in community-acquired pneumonia: utility in diagnosis-prognosis and follow-up. Revue Medicale Suisse 6:2068-73	Not in English
Baysari MT, Oliver K, Egan B, et al. (2013) Audit and feedback of antibiotic use: utilising electronic prescription data. Applied Clinical Informatics 4(4):583-595	IS unable to obtain
Bekkers MJ, Simpson SA, Dunstan F, et al. (2010) Enhancing the quality of antibiotic prescribing in primary care: qualitative evaluation of a blended learning intervention. BMC family practice 11:34	Not an RCT
Belongia EA, Sullivan BJ, Chyou PH, et al. (2001) A community intervention trial to promote judicious antibiotic use and reduce penicillin- resistant streptococcus pneumonia carriage in children. Pediatrics 108(3):575-583	Intervention with both clinicians and parents
Berg P and Lindhardt BO. (2012) The role of procalcitonin in adult patients with community-acquired pneumonia. Danish Medical	Review

Author	Reason for exclusion
Journal 59(3):A4357	
Bjerrum L, Munck A, Gahrn-Hansen B, et al. (2011) Health alliance for prudent antibiotic prescribing in patients with respiratory tract infections (HAPPY AUDIT) – impact of a non-randomised multifaceted intervention programme. BMC family practice 12:52	Intervention with both clinicians and patients
Bjerrum L, Gahrn-Hansen B and Munck A. (2004) C-reactive protein measurement in general practice may lead to lower antibiotic prescribing for sinusitis. British Journal of General Practice 54:659-662	Not an RCT
Bjorkman I, Berg J, Viberg N, et al. (2013) Awareness of antibiotic resistance and antibiotic prescribing in UTI treatment: a qualitative study among primary care physicians in Sweden. Scandinavian Journal of Primary Health Care 31(1):50-55	Not an RCT
Bjorkman I, Berg J, Roing M, et al. (2010) Perceptions among Swedish hospital physicians on prescribing of antibiotics and antibiotic resistance. Quality and Safety in Health Care 19(6):e8	Not an RCT
Borer A, Gilad J, Meydan N, et al. (2004) Impact of regular attendance by infectious disease specialists on the management of hospitalised adults with community-acquired febrile syndromes. Clinical Microbiology and Infection 10(10:911-6	Lack of detail on intervention, more a comparison of different medical specialities
Bosso JA and Drew RH. (2011) Application of antimicrobial stewardship to optimise management of community acquired pneumonia. International Journal of Clinical Practice 65(7):775-783	Narrative review, insufficient study details
Botwin KJ, Chan J, Jacobs R, et al. (2001) Restricted access to automated dispensing machines for surgical antimicrobial prophylaxis. American Journal of Health-System Pharmacy 58(9):797-799	Automated dispensing machines (not in included interventions)
Bouadama L, Luyt C-E, Tubach F, et al. (2010) Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. Lancet 375:463-74	Included in Schuetz Cochrane review
Bourgeois FC, Linder J, Johnson SA, et al. (2010) Impact of a computerized template on antibiotic prescribing for acute respiratory infections for children and adolescents. Clinical Pediatrics 49(10):976-983	Not an RCT
Briel M, Schuetz P, Mueller B, et al. (2008) Procalcitonin-guided antibiotic use vs a standard approach for acute respiratory tract infection in primary care. Archives of Internal Medicine 168(18):2000-2007	Included in Schuetz Cochrane review
Brokel J. (2014) Evidence-based clinical decision support improves the appropriate use of antibiotics and rapid strep testing. Evidence-based Medicine 19(3):118	Outcomes not relevant
Broom (2014) Cultures of resistance? A Bourdieusian analysis of doctors' antibiotic prescribing. Social Science and Medicine	Not an RCT
Brown TT, Proctor SE, Sinkowitz-Cochran RL, et al. (2001) Physician preferences for continuing medical education with a focus on the topic of antimicrobial resistance: society for healthcare epidemiology of America. Infection Control and Hospital Epidemiology 22(10):656-660	Not an RCT
Brusaffero S, Rinaldi O, Pea F, et al. (2001) Protocol implementation in hospital infection control practice: an Italian experience of preoperative antibiotic prophylaxis. The Journal of Hospital Infection 47(4):288-293	Not an RCT
Bryars CH, deGruy FV, Dickinson LC, et al. (1991) The effects of the rapid strep test on physician management of streptococcal	Not in English

Author	Reason for exclusion
pharyngitis. The Journal of the American Board of Family Practice 4:139-43	
Buchbinder N, Benzdira A, Belgaid A, et al. (2007) Streptococcal pharyngitis in pediatric emergency unit: value and impact of rapid antigen detection test. Archives de Pediatrie 14:1057-1061	Not in English
Burkhardt O, Ewig S, Haagen, et al. (2010) Procalcitonin guidance and reduction of antibiotic use in acute respiratory tract infection. The European Respiratory Journal 36:601-607	Included in Schuetz Cochrane review
Bush-Knapp ME, Brinsley-Rainisch KJ, Lawton-Ciccarone RM, et al. (2007) Spreading the word, not the infection: reaching hospitalists about the prevention of antimicrobial resistance. American Journal of Infection Control 35(10):656-661	Not an RCT
Cals JWL, Schot MJC, de Jong SAM, et al. (2010) Point-of-care C-reactive protein testing and antibiotic prescribing for respiratory tract infections: a randomised controlled trial. Annals of Family Medicine 8(2):124-133	Included in Aabenhus Cochrane review
Cals JW, Bitler CC, Hopstaken RM, et al. (2009) Effect of point of care testing for C reactive protein and training in communication skills on antibiotic use in lower respiratory tract infections: cluster randomised trial. British Medical Journal 338:b1374	Included in Aabenhus Cochrane review
Calvino O, Llor C, Gomez F, et al. (2014) Association between C-reactive protein rapid test and group A streptococcus infection in acute pharyngitis. Journal of the American Board of Family Medicine 27:424-426	Not an RCT
Chalumeau M, Leroy S, Gendrel D, et al. (2007) Procalcitonin bedside testing in the pediatric emergency department. Archives de Pediatrie 14:529-531	Not in English
Charani E, Edwards R, Sevdalis N, et al. (2011) Behavior change strategies to influence antimicrobial prescribing in acute care: a systematic review. Clinical Infectious Diseases 53(7):651-662	Outcomes not relevant
Charani E, Jyratsis Y, Lawson W, et al. (2013) An analysis of the development and implementation of a smartphone application for the delivery of an antimicrobial prescribing policy: lessons learnt. Journal of Antimicrobial Chemotherapy 68(4):960-967	Not an RCT
Charani E, Castro-Sanchez E, Sevdalis N, et al. (2013) Understanding the determinants of antimicrobial prescribing within hospitals: the role of “prescribing etiquette”. Clinical Infectious Diseases 57(2):188-196	Not an RCT
Chou AF, Yano EM, McCoy KD, et al. (2008) Structural and process factors affecting the implementation of antimicrobial resistance prevention and control strategies in US hospitals. Health Care Management Review 33(4):308-322	Not an RCT
Christakis DA, Zimmerman FJ, Wright JA, et al. (2001) A randomised controlled trial of point-of-care evidence to improve the antibiotic prescribing practices for otitis media in children. Pediatrics 107(2):e15	Intervention not relevant
Christ-Cain M, Jaccord-Stolz D, Bingisser R, et al. (2004) Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised single-blinded intervention trial. Lancet 363:600-07	Included in Schuetz Cochrane review
Christ-Cain M, Scuetz P, Huber AR, et al. (2008) Procalcitonin: importance for the diagnosis of bacterial infections. Laboratoriums Medizin 32(6):425-433	Not in English
Cisneros JM, Neth O, Gil-Navarro MV, et al. (2013) Global impact of an educational antimicrobial stewardship programme on prescribing	Training programme using counselling interviews –

Author	Reason for exclusion
practice in a tertiary hospital centre. Clinical Microbiology and Infection 20(1):82-88	very localised, not in the interventions list
Coenen S, Michiels B, Van Royen P, et al. (2002) Antibiotics for coughing in general practice: a questionnaire study to quantify and condense the reasons for prescribing. BMC family practice 3:16	Not an RCT
Coenen S, Royen P, Michiels B, et al. (2002) Promotion of rational antibiotic use in Flemish general practice: implementation of a guideline for acute cough. International Primary Care Respiratory Group Congress, June	Conference abstract
Coenen S, Van Royen P, Michiels B, et al. (2004) Optimizing antibiotic prescribing for acute cough in general practice: a cluster-randomized controlled trial. Journal of Antimicrobial Chemotherapy 54(3):661-672	Maybe
Coenen S, Michiels B, Didier R, et al. (2006) Antibiotic prescribing for acute cough: the effect of perceived patient demand. British Journal of General Practice 56(524):183-190	Outcomes not relevant
Counts JM, Astles JR, Tenover FC, et al. (2007) Systems approach to improving antimicrobial susceptibility testing in clinical laboratories in the United States. Journal of Clinical Microbiology 45(7):2230-2234	Lab practice
Dachs R. (2008) Interventions to improve antibiotic prescribing practices for hospital inpatients. American Family Physician 77(5):618-619	Clinical review of Cochrane
Danaher PJ, Milazzo NA, Kerr KJ, et al. (2009) The antibiotic support team – a successful educational approach to antibiotic stewardship. Military Medicine 174(2):201-205	Not an RCT
Davey P, Brown E, Charani E, et al. (2013) Interventions to improve antibiotic prescribing practices for hospital inpatients – Cochrane Database of Systematic Reviews	References checked
de la Poza Abad M, Mas Dalmau G, Moreno Bakedano M, et al. (2013) Rationale, design and organization of the delayed antibiotic prescription (DAP) trial: a randomized controlled trial of the efficacy and safety of delayed antibiotic prescribing strategies in the non-complicated acute respiratory tract infections in general practice. BMC family practice 14:63	Trial protocol
De Santis G, Harvey KJ, Howard D, et al. (1994) Improving the quality of antibiotic prescription patterns in general practice 160(8):502-5	Localised, results based on self-reporting via prescribing diary
Diazgranados CA. (2012) Prospective audit for antimicrobial stewardship in intensive care: Impact on resistance and clinical outcomes. American Journal of Infection Control 40(6):526-529	Both interventions in the same unit
Diederichsen HZ, Skamling M, Dierderichsen A, et al. (2000) Randomised controlled trial of CRP rapid test as a guide to treatment of respiratory infections in general practice. Scandinavian Journal of Primary Health Care 18(1):39-43	Included in Aabenhus Cochrane review
Ding H, Yang Y, Wei J, et al. (2013) Procalcitonin-guided antibiotic use in acute exacerbations of idiopathic pulmonary fibrosis. International Journal of Medical Sciences 30(6):787-793	Outwith Europe, Canada, USA, NZ, Australia
Ding J, Chen Z and Feng K. (2008) Influencing the use of antibiotics in a Chinese paediatric intensive care unit. Pharmacy World & Science 10:903-907	Minimal detail on the intervention
dos Santos RP, Magedanz L and Silprandi EMO. (2009) Antimicrobial stewardship programs must apply to all. Infection Control and Hospital Epidemiology 30(2):205-7	Not an RCT
Dowell J, Pitkethly M, Bain J, et al. (2001) A randomised controlled	Included in Spurling

Author	Reason for exclusion
trial of delayed antibiotic prescribing as a strategy for managing uncomplicated respiratory tract infection in primary care. British Journal of General Practice 51(464):200-205	Cochrane
Doron S, Nadkarni L, Lyn Price L, et al. (2013) A nationwide survey of antimicrobial stewardship practices. Clinical Therapeutics 35(6):758-765	Not an RCT
Doyne EO, Alfaro MP, Siegel RM, et al. (2004) A randomized controlled trial to change antibiotic prescribing patterns in a community. Archives of Paediatrics & Adolescent Medicine 158(6):577-583	Academic detailing and parental programme
Drancourt M, Gaydos CA, Summersgill JT, et al. (2013) Point-of-care testing for community-acquired pneumonia. Lancet Infectious Diseases 13:647-9	Not an RCT
Dumartin C, Rogues AM, Amadeo B, et al. (2011) Antibiotic usage in south-western French hospitals: trends and association with antibiotic stewardship. Journal of Antimicrobial Chemotherapy 77(2):123-128	Survey on implementation of stewardship
Ebell M. (2008) Procalcitonin-guided treatment of respiratory tract infections. American Family Physician 78(6):756-757	Not an RCT
Edeghere O, Wilson J and Hyde C. (2010) Interventions to improve the prescribing of antibiotics by healthcare professionals in ambulatory care settings. HTA Database 4	References checked
Engel MF, Paling FP, Hoepelman AIM, et al. (2012) Evaluating the evidence for the implementation of C-reactive protein measurements in adult patients with suspected lower respiratory tract infection in primary care: a systematic review. Family Practice 29:383-393	Review
Evans RS, Classen DC, Pestotnik SL, et al. (1994) Improving empiric antibiotic selection using computer decision support. Archives of Internal Medicine 154(8):878-884	Localised
Finkelstein JA, Davis RL, Dowell SF, et al. (2001) Reducing antibiotic use in children: a randomised trial in 12 practices. Pediatrics 108(1):1-7	Intervention with clinicians and parents
Finkelstein JA, Huang SS, Kleinman K, et al. (2008) Impact of a 16-community trial to promote judicious antibiotic use in Massachusetts. Pediatrics 121(1):e15-e23	Community based programme, physicians and parents
Flach SD, Diekema DJ, Yankey JW, et al. (2005) Variation in the use of procedures to monitor antimicrobial resistance in US hospitals. Infection Control and Hospital Epidemiology 26(1):31-38	Not an RCT
Flanagan M, Ramanujam R, Sutheraldn J, et al. (2007) Development and validation of measures to assess prevention and control of AMR in hospitals. Medical Care 45(6):537-544	Development of a scale to measure implementation of antimicrobial prevention measures
Flanders SA, Stein J, Shochat G, et al. (2004) Performance of a bedside C-reactive protein test in the diagnosis of community-acquired pneumonia in adults with acute cough. The American Journal of Medicine 116:529-535	Not an RCT
Fleming A, Tonna A, O'Connor S, et al. (2014) A cross-sectional survey of the profile and activities of Antimicrobial Management Teams in Irish Hospitals. International Journal of Clinical Pharmacy 36(2):377-383	Not an RCT
Fleming A, Browne J and Byrne S. (2013) The effect of interventions to reduce potentially inappropriate antibiotic prescribing in long-term care facilities: a systematic review of randomised controlled trials. Drugs & Aging 30(6):401-408	Insufficient detail in SR
Filice GA, Drekonja DM, Thurn JR, et al. (2013) Use of a computer decision support system and antimicrobial appropriateness. Infection	Retrospective, localised system

Author	Reason for exclusion
Control and Hospital Epidemiology 34(6):558-565	
Fraser GL, Stogsdill P, Dickens JD, et al. (1997) Antibiotic optimisation: an evaluation of patient safety and economic outcomes. Archives of Internal Medicine 157(15):1689-1694	Lack of detail on intervention
Friedman ND. (2013) Antimicrobial stewardship: the need to cover all bases. Antibiotics	Review
Galetto-Lacour A, Zamora SA and Gervaix A. (2003) Bedside procalcitonin and C-reactive protein tests in children with fever without localising signs of infection seen in a referral centre. Pediatrics 112(5):1054-1060	Not an RCT
George JM, Towne TG and Rodvold KA. (2012) Prolonged infusions of beta-Lactam antibiotics: Implication for antimicrobial stewardship. Pharmacotherapy 32(8):707-721	Consideration of optimal dosage and administration
Giblin TB, Sinkowitz-Cochran RL, Harris PL, et al. (2004) Clinicians' perceptions of the problem of antimicrobial resistance in health care facilities. Archives of Internal Medicine 164(15):1662-1668	Not an RCT
Gillaizeau F, Chan E, Trinquart L, et al. (2013) Computerized advice on drug dosage to improve prescribing practice Cochrane Database of Systematic Reviews	Outcomes not relevant
Gjelstad S, Fetveit A, Sr-traand J, et al. (2006) Can antibiotic prescriptions in respiratory tract infections be improved? A cluster-randomized educational intervention in general practice--the Prescription Peer Academic Detailing (Rx-PAD). BMC health services research 6:75	Study protocol
Gonzales R, Steiner JF, Lum A, et al. (1999) Decreasing antibiotic use in ambulatory practice. JAMA 281(16):1512-1519	Predominantly patient intervention
Gould IM, MacKensie FM and Shepherd L. (2007) Use of bacteriology laboratory to decrease general practitioners' antibiotic prescribing. European Journal of General Practice 13(1):13-15	Not an RCT
Gould IM, MacKensie FM and Shepherd L. (2007) Attitudes to antibiotic prescribing, resistance and bacteriology investigations amongst practitioners and patients in the Grampian region of Scotland. European Journal of General Practice 13(1):35-36	Not an RCT
Haagard M. (2011) Poor adherence to antibiotic prescribing guidelines in acute otitis media--obstacles, implications, and possible solutions. European Journal of Pediatrics 170(3):323-32	Not an RCT
Halm EA, Horowitz C, Silver A, et al. (2004) Limited impact of a multicentre intervention to improve the quality and efficiency of pneumonia care. Chest 126(1):100-7	Not an RCT
Hardy-Holbrook R, Aristidi S, Chandnani V, et al. (2013) Antibiotic resistance and prescribing in Australia: Current attitudes and practice of GPs. Healthcare Infection 18(4):147-151	Outcomes not relevant
Harris DJ. (2013) Initiatives to improve appropriate prescribing in primary care. Journal of Antimicrobial Chemotherapy 68(11):2424-2427	GP and school intervention
Harris RH, MacKensie TD, Leeman-Castillo B, et al. (2003) Optimising antibiotic prescribing for acute respiratory tract infections in an urban urgent care clinic. Journal of General Internal Medicine 18(5):326-334	Physician and patient intervention
Hart AM, Pepper GA and Gonzales R. (2006) Balancing acts: deciding for or against antibiotics in acute respiratory infections. Journal of Family Practice	Not an RCT
Haynes K, Linkin DR, Fishman NO, et al. (2011) Effectiveness of an information technology intervention to improve prophylactic antibacterial use in the postoperative period. JAMIA 18(2):164-168	Data not fully reported for relevant outcomes

Author	Reason for exclusion
Hedin K, Andre M, Hakansson A, et al. (2006) A population-based study of different antibiotic prescribing in different areas. British Journal of General Practice 56(530):680-5	Explanations for antibiotic prescribing, not an intervention etc.
Hemo B, Shamir-Shtein NH, Silverman BG, et al. (2009) Can a nationwide media campaign affect antibiotic use? American Journal of Managed Care	Intervention not relevant
Heritage J, Elliott MN, Stivers T, et al. (2010) Reducing inappropriate antibiotics prescribing: the role of online commentary on physical examination findings. Patient Education and Counseling 81(1):119-125	Online commentary
Hersh AL, Beekmann SE, Polgreen PM, et al. (2009) Antimicrobial stewardship programs in paediatrics. Infection Control and Hospital Epidemiology 30(12):1211-1217	Prevalence of antimicrobial stewardship programmes
Hess DA, Mahoneu CD, Johnson PN, et al. (1990) Integration of clinical and administrative strategies to reduce expenditures for antimicrobial agents. American Journal of Hospital Pharmacy 47(3):585-591	Intervention not relevant
Hrisos S, Eccles M, Johnston M, et al. (2008) An intervention modelling experiment to change GPs' intentions to implement evidence-based practice: using theory-based interventions to promote GP management of upper respiratory tract infection without prescribing antibiotics. BMC Health Services Research 8:10	Not an interventio
Huang T-S, Huang S-S, Shyu Y-C, et al. (2014) A procalcitonin-based algorithm to guide antibiotic therapy in secondary peritonitis following emergency surgery: a prospective study with propensity score matching analysis. PLoS One 9(3):e90539	Not an RCT
Haung Y, Chen R, Wu, et al. (2013) Association between point-of-care CRP testing and antibiotic prescribing in respiratory tract infections: a systematic review and meta-analysis of primary care studies. The British Journal of General Practice 63(616):e787-e794	Review
Hulgan T, Rosenbloom ST, Hargrove F, et al. (2004) Oral quinolones in hospitalised patients: an evaluation of a computerised decision support intervention. Journal of Internal Medicine 256(4):349-57	Nor an RCT
Huttner B, Goossens H, Verheij T, et al. (2010) Characteristics and outcomes of public campaigns aimed at improving the use of antibiotics in outpatients in high-income countries. Lancet Infectious Diseases 10(1):17-31	Public campaign
Hux JE, Melady MP and DeBoer D. (1999) Confidential prescriber feedback and education to improve antibiotic use in primary care. CMAJ 161(4):388-392	Too localised an intervention, little detail on contents
Ilett KF, Johnson S, Greenhill G, et al. 2000) Modification of general practitioner prescribing of antibiotics by use of a therapeutics adviser (academic detailer). British Journal of Clinical Pharmacology 49(2):168-173	Too localised an intervention, little detail on contents
Jakobsen KA, Melbye H, Kelly MJ, et al. (2010) Influence of CRP testing and clinical findings on antibiotic prescribing in adults presenting with acute cough in primary care. Scandinavian Journal of Primary Health Care 28:229-236	Not an RCT
Jenkins TC, Irwin A, Coombs L, et al. (2013) Effects of clinical pathways for common outpatient infections on antibiotic prescribing. American Journal of Medicine 126(4):327-335	Not an intervention
Johannsson B, (2011) Improving antimicrobial stewardship: the evolution of programmatic strategies and barriers. Infection Control and Hospital Epidemiology	Intervention not relevant
Joshi A, Perin DP, Gehle A, et al. (2013) Feasibility of using C-	Outcomes not relevant

Author	Reason for exclusion
reactive protein for point-of-care testing. Technology and Health Care 21:233-240	
Juzych NS, Banerjee M, Essenmacher L, et al. (2005) Improvements in antimicrobial prescribing for treatment of upper respiratory tract infections through provider education. Journal of General Internal Medicine 20(10):901-905	Not an RCT
Kaki R, Elligsen M, Walker S, et al. (2011) Impact of antimicrobial stewardship in critical care: a systematic review. Journal of Antimicrobial Chemotherapy 66(6):1223-30	References checked
Kellie SM. (2012) Antimicrobial stewardship on the frontier: a pilot study. Infection Control and Hospital Epidemiology 33(11):1181-1183	Brief report
Kern WV, Rose AD, Hay B, et al. (2001) Antimicrobial expenditures and usage at four university hospitals. Infection 29(3):127-137	Antimicrobial use survey
Larson EL, Quiros D, Giblin T, et al. (2007) Relationship of antimicrobial control policies and hospital and infection control characteristics to antimicrobial resistance rates. American Journal of Critical Care 16(2):110-120	Not an RCT
Lecky DM, McNulty CAM, Adriaenssens N, et al. (2011) What are school children in Europe being taught about hygiene and antibiotic use? Journal of Antimicrobial Chemotherapy 66(suppl5):v13-v21	Intervention not relevant
Lee GC, Reveles KR, Attridge RT, et al. (2014) Outpatient antibiotic prescribing in the United States: 2000 to 2010. BMC Medicine 12(1):96	Trends of antibiotic use
Legare F, Labrecque M, LeBlanc A, et al. (2007) Does training family physicians in shared decision making promote optimal use of antibiotics for acute respiratory infections? Study protocol of a pilot clustered randomised controlled trial. BMC Family Practice 8:65	Study protocol
Legare F, Labrecque M, Godin G, et al. (2011) Training family physicians and residents in family medicine in shared decision making to improve clinical decisions regarding the use of antibiotics for respiratory infections: protocol for a clustered randomised trial. BMC Family Practice 12:3	Study protocol
Liew YX, Chelbicki MP, Lee W, et al. (2011) Use of procalcitonin (PCT) to guide discontinuation of antibiotic use in an unspecified sepsis is an antimicrobial stewardship programme (ASP). European Journal of Clinical Microbiology and Infectious Diseases 30:853-855	Not an RCT
Little P, Rumsby K, Kelly J, et al. (2005) Information leaflet and antibiotic prescribing strategies for acute lower respiratory tract infection. JAMA 293(24):3029-3035	Included in Spurling Cochrane review
Little P, Hobbs FDR, Moore M, et al. (2013) Clinical score and rapid antigen detection test to guide antibiotic use for sore throats: randomised controlled trial of PRISM (primary care streptococcal management). BMJ 347:f5806	Delayed antibiotics as a control, no baseline of previous prescribing practice
Little P, Moore M, Kelly J, et al. (2014) Delayed antibiotic prescribing strategies for respiratory tract infections in primary care: pragmatic, factorial, randomised controlled trial. BMJ 348	Different strategies of delayed prescribing
Little P, Gould C, Williamson I, et al. (2001) Pragmatic randomised controlled trial of two prescribing strategies for childhood acute otitis media. BMJ 322:336-12	Included in Spurling Cochrane review
Little P, Williamson I, Warner G, et al. (1997) Open randomised trial of prescribing strategies in managing sore throat. BMJ 314:722-7	Included in Spurling Cochrane review
Little P, Gould C, Williamson I, et al. (2001) Delayed prescribing of antibiotics increased duration of acute otitis media symptoms in children but reduced diarrhoea. Evidence Based Nursing 4:107	Brief report
Liu B-H, Li H-F, Lei Y, et al. (2013) Clinical significance of dynamic	Not in English

Author	Reason for exclusion
monitoring in guiding the use of antibiotics in patients with sepsis in ICU. Chinese Critical Care Medicine 25(11):690-693	
Llor (2011) Impact on antibiotic prescription of rapid antigen detection testing in acute pharyngitis in adults: a randomised clinical trial. British Journal of General Practice	Antigen testing (not an intervention, system or process)
Llor C, Cots JM, Lopez-Valcarcel BG, et al. (2012) Interventions to reduce antibiotic prescription for lower respiratory tract infections: Happy Audit study. The European Respiratory Journal 40:436-441	Not an RCT
Loeb M, Brazil K, Lohfeld L, et al. (2005) Effect of a mulitfaected intervention on number of antimicrobial prescriptions for suspected urinary tract infections in residents of nursing homes: cluster randomised controlled trial. BMJ 331(7518):669	Treatment algorithms
Long W, Deng X, Zhang Y, et al. (2011) Procalcitonin guidance for reduction of antibiotic use in low-risk outpatients with community-acquired pneumonia. Respiratory 16:819-824	Included in Schuetz Cochrane review
Mainous AG, Lambourne CA and Nietert PJ. (2013) Impact of a clinical decision support system on antibiotic prescribing for acute respiratory infections in primary care: quasi-experimental trial. JAMA 20(2):317-324	Localised intervention, some detail on intervention
Mansouri MD, Cadle RM, Agbahiwe SO, et al. (2011) Impact of an antibiotic restriction program on antibiotic utilization in the treatment of community-acquired pneumonia in a Veterans Affairs Medical Center. Infection 39(1):53-58	Not an RCT
Maravic-Stojkovic V, Lausevic-Vuk, L, Jovic M, et al. (2011) Procalcitonin-based therapeutic strategy to reduce antibiotic use in patients after cardiac surgery: a randomised controlled trial. Srpski Arhiv za Celokupno Lekarestvo 139(11-12):736-742	Specific patient group
McIsaac WJ and Goel V. (1998) Effect of an explicit decision-support tool on decisions to prescribe antibiotics for sore throat. Medical Decision Making 18(2):220-228	Single intervention
McIsaac WJ, Goel V, To T, et al. (2002) Effect on antibiotic prescribing of repeated clinical prompts to use a sore throat score. Journal of Family Practice 51(4):339-344	Intervention not relevant
McNulty CA, Kane A, Foy CJ, et al. (2000) primary care workshops can reduce and rationalize antibiotic prescribing. Journal of Antimicrobial Chemotherapy 46(3):493-499	Comparison of two different interventions
Meeker D, Knight TK, Friedberg MW, et al. (2014) Nudging guideline-concordant antibiotic prescribing, a randomized trial. JAMA Internal Medicine 174(3):425-431	Intervention not relevant
Metlay JP, Camargo C, MacKensie T, et al. (2007) Cluster-randomized trial to improve antibiotic use for adults with acute respiratory infections treated in emergency department. Annals of Emergency Medicine 50(3):221-230	Patient and clinician educational programme
Milos V, Jakobsson U, Westerlund T, et al. (2013) Theory-based interventions to reduce prescription of antibiotics – a randomized controlled trial in Sweden. Family Practice 30(6):634-640	Intervention not relevant
Monette J, Miller MA, Monette M, et al. (2007) Effect of an educational intervention on optimizing antibiotic prescribing in long-term care facilities. Journal of the American Geriatrics Society 55(8):1231-1235	Localised intervention, lack of detail on intervention
Morrissey CO, Chen S C-A, Sorrell TC, et al. (2013) Galactomannan and PCR versus culture and histology for directing use of antifungal treatment for invasive aspergillosis in high-risk haematology patients: a randomised controlled trial. Lancet Infectious Diseases 13(6):519-528	Intervention not relevant

Author	Reason for exclusion
Ng CK, Wu TC, Chan WM, et al. (2008) Clinical and economic impact of an antibiotics stewardship programme in a regional hospital in Hong Kong. Quality and Safety in Health Care 17(5):387-392	Not an RCT
Nijssen S, Bootsma M and Bonten M. (2006) Potential confounding in evaluating infection-control interventions in hospital settings: changing antibiotic prescription. Clinical Infectious Diseases 43(5):616-623	SR on the modification of antibiotic prescriptions to reduce resistance
Nijssen S, Fluit A, van de Vijver D, et al. (2010) Effects of reducing beta-lactam antibiotic pressure on intestinal colonization of antibiotic-resistant gram-negative bacteria. Intensive Care Medicine 36(3):512-519	Outcomes not relevant
Nobre (2007) Use of procalcitonin to shorten antibiotic treatment duration in septic patients. American Journal of Respiratory and Critical Care Medicine	Setting not relevant
Ogasawara T, Umezawa H, Naito Y, et al. (2014) Procalcitonin-guided antibiotic therapy in aspiration pneumonia and an assessment of the continuation of oral intake. Respiratory Investigation 52:107-113	Intervention not point-of-care
Olsho LEW, Betrand RM, Edwards AS, et al. (2013) Does adherence to the Loeb minimum criteria reduce antibiotic prescribing rates in nursing homes? Journal of the American Medical Directors Association 14(4):309-317	Adherence to standards for initiation of antibiotics
Parrino TA. (2005) Controlled trials to improve antibiotic utilization: a systematic review of experience, 1984-2004. Pharmacotherapy 25(2):289-298	SR, narrative review, insufficient detail on included studies
Parsons S, Morrow S and Underwood M. (2004) Did local enhancement of a national campaign to reduce high antibiotic prescribing affect public attitudes and prescribing rates? European Journal of General Practice 10(1):18-23	Not an RCT
Patel SJ, Saiman L, Duchon JM, et al. (2012) Development of an antimicrobial stewardship intervention using a model of actionable feedback. Interdisciplinary Perspectives on Infectious Diseases 2012:150367	Development of an interventions
Paul M, Andreassen S, Tacconelli E, et al. (2006) Improving empirical antibiotic treatment using TREAT, a computerized decision support system: cluster randomized trial. Journal of Antimicrobial Chemotherapy 58(6):1238-1245	Not an RCT
Perz JF, Craig AS, Coffey CS, et al. (2002) Changes in antibiotic prescribing for children after a community-wide campaign. JAMA 287(23):3103-9	Community-wide campaign
Pettersson E, Vernby A, Molstad S, et al. (2011) Can a multifaceted educational intervention targeting both nurses and physicians change the prescribing of antibiotics to nursing home residents? A cluster randomised controlled trial. Journal of Antimicrobial Chemotherapy 66(11):2659-2666	Limited intervention detail
Prior M, Elouafkaoui P, Elders A, et al. (2014) Evaluating an audit and feedback intervention for reducing antibiotic prescribing behaviour in general practice (the RAPID trial): a partial factorial cluster randomised trial protocol. Implementation Science 9:50	Trial protocol
Qu R, Ji Y, Ling Y, et al. (2012) Procalcitonin is a good tool to guide duration of antibiotic therapy in patients with severe acute pancreatitis. Saudi Medical Journal 33:382-387	Setting not included
Ramsay C, Brown E, Hartman G, et al. (2003) Room for improvement: a systematic review of the quality of evaluations of interventions to improve hospital antibiotic prescribing. Journal of	Methods paper

Author	Reason for exclusion
Antimicrobial Chemotherapy 52(5):764-771	
Ranji SR, Steinman MA< Shojania KG, et al. (2008) Interventions to reduce unnecessary antibiotic prescribing: a systematic review and quantitative analysis. Medical Care 46(8):847-862	Quality improvement outcomes and analysis not relevant to this review, references checked
Razon Y, Ashenazi S, Cohen A, et al. (2005) Effect of educational intervention on antibiotic prescription practices for upper respiratory infections in children: a multicentre study. Journal of Antimicrobial Chemotherapy 56(5):937-40	Outwith Europe, Canada, USA, NZ, Australia
Regev-Yochay G, Raz M, Dagan R, et al. (2011) Reduction in antibiotic use following a cluster randomized controlled multifaceted intervention: the Israeli judicious antibiotic prescription study. Clinical Infectious Diseases 53(1):33-41	Interventions not relevant
Richards MJ, Robertson MB, Dartnell JGA, et al. (2003) Impact of a web-based antimicrobial approval system on broad-spectrum cephalosporin use at a teaching hospital. Medical Journal of Australia 178(8):386-390	Insufficient detail reported in results
Samore (2005) Clinical decision support and appropriateness of antimicrobial prescribing. JAMA	Localised intervention, insufficient information on clinical decision support systems
Sanders (2008) Previous cultures are not clinically useful for guiding empiric antibiotics in suspected ventilator-associated pneumonia: secondary analysis from a randomized trial. Journal of Critical Care	Predictive value of previous cultures
Sandifer JP and Jones AE. (2012) Can procalcitonin levels guide antibiotic therapy in bacterial infections and reduce antibiotic overconsumption without having a negative effect on clinical outcomes? Annals of Emergency Medicine 60(3):370-371	Not an RCT
Santolaya ME, Villarroel M, Avendano LF, et al. (1997) Discontinuation of antimicrobial therapy for febrile, neutropenic children with cancer: a prospective study. Clinical Infectious Diseases 25(1):92-97	Outcomes not relevant
Schouten JA, Hulscher ME, Trap-Liefers J, et al. (2007) Tailored interventions to improve antibiotic use for lower respiratory tract infections in hospitals: a cluster-randomized, controlled trial. Clinical Infectious Diseases	Outcomes not relevant
Schroeder S, Hochreiter M, Koehler T, et al. (2009) Procalcitonin (PCT)-guided algorithm reduces length of antibiotic treatment in surgical intensive care patients with severe sepsis: results of a prospective randomised study. Langenbeck's Archives of Surgery 394(2):221-226	Setting not included
Schuetz P, Muller B and Christ-Crain M. (2013) Meta-analysis: Procalcitonin-guided antibiotic therapy reduces treatment failure in acute respiratory infection. Annals of Internal Medicine 158(4):JC5	Brief report
Schuetz P, Christ-Cain M, Thomann R, et al. (2009) Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial. JAMA 13(suppl1):p386	Included in Schuetz Cochrane review
Schuetz P, Chiappa V, Briel M, et al. (2011) Procalcitonin algorithms for antibiotic therapy decisions: a systematic review of randomized controlled trials and recommendations for clinical algorithms. Archives of Internal Medicine 171(15):1322-1331	Intervention not relevant
Senn L, Burnand B, Francioli P, et al. (2004) Improving appropriateness of antibiotic therapy: randomised trial of an intervention to foster reassessment of prescription after 3 days. Journal of Antimicrobial Chemotherapy 53(6):1062-1067	Outcomes not relevant

Author	Reason for exclusion
Shebl NA, Franklin BD and Baerber N. (2007) Clinical decision support systems and antibiotic use. Pharmacy World & Science 29(4):342-349	Review
Siegel RM, Kiely M, Bien JP, et al. (2003) Treatment of otitis media with observation and a safety-net antibiotic prescription. Pediatrics 112(3):527-531	Intervention not relevant
Silva BNG, Andriolo RB, Atallah AN, et al. (2013) De-escalation of antimicrobial treatment for adults with sepsis, severe sepsis, or septic shock. Cochrane Database of Systematic Reviews	Intervention not relevant
Simpson SA, Butler CC, Hood K, et al. (2009) Stemming the Tide of Antibiotic Resistance (STAR): a protocol for a trial of a complex intervention addressing the 'why' and 'how' of appropriate antibiotic prescribing in general practice. BMC family practice	Trial protocol
Sirinavin S, Suvanakoot P, Sathapatayavongs B, et al. (1998) Effect of antibiotic order form guiding rational use of expensive drugs on cost containment. Southeast Asian Journal of Tropical Medicine and Public Health 29(3):636-642	Intervention not relevant
Smabrekke L, Berild D, Giasver A, et al. (2002) Educational intervention for parents and healthcare providers leads to reduced antibiotic use in otitis media. Scandinavain Journal of Infectious Diseases 34(9):657-659	Parent and clinician educational programme
Smeets (2009) Intervention with educational outreach at large scale to reduce antibiotics for respiratory tract infections: a controlled before and after study	Not an RCT
Smith KJ, Wateska A, Nowalk M, et al. (2013) Cost-effectiveness of procalcitonin-guided antibiotic use in community acquired pneumonia. Journal of General Internal Medicine 28(9):1157-1164	Outcomes not relevant
Snow V, Mottur-Pilson C and Hickner JM. (2001) Principles of appropriate antibiotic use for acute sinusitis in adults. Annals of Internal Medicine 134(6):495-497	Intervention not relevant
Soler N, Esperatti M, Ewig S, et al. (2012) Sputum purulence-guided antibiotic use in hospitalised patients with exacerbations of COPD. European Respiratory Journal 40(6):1344-1353	Intervention not relevant
Soni NJ, Samson DJ, Galaydick JL, et al. (2013) Procalcitonin-guided antibiotic therapy: a systematic review and meta-analysis. Journal of Hospital Medicine 8(9):530-540	Review
Soumerai SB, Avorn J, Taylor WC, et al. (1993) Improving choice of prescribed antibiotics through concurrent reminders in an educational order form. Medical Care 31(6):552-558	Intervention not relevant
Soumerai SB and Avorn J. (1983) Improving drug-therapy decisions through educational outreach: a randomised controlled trial of academic detailing. NEJM 24(4):313-31	Several drugs, not AMS
Spiro DM, Tay KY, Arnold DH, et al. (2006) Wait-and-see prescription for the treatment of acute otitis media: a randomized controlled trial. JAMA 296(10):1235-41	In Spurling Cochrane
Stewart J, Pilla J and Dunn L. (2000) Pilot study for appropriate anti-infective community therapy. Canadian Family Physician 46(4):851-859	Community and clinician educational programme
Steinman MA, Ranji SR, Shojania KG, et al. (2006) Improving antibiotic selection. A systematic review and quantitative analysis of quality improvement strategies. Medical Care 44(7):617-628	Limited study description, analysis not relevant to this review,
Stille CJ, Rifas-Shiman SL, Kleinman K, et al. (2008) Physician responses to a community-level trail promoting judicious antibiotic use. Annals of Family Medicine 6(3):206-2112	Physician and parent intervention

Author	Reason for exclusion
Stocker M, Fontana M, El Helou S, et al. (2009) Use of procalcitonin-guided decision-making to shorten antibiotic therapy in suspected neonatal early-onset sepsis: prospective randomized intervention trial. Neonatology 97(2):165-174	Setting not included
Stolz D, Smyrnios N, Eggimann P, et al. (2009) Procalcitonin for reduced antibiotic exposure in ventilator-associated pneumonia: a randomised study. European Respiratory Journal 34(6):1364-1375	Setting not included
Storey DF, Pate PG, Nguyen AT, et al. (2012) Implementation of an antimicrobial stewardship program on the medical-surgical service of a 100-bed community hospital. Antimicrobial Resistance & Infection Control 32(4)	Not an RCT
Tahtinen PA, Laine MK, Ruuskanen O, et al. (2012) Delayed versus immediate antimicrobial treatment for acute otitis media. Pediatric Infectious Disease Journal 31(12):1227-1232	Outcomes not relevant
Tang J, Long W, Yan L, et al. (2013) Procalcitonin guided antibiotic therapy of acute exacerbations of asthma: a randomized controlled trial. BMC Infectious Diseases 13:596	Outwith Europe, Canada, USA, NZ and Australia
Teng CL, Achike FI, Phua KL, et al. (2006) Modifying antibiotic prescribing: the effectiveness of academic detailing plus information leaflet in a Malaysian primary care setting. Medical Journal of Malaysia 61(3):323-331	Outwith Europe, Canada, USA, NZ, Australia
Torres FA, Pasarelli I, Cutri A, et al. (2014) Impact assessment of a decision rule for using antibiotics in pneumonia. Pediatric Pulmonology 49(7():701-706	Outwith Europe, Canada, USA, NZ, Australia
Tsiata C. (2001) Cost effectiveness of antibacterial restriction strategies in a tertiary care university teaching hospital. Disease Management & Health Outcomes 9(1):23-32	Economic
Van der Meer V, Neven AK, van den Broek PJ, et al. (2005) Diagnostic value of C reactive protein in infections of the lower respiratory tract: systematic review. British Medical Journal	Outcomes not relevant
van Driel ML, Coenen S, Dirven K, et al. (2007) What is the role of quality circles in strategies to optimise antibiotic prescribing? A pragmatic cluster-randomised controlled trial in primary care. Quality & Safety in Health Care 16(3):197-202	Intervention not relevant
Van Kasteren ME, Mannien J, Kulberg BJ, et al. (2005) Quality improvement of surgical prophylaxis in Dutch hospitals: evaluation of a multi-site intervention by time series analysis 56(6):1094-102	Guideline implementation
Varonen H, Rantakorpi UM, Nyberg S, et al. (2007) Implementing guidelines on acute maxillary sinusitis in general practice – a randomised controlled trial. Family Practice 24(2):201-206	Guideline implementation
Vettese N, Hendershot J, Irvine M, et al. (2013) Outcomes associated with a thrice-weekly antimicrobial stewardship programme in a 253-bed community hospital. Journal of Clinical Pharmacy and Therapeutics 38(5):401-404	Not an RCT
Vlahovic-Palcevski V, Morovic M and Palcevski G. (2000) Antibiotic utilization at the university hospital after introducing an antibiotic policy. European Journal of Clinical Pharmacology 56(1):97-101	Antibiotic restriction policy, limited description
Vodicka TA, Thompson M, Lucas P, et al. (2013) Reducing antibiotic prescribing for children with respiratory tract infections in primary care: a systematic review. British Journal of General Practice 63(612):e445-e454	Review
von Gunten V, Troillet N, Beney J, et al. (2005) Impact of an interdisciplinary strategy on antibiotic use: a prospective controlled study in three hospitals. Journal of Antimicrobial Chemotherapy 55(3):362-366	Local practice guidelines, little detail on implementation

Author	Reason for exclusion
Vouloumanou EK, Karageorgopoulos DE, Kazanti MS, et al. (2009) Antibiotics versus placebo or watchful waiting for acute otitis media: a meta-analysis of randomized controlled trials. Journal of Antimicrobial Chemotherapy 64 (1):16-24	Intervention not relevant
Wagstrom EA. (2006) The take care program and responsible use of antibiotics. Animal Biotechnology 17(2):233-238	Intervention not relevant
Walker SE. (1998) Physicians' acceptance of a preformatted pharmacy intervention chart note in a community hospital antibiotic step down program. Journal of Pharmacy Technology 14(4):141-145	Lack of detail on intervention
Weischen I, Kuyvenhoven M, Hoes A, et al. (2005) Reduced antibiotic prescribing for respiratory tract symptoms after following a postgraduate program: a randomised controlled study. Huisarts en wetenschap 48(4):154-157	Not in English
Weiss CH, Dibardino D, Rho J, et al. (2013) A clinical trial comparing physician prompting with an unprompted automated electronic checklist to reduce empirical antibiotic utilization. Critical Care Medicine 41(11):2563-2569	No comparison with usual care/control
Welschen I, Marijke MK, Hoes AW, et al. (2004) Effectiveness of a multiple intervention to reduce antibiotic prescribing for respiratory tract symptoms in primary care: randomised controlled trial. BMJ 329:431	Joint intervention
Weston A, Epstein L, Davidson LE, et al. (2013) The impact of a Massachusetts state-sponsored educational program on antimicrobial stewardship in acute care hospitals. Infection Control and Hospital Epidemiology 34(4):437-439	Not an RCT
Wickens HJ, Farrell S, Ashiru-Oredope DAI, et al. (2013) The increasing role of pharmacists in antimicrobial stewardship in English hospitals. Journal of Antimicrobial Chemotherapy 68(11):2675-2681	Not an RCT
Wild C and Hahn R. (2000) Near-patient CRP testing by physicians in private practice to reduce antibiotic prescriptions. HTA Database 4	Not an intervention
Wilton P, Smith R, Coast J, et al. (2002) Strategies to contain the emergence of antimicrobial resistance: a systematic review of effectiveness and cost-effectiveness. Journal of Health Services Research & Policy 7(2):111-117	Antimicrobial resistance strategies
Wong JR, Bauer KA, Mangino JE, et al. (2012) Antimicrobial stewardship pharmacist interventions for coagulase negative staphylococci positive blood cultures using rapid polymerase chain reaction. Annals of Pharmacotherapy 46(11):1484-1490	Not an intervention, system or process
Worrall G, Kettle A, Graham W, et al. (2010) Postdated versus delayed antibiotic prescriptions in primary care, Canadian Family Physician 56(10):1032-1036	Not an RCT
Wurzel D, Marchant JM, Yerkovich ST, et al. (2011) Short courses of antibiotics for children and adults with bronchiectasis. Cochrane Database of Systematic Reviews	Intervention not relevant
Yang YN, Tseng HI, Yang SN, et al. (2012) A strategy for reduction of antibiotic use in new patients admitted to a neonatal intensive care unit. Pediatrics & Neonatology 53(4):245-251	Intervention not relevant
Yardley L, Douglas E, Anthierens S, et al. (2013) Evaluation of a web-based intervention to reduce antibiotic prescribing for LRTI in six European countries: quantitative process analysis of the GRACE/INTRO randomised controlled trial. Implementation Science 8:134	Not an RCT
Yip W, Powell-Jackson T, Chen W, et al. (2014) Capitation combined with pay-for-performance improves antibiotic prescribing practices in rural China. Health Affairs 33(3):502-510	Outcomes not relevant

Author	Reason for exclusion
Zahar JR, Rioux C, Girou E, et al. (2006) Inappropriate prescribing of aminoglycosides: risk factors and impact of an antibiotic control team. Journal of Antimicrobial Chemotherapy 58(3):651-656	Localised intervention, limited details
Zhang L, Huang J, Xu T, et al. (2012) Procalcitonin-guided algorithms of antibiotic therapy in community-acquired lower respiratory tract infections: a systematic review and meta-analysis of randomized controlled trials. Database of Reviews of Effects	Not in English
Zwar N, Wolk J, Gordon J, et al. (1999) Influencing antibiotic prescribing in general practice: a trial of prescriber feedback and management guidelines. Family Practice 16(5):495-500	Intervention not relevant
Zwar N, Henderson J, Britt H, et al. (2002) Influencing antibiotic prescribing by prescriber feedback and management guidelines: a 5-year follow-up. Family Practice 19(1):12-17	Intervention not relevant

C.5.3 Barriers to decision making

Author	Reason for exclusion
Aagaard EM, Gonzales R, Camargo CA, et al. (2010) Physician champions are key to improving antibiotic prescribing quality Joint Commission Journal on Quality and Patient Safety 36(3):109-16	No relevant outcomes
Abbo L, Sinkowitz-Cochran R, Simth L, et al. (2011) BBO,L., SINKOWITZ-COCHRAN, RONDA et al. Faculty and resident physicians' attitudes, perceptions, and knowledge about antimicrobial use and resistance. Infection Control and Hospital Epidemiology 32(7):714-18	Not relevant
Ackerman SL, Gonzales R, Stahl MS, et al. (2013) One size does not fit all: evaluating an intervention to reduce antibiotic prescribing for acute bronchitis. BMC Health Services Research (4)13:462	Not relevant
Adu A, Simpson JM, Armour CL. (2001) Pharmacists' and physicians' perception of antibiotic policies in New South Wales public hospitals. International Journal of Pharmacy Practice 9(1):31-36	No relevant outcomes
Alden D, Tice A, Berthiaume JT. (2010) Investigating approaches to improving appropriate antibiotic use among higher risk ethnic groups. Hawaii Medical Journal 69(11):260-3	Not relevant intervention
Alder SC, Trunnell EP, White GL, et al. (2005) Reducing parental demand for antibiotics by promoting communication skills. American Journal of Health Education 363(3):132-9	Not relevant intervention
Aldeyab MA, Kearney MP, McElnay JC, et al. (2012) A point prevalence survey of antibiotic use in four acute-care teaching hospitals utilizing the European Surveillance of Antimicrobial Consumption (ESAC) audit tool. Epidemiology and Infection 140(9):1714-20	Not relevant
Ali MH, Kalima P, Maxwell SRJ, et al. (2006) Failure to implement hospital antimicrobial prescribing guidelines: a comparison of two UK academic centres The Journal of Antimicrobial Chemotherapy. 57(5):959-62	No relevant outcomes
Altiner A, Knauf A, Moebes J, et al. (2004) Acute cough: a qualitative analysis of how GPs manage the consultation when patients explicitly or implicitly expect antibiotic prescriptions. Family Practice 21(5):500-06	No relevant outcomes
Andre M, Hedin K, Hakansson A, et al. (2007) More physician consultations and antibiotic prescriptions in families with high concern about infectious illness--adequate response to infection-prone child or self-fulfilling prophecy? Family Practice 24(4):302-7	Not relevant
Arnold SR, Strauss SE. (2005) Interventions to improve antibiotic prescribing practices in ambulatory care The Cochrane database of	Systematic review,

Author	Reason for exclusion
systematic reviews. (4) :CD003539	additional papers ordered
Barlam TF, Divall M. (2006) Antibiotic-stewardship practices at top academic centers throughout the United States and at hospitals throughout Massachusetts. Infection Control and Hospital Epidemiology 27(7):695-703	Not relevant
Baysari MT, Oliver K, Egan B, et al. (2013) Audit and feedback of antibiotic use: utilising electronic prescription data. Applied Clinical Informatics 4(4):583-95	Paper not available
Bekkers MJ, Simpson SA, Dunstan F, et al. (2010) Enhancing the quality of antibiotic prescribing in primary care: qualitative evaluation of a blended learning intervention. BMC Family Practice 7(11):34	Not relevant
Belongia EA, Sullivan BJ, Chyou PH, et al. (2001) A Community Intervention Trial to Promote Judicious Antibiotic Use and Reduce Penicillin-Resistant Streptococcus pneumoniae Carriage in Children. Pediatrics 108(3):575-83	Not relevant
Bjorkman I, Berg J, Roing M, et al. (2010) Perceptions among Swedish hospital physicians on prescribing of antibiotics and antibiotic resistance. Quality & Safety in Health Care 19(6):e8	Not relevant
Bjorkman I, Berg J, Veiberg N, et al. (2013) Awareness of antibiotic resistance and antibiotic prescribing in UTI treatment: a qualitative study among primary care physicians in Sweden. Scandinavian Journal of Primary Health Care 31(1):50-5	Not relevant
Bjornsdottir I, Hansen EH. (2001) Telephone prescribing of antibiotics. General practitioners' views and reflections. European Journal of Public Health 11(3):260-3	Not relevant
Bjornsdottir I and Hansen EH. (2002) Intentions, strategies and uncertainty inherent in antibiotic prescribing. European Journal of General Practice 8(1):18-24	Not relevant
Bjornsdottir I, Hansen EH. (2002) Intentions, strategies and uncertainty inherent in antibiotic prescribing. European Journal of General Practice 8(1):18-24	Not relevant
Bjornsdottir I, Kristinsson KG, Hansen EH. (2010) Diagnosing infections: A qualitative view on prescription decisions in general practice over time. Pharmacy World and Science 32(6):805-14	Not relevant
Brinsley KJ, Sinkowitz-Cochran RL, Cardo DM, et al. (2005) Assessing motivation for physicians to prevent antimicrobial resistance in hospitalized children using the Health Belief Model as a framework. American Journal of Infection Control 33(3):175-81	No relevant outcomes
Brusaferro S, Rinaldi O, Pea F, et al. (2001) Protocol implementation in hospital infection control practice: an Italian experience of preoperative antibiotic prophylaxis. The Journal of Hospital Infection 47(4):288-93	Not relevant
Brusaffero S, Rinaldi O, Pea F, et al. (2001) Protocol implementation in hospital infection control practice: an Italian experience of preoperative antibiotic prophylaxis. Journal of Hospital Infection 47(4):288-93	Not relevant
Bush-Knapp ME, Brinsley-Rainisch KJ, Lawton-Ciccarone RM, et al. (2007) Spreading the word, not the infection: reaching hospitalists about the prevention of antimicrobial resistance. American Journal of Infection Control 35(10):656-61	Not relevant
Cals JWL, van Leeuwen ME, Chappin FHF, et al. (2013) "How do you feel about antibiotics for this?" A qualitative study of physician attitudes towards a context-rich communication skills method. Antibiotics 2(3):439-49	Not relevant
Charani E, Edwards R, Sevdalis N, et al. (2011) Behavior change	Systematic review,

Author	Reason for exclusion
strategies to influence antimicrobial prescribing in acute care: a systematic review. Clinical Infectious Diseases 53(7): 651-62	additional papers ordered
Coenen S, Michiels B, van Royen P, et al. (2002) Antibiotics for coughing in general practice: a questionnaire study to quantify and condense the reasons for prescribing. BMC Family Practice 3:16	Not relevant intervention
Davey P, Brown E, Charani E, et al. (2013) Interventions to improve antibiotic prescribing practices for hospital inpatients The Cochrane database of systematic reviews. Art. No CD003543. DOI: 10.1002/14651858.CD003543.pub3	Not relevant
Dowell J, Pitkethly M, Bain J, et al. (2001) A randomised controlled trial of delayed antibiotic prescribing as a strategy for managing uncomplicated respiratory tract infection in primary care. British Journal of General Practice 51:200-05	Not relevant
Dranitsaris G, Spizzirri D, Pitre M, et al. (2001) A randomized trial to measure the optimal role of the pharmacist in promoting evidence-based antibiotic use in acute care hospitals. International Journal of Technology Assessment in Health Care 17(2):171-80	Not relevant
Ecker L, Ochoa TJ, Vargas M, et al. (2013) Preferences of antibiotic use in children less than five in physicians working health centers of primary level in peri-urban areas of Lima, Peru. Revista Peruana de Medicina Experimental y Salud Publica 30(2):181-89	Paper not in English (Abstract was)
Fishman N. (2006) Antimicrobial stewardship. American Journal of Infection Control 34(5 Suppl 1):S55-73	Not relevant
Flach SD, Diekema DJ, Yankey JW, et al. (2005) Variation in the use of procedures to monitor antimicrobial resistance in U.S. hospitals. Infection Control and Hospital Epidemiology 36(1):31-8	Not relevant
Fleming A, Tonna A, O'Connor S, et al.(2014) A cross-sectional survey of the profile and activities of Antimicrobial Management Teams in Irish Hospitals. International Journal of Clinical Pharmacy 36(2):377-83	Interventions or barriers not identified
Giblin TB, Sinkowitz-Cochran RL, Harris PL, et al. (2004) Clinicians' perceptions of the problem of antimicrobial resistance in health care facilities. Archives of Internal Medicine 164(15):1662-8	Not relevant
Gould IM, MacKensie FM, Shepherd L. (2007) Attitudes to antibiotic prescribing, resistance and bacteriology investigations amongst practitioners and patients in the Grampian region of Scotland. The European Journal of General Practice 13(1):35-6	Not relevant
Haggard M. (2011) Poor adherence to antibiotic prescribing guidelines in acute otitis media--obstacles, implications, and possible solutions. European Journal of Pediatrics 170(3):323-32	Not relevant
Hedin K, Andre M, Hakansson A, et al. (2006) A population-based study of different antibiotic prescribing in different areas. The British Journal of General Practice 56(530):680-5	Not relevant
Jaruseviciene L, Radzeviciene-Jurgute R, Lazarus JV, R.et al. (2012) A study of antibiotic prescribing: The experience of Lithuanian and Russian GPs. Central European Journal of Medicine 7(6):790-99	Not relevant
Kern WV, Steib-Bauert M, Amann S, et al. (2008) Hospital antibiotic management in Germany--results of the ABS maturity survey of the ABS International group. Wiener klinische Wochenschrift 120(9-10):294-8	Not relevant intervention
Kuehlein T, Goetz K, Laux G, et al. (2011) Antibiotics in urinary-tract infections. Sustained change in prescribing habits by practice test and self-reflection: a mixed methods before-after study. BMJ Quality and Safety 20(6):522-26	No relevant outcomes
Kumar S, Little P, Britten N. (2003) Why do general practitioners	No relevant outcomes

Author	Reason for exclusion
prescribe antibiotics for sore throat? Grounded theory interview study. BMJ 326:138	
Lagerløv P, Loeb M, Marit A, et al. (2000) Improving doctors' prescribing behaviour through reflection on guidelines and prescription feedback:a randomised controlled study. Quality in Health Care 9:159–65	Not relevant
Larson EL, Quiros D, Giblin T, et al. (2007) Relationship of antimicrobial control policies and hospital and infection control characteristics to antimicrobial resistance rates American Journal of Critical Care 16(2):110-20	No relevant outcomes
Linder JA, Schnipper JL, Tsurikova R, et al. (2010) Electronic health record feedback to improve antibiotic prescribing for acute respiratory infections. The American Journal of Managed Care 16(12Suppl):e311-9	Not relevant
Lines L. (2006) A study of senior staff nurses' perceptions about MRSA. Nursing Times 102(15):32-5	Not relevant
Litvin CB, Ornstein SM, Wessell AM, et al. (2012) Adoption of a clinical decision support system to promote judicious use of antibiotics for acute respiratory infections in primary care. International Journal of Medical Informatics 81(8):521-26 ,	Not relevant
Lopez-Vazquez P, Vazquez-Lago JM, Figueiras A. (2012) Misprescription of antibiotics in primary care: a critical systematic review of its determinants. Journal of Evaluation in Clinical Practice 18(2):473-84	Systematic review, additional papers ordered
MacCara ME, Sketris IS, Comeau DG, et al. (2001) Impact of a Limited Fluoroquinolone Reimbursement Policy on Antimicrobial Prescription Claims. Ann Pharmacother 35(7-8):852-58	Not relevant
Macfarlane J, Holmes W, Gard P, et al. (2002) Reducing antibiotic use for acute bronchitis in primary care: blinded, randomised controlled trial of patient information leaflet. BMJ 324(7329): 91.	Not relevant
Mainous AG, Hueston WJ, Love MM, et al. (2000) To Reduce Antibiotic Overuse. Family Medicine 32(1):22-9	Not relevant
McGregor JC, Harris AD, Furuno JP, et al. (2007) Relative influence of antibiotic therapy attributes on physician choice in treating acute uncomplicated pyelonephritis. Medical Decision Making 27(4):387-94	Not relevant
Metlay JP, Shea JA, Crossette LB, et al. (2002) Tensions in antibiotic prescribing: pitting social concerns against the interests of individual patients. Journal of General Internal Medicine 17(2):87-94	No relevant outcomes
Minen MT, Duquaine D, Marx MA, et al. (2010) A survey of knowledge, attitudes, and beliefs of medical students concerning antimicrobial use and resistance. Microbial Drug Resistance 16(4):285-89	Not relevant
Mohan S, Dharamraj K, Dindial R, et al. (2004) Physician behaviour for antimicrobial prescribing for paediatric upper respiratory tract infections: a survey in general practice in Trinidad, West Indies. Annals of Clinical Microbiology and Antimicrobials 3:11	No relevant outcomes
Mol PGM, Rutten WJMJ, Gans ROB, et al. (2004) Adherence barriers to antimicrobial treatment guidelines in teaching hospital, the Netherlands. Emerging Infectious Diseases 10(3):522-25	Not generizable or applicable to UK healthcare
Munro CL, Grap MJ. (2001) Nurses' knowledge and attitudes about antibiotic therapy in critical care. Intensive & Critical Care Nursing 17(4):213-18	No relevant outcomes
Mustafa M, Wood F, Butler CC, et al. (2014) Managing expectations of antibiotics for upper respiratory tract infections: a qualitative study. Annals of Family Medicine 12(1):29-36	No relevant outcomes

Author	Reason for exclusion
Nambiar S, Schwartz R, Sheridan MJ. (2002) Antibiotic use for upper respiratory tract infections: how well do pediatric residents do? Archives of Pediatrics & Adolescent Medicine 156(6):621-4	Not relevant intervention
Nash DR, Harman J, Wald ER, et al. (2002) Antibiotic Prescribing by Primary Care Physicians for Children With Upper Respiratory Tract Infections . Archives of Pediatrics and Adolescent Medicine 156(11):1114-9	Not relevant
Navarro C, Del Toro MD, Cobo J, et al. (2013) Knowledge and perceptions of junior and senior Spanish resident doctors about antibiotic use and resistance: results of a multicenter survey. Enfermedades infecciosas y microbiologia clinica 31(4):199-204	Not relevant
Naz F, Rehman AJ. (2008) Antibiotic treatment of children with upper respiratory infections in Karachi Pakistan. Paediatric Journal 32(2):111-116	Not relevant
Ong S, Nakase J, Moran GJ, et al. (2007) Antibiotic Use for Emergency Department Patients With Upper Respiratory Infections: Prescribing Practices, Patient Expectations ,and Patient Satisfaction Annals of Emergency Medicine 50(3):213-20	No relevant outcomes
Ong S, Moran GJ, Krishnadasan A, (2011) Antibiotic Prescribing Practices of Emergency Physicians and Patient Expectations for Uncomplicated Lacerations. The Western Journal of Emergency Medicine 12(4): 375–80.	Not relevant
Paluck E, Katzenstein D, Frankish CJ, et al. (2001) Prescribing practices and attitudes toward giving children antibiotics. Canadian Family Physician 47:521-27	No relevant outcomes
Patel SJ, Saiman L, Duchon JM, et al. (2012) Development of an antimicrobial stewardship intervention using a model of actionable feedback. Interdisciplinary Perspectives on Infectious Diseases 2012:150367	Not relevant
Pettersson E, Vernby A, Molsatd S, et al. (2011) Can a multifaceted educational intervention targeting both nurses and physicians change the prescribing of antibiotics to nursing home residents? A cluster randomised controlled trial. Journal of Antimicrobial Chemotherapy 66(11):2659-66	Not relevant
Pulcini C, Willaims F, Molinri N, et al. (2011) Junior doctors' knowledge and perceptions of antibiotic resistance and prescribing: a survey in France and Scotland. Clinical Microbiology and Infection 17(1):80-7	No relevant outcomes
Remesh A, Gayathri AM, Singh R, et al. (2013) The knowledge, attitude and the perception of prescribers on the rational use of antibiotics and the need for an antibiotic policy-a cross sectional survey in a tertiary care hospital. Journal of Clinical and Diagnostic Research 7(4):675-9	Not relevant
Roque F, Soares S, Breitenfeld L et al. (2013) Attitudes of community pharmacists to antibiotic dispensing and microbial resistance: a qualitative study in Portugal. International Journal of Clinical Pharmacy 35(3):417-24	Not relevant to UK healthcare
Rowbotham S, Chisholm A, Moschogianis S, et al. (2012) Challenges to nurse prescribers of a no-antibiotic prescribing strategy for managing self-limiting respiratory tract infections. Journal of Advanced Nursing 68(12):2622-32	Not relevant
Santiano N, Caldwell J, Ryan E, et al. (2014) Knowledge and understanding of patients and health care workers about multi-resistant organisms. Healthcare Infection 19(2):45-52	Not relevant
Scheinfeld N, Struach S, Ross B, et al. (2002) Antibiotic prophylaxis	Not relevant

Author	Reason for exclusion
guideline awareness and antibiotic prophylaxis use among New York State dermatologic surgeons Dermatologic Surgery 28(9):841-4	
Schouten JA, Hulscher ME, Kullberg B-J, et al. (2005) Understanding variation in quality of antibiotic use for community-acquired pneumonia: effect of patient, professional and hospital factors. The Journal of Antimicrobial Chemotherapy 56(3):575-82	Not relevant to UK healthcare
Sintchenko V, Iredell JR, Gilbert GL, et al. (2001) What do physicians think about evidence-based antibiotic use in critical care? A survey of Australian intensivists and infectious disease practitioners. Internal Medicine Journal 31(8):462-69	No relevant outcomes
Sivagnanam G, Mohanasundaram J, Thirumalaikolundusubramanian P, et al.(2004) A survey on current attitude of practicing physicians upon usage of antimicrobial agents in southern part of India. Medscape General Medicine 6(2):1	Unable to extrapolate to UK setting
Srinivasan A, Song X, Rixhards A, et al. (2004) A survey of knowledge, attitudes, and beliefs of house staff physicians from various specialties concerning antimicrobial use and resistance. Archives of Internal Medicine 164(13):1451-56	Not relevant
Stach LM, Hedican EB, Herigon JC, et al. (2012) Clinicians' attitudes towards an antimicrobial stewardship program at a children's hospital. Journal of the Pediatric Infectious Diseases Society 1(3):190-7	No relevant outcomes
Stille CJ, Rifas-Shiman SL, Kleinman K, et al. (2008) Physician responses to a community-level trial promoting judicious antibiotic use. Annals of Family Medicine 6(3):206-12	Not relevant
Strandberg EL, Brorsson A, Hagstam C, et al. (2013) "I'm Dr Jekyll and Mr Hyde": are GPs' antibiotic prescribing patterns contextually dependent? A qualitative focus group study. Scandinavian Journal of Primary Health Care 31(3):158-65	No relevant outcomes
Tan JA, Naik VN, Lingard L. (2006) Exploring obstacles to proper timing of prophylactic antibiotics for surgical site infections. Quality and Safety in Health Care 15:32-38	No relevant outcomes
Teixeira Rodrigues A, Roque F, Falcao A, et al.(2013) Understanding physician antibiotic prescribing behaviour: a systematic review of qualitative studies. International Journal of Antimicrobial Agents 41(3):203-12	Systematic review, additional papers ordered
Tennant I, Nicholson A, Gordon-Strachan GM, et al. (2010) A survey of physicians' knowledge and attitudes regarding antimicrobial resistance and antibiotic prescribing practices at the University Hospital of the West Indies. The West Indian Medical Journal 59(2):165-70	Not applicable to UK healthcare
Tonkin-Crine S, Yardley L, Coenen S, et al. (2013) Strategies to promote prudent antibiotic use: exploring the views of professionals who develop and implement guidelines and interventions. Family Practice 30(1):88-95	No relevant outcomes
Tonkin-Crine S, Yardley L, Coenen S, et al.(2011) GPs' views in five European countries of interventions to promote prudent antibiotic use. The British Journal of General Practice 61(586):e252-61	No relevant outcomes
Tonna AP, Stewart DC, West B, et al. (2010) Exploring pharmacists' perceptions of the feasibility and value of pharmacist prescribing of antimicrobials in secondary care in Scotland. The International Journal of Pharmacy Practice 18(5):312-19	Not relevant
Trepka MJ, Belongia EA, Chyou PH, et al. (2001) The Effect of a Community Intervention Trial on Parental Knowledge and Awareness of Antibiotic Resistance and Appropriate Antibiotic Use in Children. Pediatrics 107()1):E6	Not relevant

Author	Reason for exclusion
Trivedi KK and Rosenberg J. (2013) The state of antimicrobial stewardship programs in California. Infection Control and Hospital Epidemiology 34(4):379-84	Not relevant
Van Duijn HJ, Kuyvenhoven MM, Tiebosch HM, et al. (2007) Diagnostic labelling as determinant of antibiotic prescribing for acute respiratory tract episodes in general practice BMC Family Practice 8:55	Not relevant
Vazquez-Lago JM, Zquez- Lago JM, Lopez-Vazquez P, et al. Attitudes of primary care physicians to the prescribing of antibiotics and antimicrobial resistance: a qualitative study from Spain. Family Practice 29(3):352-60	Not applicable to UK healthcare
Velasco E, Espelage W, Faber M, et al. (2011) A national cross-sectional study on socio-behavioural factors that influence physicians' decisions to begin antimicrobial therapy. Infection 39(4):289-97	Not relevant
Velasco E, Ziegelmann A, Eckmanns T, et al. (2012) Eliciting views on antibiotic prescribing and resistance among hospital and outpatient care physicians in Berlin, Germany: results of a qualitative study. BMJ Open 2(1):e000398	Not relevant
Vlahovic-Palcevski V, Dumpis U, Mitt P, et al. (2007) Benchmarking antimicrobial drug use at university hospitals in five European countries. Clinical Microbiology and Infection 13(3):277-83	Not relevant
Vlahovic-Palcevski V, Francetic I, Palcevski G, et al. (2007) Antimicrobial use at a university hospital: appropriate or misused? A qualitative study. International Journal of Clinical Pharmacology and Therapeutics 45(3):169-74	Not relevant
Walker AE, Grimshaw JM, Armstrong EM. (2001) Salient beliefs and intentions to prescribe antibiotics for patients with a sore throat. British Journal of Health Psychology 6(4):347-60	No relevant outcomes
Walther SM, Erlandsson M, Berman LG,et al. (2002) Antibiotic prescription practices, consumption and bacterial resistance in a cross section of Swedish intensive care units. Acta Anaesthesiologica Scandinavica 46(9):1075-81	Not relevant
Warters RD, Szmuk P, Pivalizza EG, et al. (2006) The role of anesthesiologists in the selection and administration of perioperative antibiotics: a survey of the American Association of Clinical Directors. Anesthesia and Analgesia 102(4):1177-82	Not relevant
Weissa MC, Deaveb T, Petersc TJ, et al. (2004) Perceptions of patient expectation for an antibiotic: a comparison of walk-in centre nurses and GPs. Family Practice 21(5):492-99	Not relevant
Werner NL, Hecker MT, Sethi AK, et al. (2011) Unnecessary use of fluoroquinolone antibiotics in hospitalized patients. BMC Infectious Diseases 11:187	Not relevant
Wester CW, Durairaj L, Evans AT, et al.(2002) Antibiotic resistance: a survey of physician perceptions. Archives of Internal Medicine 162(19):2210-16	No relevant outcomes
Weston A, Epstein L, Davidson LE, et al. (2013) The impact of a Massachusetts state-sponsored educational program on antimicrobial stewardship in acute care hospitals. Infection Control and Hospital Epidemiology 34(4):437-39	Not relevant
Wiffen PJ, White RTM. (2001) Encouraging good antimicrobial prescribing practice: a review of antibiotic prescribing policies used in the South East Region of England. BMC Public Health 1:4	Not relevant
Wood F, Phillips C, Brookes-Howell L, et al. (2013) Primary care clinicians' perceptions of antibiotic resistance: a multi-country qualitative interview study. The Journal of Antimicrobial	Not relevant

Author	Reason for exclusion
Chemotherapy 68(1):237-43	
Woodford EM, Wilson KA, Marriott JF. (2004) Antibiotic prescribing control by pharmacists within UK NHS hospitals. International Journal of Pharmacy Practice 12(2):101-06	No relevant outcomes
Woodford EM, Wilson KA, Marriott JF. (2004) Documentation of antibiotic prescribing controls in UK NHS hospitals. The Journal of Antimicrobial Chemotherapy 53(4):650-2	Not relevant
Wright SK, Neill KM. (2001) Factors influencing the antibiotic-prescribing decisions of nurse practitioners. Clinical Excellence for Nurse Practitioners 5(3):159-67	Not relevant
Yardley L, Douglas E, Anthierens S, et al. (2013) Evaluation of a web-based intervention to reduce antibiotic prescribing for LRTI in six European countries: quantitative process analysis of the GRACE/INTRO randomised controlled trial. Implementation Science	No relevant outcomes
Zaidi ST, Marriott JL, Nation RL. (2008) The role of perceptions of clinicians in their adoption of a web-based antibiotic approval system: do perceptions translate into actions? International Journal of Medical Informatics 77(1):33-40	Not relevant
Zaidi STR and Thursky KA. (2013) Using formative evaluation to improve uptake of a web-based tool to support antimicrobial stewardship. Journal of Clinical Pharmacy and Therapeutics 38(6):490-97	No relevant outcomes

C.5.4 Timely adoption and diffusion of a new antimicrobial

No Studies were excluded

C.6 Economic excluded studies

C.6.1 Reducing antimicrobial resistance

No studies were excluded

C.6.2 Decision making

Author	Reason for exclusion
Bailey TC, Ritchie DJ, McMullin ST, et al. (1997) A randomized, prospective evaluation of an interventional program to discontinue intravenous antibiotics at two tertiary care teaching institutions. Pharmacotherapy 17(2):277-81	Not relevant
Chen H, Suda KJ, Turpin RS, et al. (2007) High- versus low-dose fluconazole therapy for empiric treatment of suspected invasive candidiasis among high-risk patients in the intensive care unit: a cost-effectiveness analysis (Structured abstract). Current Medical Research and Opinion 23(5):1057-65	Not relevant
Cranny G, Elliott R, Weatherly H, et al. (2008) A systematic review and economic model of switching from non-glycopeptide to glycopeptide antibiotic prophylaxis for surgery. Health Technology Assessment 12(1):iii-147	Not relevant
Cummins JS. (2009) Cost-effectiveness of antibiotic-impregnated bone cement used in primary total hip arthroplasty. The Journal of Bone and Joint Surgery 91:634-41	Not relevant

Author	Reason for exclusion
Ref Type: Abstract	
Elliott RA. (2010) An economic model for the prevention of MRSA infections after surgery: non-glycopeptide or glycopeptide antibiotic prophylaxis? European Journal of Health Economics 11(1):57-66. Ref Type: Abstract	No relevant outcomes
George JM, Towne TG, Rodvold KA.(2012) Prolonged infusions of beta-lactam antibiotics: implication for antimicrobial stewardship. Pharmacotherapy 32(8):707-21	Not relevant
Hagert BL, Williams C, Wiesner CM, et al. (2012) Implementation and outcome assessment of an inpatient antimicrobial stewardship program. Hospital Pharmacy 47(12):939-45	Not relevant
Heyland DK, Johnson AP, Reynolds SC, et al. (2011) Procalcitonin for reduced antibiotic exposure in the critical care setting: a systematic review and an economic evaluation. Critical Care Medicine 39(7):1792-99	Not relevant
Hubner C, Hubner NO, Kramer A, et al. (2012) Cost-analysis of PCR-guided pre-emptive antibiotic treatment of Staphylococcus aureus infections: an analytic decision model. Eur Journal of Clinical Microbiology Infectious Diseases 31(11):3065-72	Not relevant
Laham J, Breheny P, Gardner B. (2012) Procalcitonin predicts bacterial co-infection and reduces antibiotic costs. Pediatric Critical Care Medicine 13(6):711. Ref Type: Journal (Full)	Conference abstract only
Michaelidis CI, Kern MS, Smith KJ.(2014) Cost-effectiveness of decision support strategies for safely reducing antibiotic use in acute bronchitis. Journal of General Internal Medicine 29: S59 Ref Type: Abstract	Conference abstract only
Michaelidis CI, Zimmerman RK, Nowalk MP, et al.(2014) Cost-effectiveness of procalcitonin-guided antibiotic therapy for outpatient management of acute respiratory tract infections in adults. Journal General Internal Medicine 29(4):579-86	Not relevant
Perez KK, Olsen RJ, Musick WL, et al. (2013) Integrating rapid pathogen identification and antimicrobial stewardship significantly decreases hospital costs. Archives of Pathology and Laboratory Medicine 137(9):1247-54	Not relevant
Slobogean GP. (2010) Single-dose versus multiple-dose antibiotic prophylaxis for the surgical treatment of closed fractures: A cost-effectiveness analysis. Acta Orthopaedica 81(2):258 Ref Type: Abstract	Not relevant
Smith KJ, Zimmerman RK, Wateska A, et al. Cost-effectiveness of procalcitonin-guided antibiotic use in community acquired pneumonia. Journal of General Internal Medicine 27: S150. Ref Type: Journal (Full)	Conference abstract only
Smith KJ, Wateska A, Nowalk MP, et al. (2013) Cost-effectiveness of procalcitonin-guided antibiotic use in community acquired pneumonia. Journal of General Internal Medicine 28(9):1157-64	Not relevant

C.6.3 Barriers to decision making

No studies were excluded

C.6.4 Timely adoption and diffusion of a new antimicrobial

No studies were excluded

Appendix D: Clinical evidence tables and GRADE profiles

D.1 Evidence tables

D.1.1 Reducing antimicrobial resistance.

Evidence table 1: Bouadma, L; Luyt, CE et al, 2010

Bibliographic reference	Bouadma, L; Luyt, CE; Tubach, F, et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. *Lancet* 375(9713) pp463-474
Study type	Multicentre, prospective, parallel–group, open–label trial.
Study quality	Moderate
Number of patients	n=630, with nine patients (four in the procalcitonin (PCT) group and five in the control group) subsequently excluded from the analysis.
Patient characteristics	Adults with suspected bacterial infection admitted to, or who developed sepsis while in intensive care.
Intervention	Two interventions were used (1) procalcitonin concentration to decide whether antibiotics should be commenced. (2) Serial serum procalcitonin to help decide when to stop antibiotic therapy.
Comparison	A single pre–study commencement reminder including recommendations for the duration of antimicrobial treatment for most common infections derived from international and local guidelines.
Length of follow up	At days 28 and 60 for primary outcome measure (death from any cause, and days without antibiotics after inclusion)
Location	Seven (five medical and two surgical) intensive care units in six hospitals comprising 140 beds in France between June 2007 and May 2008.
Outcomes measures and effect size	

Clinical outcomes	**PCT n (%)**	**Control n (%)**	**Absolute difference**	***P***
28 day mortality*	65 (21.2)	64 (20.4)	0.8% (-4.6 to 6.2)	NA
60 day mortality*	92 (30.0)	82 (26.1)	3.8% (-2.1 to 9.7)	NA
Days without Antibiotics†	14.3 (9.1)	11.6 (8.2)	2.7 (1.4 to 4.1)	<0.0001
Relapse	20 (6.5)	16 (5.1)	1.4% (-2.3 to 5.1)	0.45
Superinfection	106(34.5)	97 (30.9)	3.6% (-3.8 to 11.0)	0.29
Days without mechanical ventilation†	16.2 (11.1)	16.9 (10.9)	-0.7 (-2.4 to 1.1)	0.47
LoS (ICU) days †	15.9 (16.1)	14.4 (14.1)	1.5 (-0.9 to 3.9)	0.23
LoS (hospital) days †	26.1 (19.3)	26.4 (18.3)	-0.3 (-3.2 to 2.7)	0.87

Also there were no statistically significant differences in SOFA score at 1, 7, 14, 21 and 28 days. There were statistically significant differences for the duration of first antibiotic therapy (days) for the overall population, community–acquired pneumonia and ventilator–associated pneumonia.

Emergence of resistance	**PCT**	**Control**	**Absolute difference**	***P***
Multidrug–resistant bacteria	55 (17.9%)	52 (16.6%)	1.3% (-4.6 to 7.2)	0.67

	*Data are number (%), difference (95% confidence interval or *90% confidence interval) or †mean (standard deviation). SOFA is sequential organ–failure assessment score. ICU is intensive care unit. AB is antibiotic. LoS is length of stay.*
Source of funding	Study supported by a research grant from the Département à la Recherche Clinique et au Développement, Assistance Publique–Hôpitaux de Paris, which also sponsored the study (PHRC AOR06019). Brahms, manufacturer of the procalcitonin assay, provided all assay-related materials free of charge and kits and maintenance required for study-related measurements; Brahms did not provide any further funding for the study.
Comments	

Evidence table 2: Brust, JCM; Litwin, AH; Berg, KM et al, 2011

Bibliographic reference	Brust, JCM; Litwin, AH; Berg, KM. et al. Directly observed antiretroviral therapy in substance abusers receiving methadone maintenance therapy does not cause increased drug resistance. *AIDS Research and Human Retroviruses* 27(5), pp535-541
Study type	Randomised controlled trial
Study quality	Low
Number of patients	n=77, 39 participants randomised to Directly Observed Therapy (DOT) and 38 to Treatment as Usual (TAU).
Patient characteristics	Adult methadone maintained patients who were HIV positive, in receipt of HIV medical care at the methadone clinic and attended methadone clinic 5 or 6 days per week to receive methadone, on antiretroviral therapy (ART), on a stable dose of methadone for 2 weeks before the baseline study visit and genotypically sensitive to their prescribed ART regimen.
Intervention	Patients were randomly assigned to DOT or TAU.
Comparison	Treatment as usual control (not described).
Length of follow up	Follow-up was conducted at 8 and 24 weeks.
Location	The trial was conducted at a network of methadone clinics at the Albert Einstein College of Medicine and Montefiore Medical Centre in the Bronx, New York.
Outcomes measures and effect size	21 subjects had detectable viral load at baseline and follow-up (either weeks 8 or 24). The authors do not report how many individuals remained in each arm after withdrawals and exclusions. After 24 weeks 9 of the 21 subjects had new drug mutations, six in the TAU group and 3 in the DOT group (P=0.27). Two of these did not confer drug resistance to drugs in their current regimen. The median pill count adherence rate for the seven subjects who developed new mutations was 0.76 (IQR 0.72 – 0.92), in comparison to 0.74 (IQR 0.63 – 0.79) for the 14 subjects who did not develop new mutations (P=0.51). Overall of the 21 subjects 5 in the TAU developed major mutations correlating with their current ART regimen, while no subjects in the DOT arm developed such mutations.
Source of funding	Study funded by National Institutes of Health Grants (R01 DA015302, R52 DA14551, K23 DA021087) and a Center for AIDS Research Grant (P30 AI051519).
Comments	Retention rate for the study was 85% (n=65) at 24 weeks. As all viral analysis was done at the end of the study 30 subjects were excluded at baseline as they had no detectable viral load, with a further 14 excluded

	at 24 weeks as they had no detectable viral load at follow-up.

Evidence table 3: Capellier, G; Mockly, H; Charpentier, C et al, 2012

Bibliographic reference	Capellier, G; Mockly, H; Charpentier, C. et al. Early-onset ventilator-associated pneumonia in adults randomized clinical trial: comparison of 8 versus 15 days of antibiotic treatment *PloS one*. 7(8) pp e41290
Study type	Randomised, prospective, open, multicentre trial.
Study quality	Low
Number of patients	n=225, 109 randomised to the 15 day treatment cohort and 116 to the 8 day treatment cohort.
Patient characteristics	Adults (aged 18+ years), who had developed early–onset ventilator associated pneumonia (EOVAP, ventilated for more than 24 hours and less than eight days). Pneumonia diagnosis criteria (2 or 3 of the following); temperature >38.3°C, leucocyte count >10000/mm^3, excessive purulent or mucopurulent bronchial secretion and radiology findings as scored using Weinberg. Pneumonia confirmed by bronchial alveolar lavage (BAL) culture of ≥10^4 colony-forming units/ml.
Intervention	All patients received immediate treatment according to severity and any direct bacteriological results from BAL if available. All patients were treated with beta–lactams for 8 or 15 days combined with an aminoglycoside for the first 5 days.
Comparison	15 days of treatment.
Length of follow up	Follow–up was at 21 days and at 90 days for mortality.
Location	Unclear as to exact location but the study describes a French study in intensive care setting from 13 different centres over 4 years (1998 to 2002).
Outcomes measures and effect size	See tables below.

Clinical Outcome	Overall	8 days	15 days	*P*
Cure at 21 days	191 (84.9%)	99 (85.3%)	92 (84.4%)	*N/A*
Difference 0.9% (95% CI -8.4% to 10.3%), odds ratio [OR] 0.929 (95% CI 0.448 to 1.928)				
Mortality at 21 days	19	10 (8.6%)	9 (8.3%)	0.92
Mortality at 90 days	Not stated	17.2%	17.4%	0.99
Adverse events	9	4	5	-
Septic shock	19	9	10	-
Relapse	8	6	2	NS
Secondary Infection	-	35.3%	19.3%	<0.01
Cure at 21 days including secondary Infection as failure	-	49.1%	64.2%	-
Difference 15.1% (95% CI 2.3 to 27.9%)				

No statistically significant differences were found between 8 and 15 day therapy for discharge from ICU at 21 days, ICU length of stay, ICU length of stay after treatment initiation, ICU length of stay intubated or the numbers of patients intubated at day 21.

Emergence of resistance	8 days	15 days	*P*
Number of patients with secondary infection, n (%)	41 (35.3)	21 (19.3)	<0.01*
Number of secondary infections, n (%)	46 (39.7)	22 (20.2)	<0.01*
Sensitivity of secondary infections to first line treatment			
Sensitive, n (%)	28 (60.8)	12 (54.5)	0.76*
Resistant, n (%)	18 (39.2)	10 (45.5)	-

Source of funding	French Ministry of Health, Societe de Reanimation de Langue Francaise, Glaxo and Beecham Laboratory.
Comments	*Fischer exact test

Evidence table 4: Chardin, H; Yasukawa, K; Nouacer, N et al, 2009

Bibliographic reference	Chardin, H; Yasukawa, K; Nouacer, N.et al. Reduced susceptibility to amoxicillin of oral streptococci following amoxicillin exposure. *Journal of medical microbiology* 2009 58 (Pt 8) pp1092-1097
Study type	Intention to treat [a] randomised controlled trial
Study quality	Low
Number of patients	n=81, 42 randomised to intervention and 39 to control
Patient characteristics	Adults (19 to 45 years) undergoing tooth extraction eligible for antibiotic prophylaxis according to Agence Francaise de Securite Sanitaire des Produits de Sante (AFSSAPS) 2002 good practice rules on antibiotic therapy in odontology and stomatology.
Intervention	Three days of amoxicillin (1g twice daily by mouth) and placebo for four days.
Comparison	Seven days of amoxicillin (dose not described).
Length of follow up	Follow–up was at day 9 and day 30 post treatment.
Location	Emergency dental consultations at three French university hospitals.
Outcomes measures and effect size	**Clinical outcomes (non-inferiority[b])** / **Intervention** / **Control** / **95% CI** Intensity of pain: 3.5 (3, 6) / 4 (2, 6) / 0 (-1, 2) Total paracetamol taken [mg] (range): 5000 (1600, 9000) / 4000 (1000, 6000) / 1 (-2, 3) Wound healing score: 1 (1, 2) / 1 (1, 2) / 0 (0, 1) *All outcomes were not significantly different between the groups.* **Emergence of resistance** **Streptococci resistant to amoxicillin at day** / **Intervention (95% CI)** / **Control (95% CI)** 0: 1.3% (0.5 to 2.8) / 1.7% (1.0 to 3.8) 9: 23% (14.6 to 39.8) / 24.7% (8.3 to 70.6) 30: 7.7% (3.4 to 15.3) / 7% (1.1 to 8.3)
Source of funding	This study was supported by grant PHRC P040408, from Assistance Publique – Hopitaux de Paris.
Comments	[b] An assessment of the people taking part in a clinical trial, based on the group they were initially (and randomly) allocated to. The experimental treatment was considered non inferior if the upper confidence level fell below a predetermined level.

Evidence table 5: Chastre, J; Wolff, M; Fagon, JY et al, 2003

Bibliographic reference	Chastre, J; Wolff, M; Fagon, JY. et al. Comparison of 8 vs 15 Days of Antibiotic Therapy for Ventilator-Associated Pneumonia in Adults: A Randomized Trial. *Journal of the American Medical Association* 290 (19) pp2588-2598
Study type	Prospective, randomised, double blind (until day 15) clinical trial.
Study quality	Moderate

<table>
<tr><td>Number of studies</td><td>n=401 (197 randomised to receive 8 days therapy and 204 to receive 15 days therapy)</td></tr>
<tr><td>Participant characteristics</td><td>Adults, aged 18 years or older, admitted to intensive care unit and mechanically ventilated for at least 48 hours with suspected ventilator associated pneumonia (VAP) meeting the studies diagnostic criteria and commenced on appropriate empirical antibiotics.</td></tr>
<tr><td>Intervention</td><td>Treatment for 8 days with an aminoglycoside or a fluoroquinolone and a broad spectrum beta-lactam unless the organism was not thought to be sensitive or there was a contraindication to their use.</td></tr>
<tr><td>Comparison</td><td>Treatment for 14 days using the same protocol as per intervention.</td></tr>
<tr><td>Length of follow up</td><td>Follow-up was assessed at 28 days.</td></tr>
<tr><td>Location</td><td>51 intensive care units in France</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><th>Primary clinical outcomes [a]</th><th>8 days n(%) n=197</th><th>15 days n(%) n=204</th><th>Between group RD [b]</th></tr>
<tr><td>All-cause mortality</td><td>37 (18.8)</td><td>35 (17.2)</td><td>1.6 (-3.7 to 6.9)</td></tr>
<tr><td>Pulmonary infection recurrence [c]</td><td>57 (28.9)</td><td>53 (26.0)</td><td>2.9 (-3.2 to 9.1)</td></tr>
<tr><td>Antibiotic free days (mean (SD))</td><td>13.1 (7.4)</td><td>8.7 (5.2)</td><td>4.4 (3.1 to 5.6 [d])</td></tr>
</table>
The interaction between the duration of antibiotic administration and stratification for the responsible microorganism at baseline was not significant with respect to the risk of death (P=0.41), pulmonary infection recurrence (P=0.16), or the number of antibiotic free days (P=0.25)
<table>
<tr><th>Secondary outcomes</th><th>8 days</th><th>15 days</th><th>Mean between group RD (90% CI)</th></tr>
<tr><td>Mechanical ventilation-free days [Mean(SD)]</td><td>8.7 (9.1)</td><td>9.1 (9.4)</td><td>-0.4 (-1.9 to 1.1)</td></tr>
<tr><td>Organ-failure free days (days 1 to 28)</td><td>7.5 (8.7)</td><td>8.0 (8.9)</td><td>-0.5 (-1.9 to 1.0)</td></tr>
<tr><td>Length of stay (ICU)</td><td>30.0 (20.0)</td><td>27.5 (17.5)</td><td>2.5 (-0.7 to 5.2)</td></tr>
<tr><th>All patients (No. (%))</th><th>8 days</th><th>15 days</th><th>Risk Difference (90% CI)</th></tr>
<tr><td>Unfavourable outcome [e]</td><td>91 (46.2)</td><td>89 (43.6)</td><td>2.6 (-5.6 to 10.7)</td></tr>
<tr><td>Death, (day 60)</td><td>50 (25.4)</td><td>57 (27.9)</td><td>-2.6 (-9.8 to 4.7)</td></tr>
<tr><td>In-hospital mortality</td><td>63 (32)</td><td>61 (29.9)</td><td>-1.2 (-5.5 to 9.7)</td></tr>
</table>
</td></tr>
<tr><td>Source of funding</td><td>This study was supported by grant PHRC AOM 97147 from Assistance Publique-Hopitaux de Paris</td></tr>
<tr><td>Comments</td><td>All patients (study has breakdowns for non-fermenting gram negative bacilli, MRSA and other bacteria)
b RD = risk difference (90% CI),%
c Amongst those developing recurrent pulmonary infection, multi-resistant organisms occurred significantly less in the 8 days intervention group (42.1% vs. 62.3%; P=0.04)
d 95% Confidence Interval
e An unfavourable outcome was defined as death, pulmonary infection recurrence, or prescription of new antibiotic for any reason provided that this new treatment exceeded 48 hours before day 28</td></tr>
</table>

Evidence table 6: Copenhagen study group of urinary tract infections in children, 1991

Bibliographic reference	Copenhagen study group of urinary tract infections in children (1991) Short-term treatment of acute urinary tract infection in girls. *Scandinavian Journal of Infectious Disease* 23 pp213-220
Study type	Prospective, open, randomised, multi-centre study
Study quality	Low
Number of patients	n=359* (96 randomised to 3 days Sulfamethizole [Group I], 78

<table>
<tr><td></td><td>randomised to 10 days Sulfamethizole [Group II] and 90 randomised to 3 days Pivemecillinam) [Group III].</td></tr>
<tr><td>Patient characteristics</td><td>Girls aged 1 -15 years with clinical symptoms of acute urinary tract infection.</td></tr>
<tr><td>Intervention</td><td>3 days therapy with Sulfamethizole (40-80mg/kg/24hr in two doses) or 3 days Pivemecillinam (20-40mg/kg/24hr in two doses).</td></tr>
<tr><td>Comparison</td><td>10 days therapy with Sulfamethizole (40-80mg/kg/24hr in two doses).</td></tr>
<tr><td>Length of follow up</td><td>Follow-up was 1-10days and 1 month after treatment.</td></tr>
<tr><td>Location</td><td>Danish study (not further defined)</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><th>Clinical outcomes</th><th>Group I (n=96)</th><th>Group II (n=78)</th><th>Group III (n=90)</th></tr>
<tr><td>No growth at 1-10 days after treatment [a]</td><td>78 (81%)</td><td>60 (77%)</td><td>67 (74%)</td></tr>
<tr><td>Growth of original bacteria</td><td>14 (15%)</td><td>7 (9%)</td><td>11 (12%)</td></tr>
<tr><td>Growth of new bacteria</td><td>4 (4%) [b]</td><td>11 (14%)</td><td>12 (13%)</td></tr>
<tr><td colspan="4">New bacteria after treatment was S. Faecalis in ¼ in Group I and 2/11 in Group II versus 9/12 in Group III (Chi-square test = 8.22, P=0.016). The S. Faecalis strains were insensitive to both antibiotics used in the study.</td></tr>
<tr><td colspan="4">No growth after treatment was significantly associated with abnormality [c] 57/89 (64%) (Intravenous pyelography [IVP] and micturition cystourethrography [MCU] diagnosed) versus normal 86/105 (82%) [p=0.004], however there was no significant difference between treatment groups for abnormality/normality, except for Group I [P=0.015].</td></tr>
<tr><td>Side effects (n=359)</td><td>2 GI [d] (n=121)</td><td>0 (n=121)</td><td>6 [e] (n=117)</td></tr>
<tr><th>Emergence of resistance</th><th>Group I</th><th>Group II</th><th>Group III</th></tr>
<tr><td>Sensitivity at baseline (to treatment drug)</td><td>80/96 (83%)</td><td>58/78 (74%)</td><td>82/86 (95%)</td></tr>
<tr><td>Sensitivity after treatment (to treatment drug)</td><td>10/18 (56%) [f]</td><td>4/18 (22%) [g]</td><td>11/21 (52%) [h]</td></tr>
<tr><td>Sensitivity at recurrence (to treatment drug)</td><td>21/24 (88%)</td><td>11/15 (73%)</td><td>13/14 (93%)</td></tr>
</table>
There was a significant difference (P=0.04) after treatment between the 3 and 10 day Sulfamethizole groups (56% versus 22% respectively).
</td></tr>
<tr><td>Source of funding</td><td>Support for the study was provided by Leo Pharmaceuticals and grants from the Danish Medical Research Council.</td></tr>
<tr><td>Comments</td><td>*264 after exclusions
[a] differences between groups not significant
[b] Chi-square test =6.06, P=0.048 compared to the other two groups
[c] for example pyelonephritis, double kidney, diverticulum of the bladder etc.
[d] gastrointestinal effects (vomiting, diarrhoea and abdominal pain)
[e] two developed urticarial rash, three had gastrointestinal effects and one developed irritability and fatigue
[f] compared with Group I at baseline P=0.01
[g] compared with Group II at baseline P<0.001, also sensitivity noted for ampicillin (Group II) 82% at baseline compared to 56% after treatment (P=0.02)
[h] compared with Group III at baseline P<0.001, also sensitivity noted for Sulfamethizole (Group III) 80% at baseline compared to 52% after treatment (P=0.009)</td></tr>
</table>

Evidence table 7: Curran, E; Harper, P; Loveday, H et al, 2008

Bibliographic reference	Curran, E; Harper, P; Loveday, H. et al. Results of a multicentre randomised controlled trial of statistical process charts and structured diagnostic tools to reduce ward–acquired *Staphylococcus aureus*: the CHART Project. *Journal of Hospital Infection* 2008, 70(2) pp 127-135

Study type	Multicentre randomised controlled trial, partial assessor blinding.
Study quality	Low
Number of patients	Not stated, however there were 25 participating hospitals comprising 75 different inpatient wards.
Patient characteristics	Not stated, no detail of the type of patient or ward settings used in the study is reported by the authors.
Intervention	Study comprised two study intervention arms: • Wards receiving statistical process chart feedback (SPC arm) • Wards receiving statistical process chart feedback and structured diagnostic tools (SPC + Tools arm)
Comparison	• Wards receiving no new feedback of either type (Control arm)
Length of follow up	Pre-intervention data on ward–acquired MRSA[a] incidence for 25 months before intervention. Follow–up, post intervention, was for 24 months.
Location	25 participating hospitals from the UK.
Outcomes measures and effect size	**MRSA incidence outcome** The primary outcome of the study was a reduction in the incidence of ward–acquired MRSA (WA MRSA) cases pre to post intervention in each of the study arms. In the SPC arm the pre intervention average (mean) number (standard deviation[b]) of new MRSA cases was 1.93 (0.72), compared to 1.26 (0.59) in the post intervention period (mean reduction of 32.3% (31.5) 95% CI 19.3 to 45.3; P<0.001). In the SPC + Tools arm the pre intervention average (mean) number (standard deviation) of new MRSA cases was 1.99 (1.08), compared to 1.47 (0.78) in the post intervention period (mean reduction of 19.6% (37.6) 95% CI 4.1 to 35.1; P=0.015). In the Control arm the pre intervention average (mean) number (standard deviation) of new MRSA cases was 2.15 (1.35), compared to 1.46 (0.78) in the post intervention period (mean reduction of 23.1% (27.4) 95% CI 11.8 to 34.4; P<0.001). In order to examine whether any effect was stepwise or gradual (a learning effect as the new process took hold) the authors also compared the final 12 month pre–intervention and final 12 month post–intervention data for each arm. The results again indicated that all three arms had a statistically significant reduction in WA MRSA. Repeated measures analysis of variance (ANOVA) was performed and found no significant difference (P=0.23 for all data and P=0.46 for the final 12 month data) between the mean percentage reductions of each arm. An analysis of out–of–control episodes (mean number of months exhibiting unnatural variation above the upper control limit) was statistically lower for the intervention arms than controls using all (Friedman's test P=0.021) and final 12 month (Friedman's test P=0.032) data sets.
Source of funding	Department of Health (England)
Comments	[a] Methicillin resistant staphylococcus aureus [b] A measure of the spread, scatter or variability of a set of measurements. Usually used with the mean (average) to describe numerical data.

Evidence table 8: Davey, P; Brown, E; Charani, E et al, 2013

Bibliographic reference	Davey, P; Brown, E; Charani, E, et al, Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database of Systematic Reviews 2013, Issue 4. Art. No.: CD003543. DOI: 10.1002/14651858.CD003543.pub3.
Study type	Systematic review of interventions to improve antibiotic prescribing for hospital inpatients.
Study quality	High

Number of studies	This systematic review includes 89 studies (56 interrupted time series, 20 randomised controlled trials, 5 controlled before and after studies, 2 controlled clinical trials (non-randomised (CCT)), one cluster-controlled clinical trial and 5 cluster-randomised controlled trials).
Participant characteristics	Healthcare professionals who prescribe antibiotics to hospital in–patients receiving acute care (including elective inpatient surgery) but excluding interventions for long–term care facilities (such as nursing homes).
Intervention	The 89 included studies largely covered the choice of drug (timing of first dose or route of administration, 80 out of 95 interventions). The remaining interventions addressed the exposure of patients to antibiotics (decision to treat or duration of treatment).
Comparison	For the effect of interventions on microbial outcomes only 21 studies were relevant, there were 19 interrupted time series studies and 1 cluster-CCT and 1 CCT (de Man study reported separately in this evidence table).
Length of follow up	Up to 24 months
Location	N/A
Outcomes measures and effect size	This review included[1] mainly ITS studies for its antimicrobial resistance data (Clostridium difficile [5 of 5 studies are ITS]; Antibiotic-resistant gram negative bacteria [7 of 9 studies were ITS, the other two studies were not RCTs (CCCT and CCT)]; Antibiotic-resistant gram-positive bacteria [6 of 7 studies, the other was a CBA]) and identified no RCTs. The data from included studies demonstrates that interventions to change antibiotic prescribing were associated with decrease in Clostridium difficile, resistant gram-negative bacteria, MRSA and VRE. However, the authors found only six interventions (29%) provided reliable data[2] about change in antibiotic prescribing, which was reported as a major confounder in the evidence base because, the authors report, that there are not enough data to estimate the likely impact of change in prescribing on microbial outcomes.
Source of funding	Not reported
Comments	[1]There is no mention or published assessment of publication bias included within the review [2]Of the included total of 16 ITS studies; eight were classed by the authors as at moderate risk of bias, a further 7 were at high risk of bias and one was at low risk of bias overall but high risk of bias for its microbiological outcomes. The included CCCT and the CBA were both high risk of bias and the CCT was regarded by the Cochrane authors as 'fatally flawed' in terms of its microbiological outcomes.

Evidence table 9: Falagas, ME; Bliziotis, IA; Rafaildis, PI. 2007

Bibliographic reference	Falagas, ME; Bliziotis, IA; Rafaildis, PI (2007) Do high doses of quinolones decrease the emergence of antibacterial resistance? A systematic review of data from comparative clinical trials. *Journal of Infection* 55 (2) pp97-105.
Study type	Systematic review [no meta-analyses]
Study quality	Low
Number of studies	This systematic review includes 12 studies (8 randomised controlled trials and 4 non-randomised comparative trials).
Participant characteristics	The 12 included studies comprised 2979 patients (range of included patients (n) 10 to 865). Type of infections were uncomplicated UTI in women, soft tissue infections/osteomyelitis, adults with cystic fibrosis and broncho-pulmonary infection, severe HAI [a] , lower extremity infection (TIIDM/PVD or both [b]), Typhoid fever, Gonococcal urethritis in males, respiratory infection (panbronchiolitis or bronchiectasis), community acquired pneumonia, acute bacterial sinusitis, and complicated UTI.
Intervention	Studies were included* if they treated documented infections with at least two treatment groups (one receiving a higher dose of quinolones than the other) and for at least one patient the causative organism persisted during or after treatment.
Comparison	Lower dose of quinolones for the same documented infection.
Length of follow up	Not reported.
Location	Not reported.
Outcomes measures and effect size	See nested table below.

Clinical outcomes					**Emergence of resistance**
1st Author / year / n included (ITT [c])	**Bacterial eradication (low dose vs. high dose)**	**Clinical failure**	**Bacteriologic failure**	**Adverse events**	**Proportion of patients with emergence of resistance in low dose vs. high dose groups**
		n_1/N_1 of patients in low dose group versus n_2/N_2 of patients in high dose group			
Garlando (1987) n=40	16/19 (84%) versus 17/19 (89%)	3/19 vs. 2/19[d]	-	NR	0/19 vs. 0/19
Nix (1987) n=48	36/48[e]	NR	NR	Not reported separately for each group.	NR[f]
Shalit (1987) n=29	NR	Failure was independent of daily dose	NR	Not reported separately for each group.	NR
Kljucar (1989) n=54	In 45 out 88 organisms	1/27 vs. 1/17	NR	Not reported separately for each group.	0/1 versus 0/1[g]
Peterson (1989)	NR	11/23 vs. 7/22	NR	NR	During therapy: 2/23 vs. 0/22

	n=48					During follow-up: 1/23 vs. 3/22[g]
	Uwaydah (1992) n=62	34/34 (100%) vs. 27/28 (96%)	0/34 vs. 0/28	NR	NR	0/34 vs. 0/28
	Moodley (2002) n=865	177/177 (100%) vs. 262/266 (98%)	0/177 vs. 0/266	0/177 vs. 4/266	NR	0/177 vs. 0/266
	Shishido (1995) n=10	1/5 (20%) vs. 3/5 (60%)	3/5 vs. 1/5[d]	-	0/5 vs. 0/5	0/5 vs. 0/5
	Dunbar (2003) n=528	85/92 (92%) vs. 96/103 (93%)	17/192 vs. 15/198	6/99 vs. 7/123	158/265 vs. 148/256	0/20 vs. 0/22[h]
	Poole (2006) n=780	132/149 (89%) vs. 139/152 (91%)	17/149 vs. 13/152[d]	-	135/391 vs. 155/389	0/17 vs. 0/13[g]
	Hoeffken [j] (2001) n=453	29/40 (73%) vs. 37/47 (79%) [i]	11/180 vs. 10/177	11/40 vs. 10/47	113/229 vs. 114/224	0/40 vs. 0/47
	Wolfhagen [k](1990) n=62	9/14 (64%) 10/17 (59%) 5/14 (36%)	2/14 (NS) 4/17 (NS) 4/14 (NS)	5/14 7/17 9/14	7/19 10/21 9/20	0/14 1/17 1/14
	Bacterial eradication was accomplished in similar proportions in both treatment arms. 5/12 studies observed development of resistance but only 3 studies had comparative data between groups but differences were not significant (NS).					
Source of funding	None					
Comments	*Studies were excluded if they did not report data regarding the emergence of resistance or the study included dose adjustment, reported mycobacteria, or brucella, or used antibiotics withdrawn from the market. [b] HAI = hospital acquired infection [c] TIIDM = type two diabetes mellitus/peripheral vascular disease [d] ITT = Intention to treat analysis, an assessment of the people taking part in a clinical trial, based on the group they were initially (and randomly) allocated to. [e] Refers to combined clinical and microbiological failure [f] Treatment groups not reported separately [g] NR = Not reported or not adequately reported [h] Refers to clinical failure [i] Patients with good clinical response who were discharged from hospital were not re-evaluated for microbiological response unless their condition deteriorated or were readmitted [j] Refers to *S. pneumonia* isolates [k] Study of Community Acquired Pneumonia using moxifloxacin Study used 3 doses of fleroxacin (200mg, 400mg and 600mg)					

Evidence table 10: Goldman, M; Cloud, GA; Wade, KD et al, 2005

Bibliographic reference	Goldman, M; Cloud, GA; Wade, KD. et al. (2005) A Randomized Study of the Use of Fluconazole in Continuous versus Episodic Therapy in Patients with Advanced HIV Infection and a History of Oropharyngeal Candidiasis: AIDS Clinical Trials Group Study 323/Mycoses Study Group Study 40. *Clinical Infectious Diseases.* 41, pp1473-1480
Study type	Prospective, randomised, multi-centre open label trial
Study quality	Low
Number of patients	n=829* (413 randomised to receive continuous fluconazole and 416 randomised to receive fluconazole for episodes of oropharyngeal candidiasis [OPC] or oesophageal candidiasis [EC]).
Patient characteristics	Adults aged 19 – 71 years with HIV infection and $CD4^+$ T cell counts of ≤150 cells/mm^3 and a history of OPC.
Intervention	200mg of fluconazole orally 3 times weekly on a continuous basis
Comparison	Fluconazole administered only for OPC or EC episodes
Length of follow up	Median duration of follow-up was 24 months (range, <1 to 44 months)
Location	Multiple US participating centres listed in the study
Outcomes measures and effect size	See nested table below
Source of funding	Study was supported by the National Institute of Allergy and Infectious Diseases, National Institutes of Health and Pfizer. COI were declared.
Comments	*Only 440 (53%) of the study population completed the treatment strategy. [a] Including EC [b] Chi-square (X^2) test [c] Excluding EC [d] $CD4^+$ T cell count was similar in both arms at baseline and counts increased in both arms during the study [e] Kruskal-Wallis test [f] Overall the authors noted no significant difference between the groups with the exception of platelet count [g] Regardless of whether infection was present

Clinical outcomes	**Continuous fluconazole**	**Episodic fluconazole**	***P* Value**
Invasive fungal infections [a] (n)	15	28	0.04[b]
Invasive fungal infections [c] (n)	4	12	0.05[b]
Deaths related to fungal infection (n)	3	1	NS
No significant difference was noted for non-fungal opportunistic complications of AIDS between the two arms (P=0.33[Z]). No significant difference was noted for survival between the two arms (7% in the continuous treatment group and 10% in the episodic treatment arm, P=0.28, by the log rank test) including when treatment group drop outs who were still observed for survival (12% in each group).			
$CD4^+$ T cell counts [d] at last study measurement (Median cells/mm^3)	108 (n=329)	151 (n=333)	0.02[e]
Laboratory anomalies [f] (Platelet count <50,000 platelets/mm^3) n (%)	8 (2.4) (n=327)	1 (0.3) (n=334)	0.02[b]
Emergence of resistance	**Continuous fluconazole**	**Episodic fluconazole**	***P* Value**
Median MIC of fluconazole for final isolate obtained [g]	32µg/mL	16µg/mL	0.0885[e]
Proportion of patients in whom the final isolate was resistant to fluconazole	50 (45%) (n=110)	79 (36%) (n=218)	0.11[e]

Evidence table 11: Hasselgren, P-O; Ivarsson, L; Risberg, B et al, 1984

Bibliographic reference	Hasselgren, PO; Ivarsson, L; Risberg, B. et al. (1984) Effects of prophylactic antibiotics in vascular surgery. *Annals of Surgery* Vol. 200(1) pp86-92
Study type	Prospective, randomised, double-blind study.
Study quality	Low
Number of patients	n=211 (77 randomised to placebo [group 1], 59 randomised to 1 day therapy [group 2] and 75 randomised to 3 days therapy [group3]). 24 patients were subsequently excluded from the analyses (11 from the placebo group, 7 from the 1 day therapy group and 6 from the 3 day therapy group in line with study protocol).
Patient characteristics	Adults (aged 30 to 89 years, mean age 67.2years) scheduled to undergo vascular reconstructive surgery of the lower limbs or undergoing acute femoral embolectomy or thrombectomy.
Intervention	Patients were randomly assigned to receive either 1 day therapy with cefuroxime or 3 days therapy with cefuroxime.
Comparison	Placebo group.
Length of follow up	Not reported
Location	Not reported
Outcomes measures and effect size	See tables below

Clinical outcomes	Group 1	Group 2	Group 3
Wound infections / patients	11/66	2/52	3/69
Patients infected (%)	16.7	3.8*	4.3*
Additional antibiotics	10/11	2/2	3/3
Debridement	7/11	2/2	2/3
Dehiscence	1/11	0/2	0/3
Graft infection, excision or revision	1/11	0/2	0/3
**P<0.05 vs. placebo (Fishers exact test - two tailed)*			

Emergence of resistance	Group 1	Group 2	Group 3
Cefuroxime resistant enterobacteria	1/66	0/52	0/69

Source of funding	Not reported
Comments	Changes made to randomisation on ethical grounds part-way through the study which resulted in no further patients being allocated to group 2 (1 day of prophylaxis with cefuroxime).

Evidence table 12: Hemsell, DJ; Hemsell, PG; Heard, ML et al, 1985

Bibliographic reference	Hemsell, DJ; Hemsell, PG; Heard, ML, et al. (1985) Preoperative cefoxitin prophylaxis for elective abdominal hysterectomy. *American Journal of Obstetrics and Gynecology.* 153 (2) pp225-226
Study type	Placebo controlled, blinded randomised controlled trial
Study quality	Low
Number of patients	n=150 (50 patients randomised to each arm)
Patient characteristics	Women undergoing elective abdominal hysterectomy
Intervention	Three treatment arms comprising of one, two or three 2 gram doses of cefoxitin, with placebo blinding.
Comparison	Was between treatment arms
Length of follow up	Not reported
Location	Not reported

Outcomes measures and effect size	<table><tr><th>Clinical outcomes</th><th>1 Dose</th><th>2 Dose</th><th>3 Dose</th></tr><tr><td>Febrile Morbidity Incidence (%) Hospital Stay (days)*</td><td>20 5.8 ± 1.7</td><td>12 7.1 ± 4.2</td><td>12 5.3 ± 0.8</td></tr><tr><td>Major Infection Incidence (%) Hospital stay (days)</td><td>4 8.0 ± 1.4</td><td>12 11.7 ± 4.4</td><td>4 8.5 ± 3.5</td></tr></table> **Emergence of resistance** Cultures were taken preoperatively, at discharge and if major infection occurred. Evidence of resistance development was sought by comparing the minimal inhibitory concentration (MIC) to cefoxitin when the same species were present in culture sets to account for differing organisms. Four such pairs (of 109) were observed in the one-dose group, significantly fewer than 15 of 90 pairs in the two-dose group (P=0.004) and 9 of 75 pairs in the three dose group (P=0.03). Differences between the two and three dose groups were not significant.
Source of funding	Cefoxitin supplied by Merck, Sharp & Dohme.
Comments	* Hospital stay (days) for all women was 5.1 ± 1.7 (1 dose group), 5.3 ± 1.3 (2 dose group) and 5.1 ± 1.1 (3 dose group)

Evidence table 13: Hemsell, DL; Heard, ML; Nobles, BJ et al, 1984

Bibliographic reference	Hemsell, DL; Heard, ML; Nobles, BJ. et al. (1984) Single-dose prophylaxis for premenopausal women undergoing vaginal hysterectomy. *Obstetrics and Gynecology.* 63 (3) pp285-290
Study type	Prospective blinded randomised trial
Study quality	Low
Number of patients	n=116 (4 later excluded from the analysis, 58 randomised to receive one dose of cefoxitin; 54 were randomised to receive three doses of cefoxitin)
Patient characteristics	Premenopausal women scheduled for abdominal hysterectomy.
Intervention	One 2 gram dose of cefoxitin and two placebo doses
Comparison	Three 2 gram doses of cefoxitin (both arms given in the same way to the same schedule).
Length of follow up	Follow-up was at discharge and at three to six weeks post discharge.
Location	Parkland Memorial Hospital, Dallas, Texas.
Outcomes measures and effect size	<table><tr><th>Clinical outcomes</th><th>1 Dose</th><th>3 Dose</th></tr><tr><td>Febrile Morbidity Incidence (%)</td><td>10/58 (17%)</td><td>11/54 (20%)</td></tr><tr><td>Mean Hospital Stay (days)[a]</td><td>4.6</td><td>4.9</td></tr><tr><td>Pelvic cellulitis</td><td>1 (1.7%)</td><td>2 (NR)</td></tr><tr><td>Adverse drug reaction</td><td>0</td><td>1[b]</td></tr></table> **Emergence of resistance** The authors compared the entry and exit culture minimal inhibitory concentrations for the same bacterial species (when present in both cultures). There were 93 such pairs. In 11 was the exit isolate resistant in vitro when it the same species when sensitive at entry culture. There were no inter-group differences.
Source of funding	Not reported
Comments	[a] Mean hospital stay for all women was 4.4 ± 1.1 days (one dose) and 4.7 ± 1.2days (three doses) [b] Patient denied previously allergy, developed rash after third dose of antibiotic but was being concomitantly treated with parenteral analgesia and medicines for nausea.

Evidence table 14: Heyland, DK; Dodek, P; Muscedere, J et al, 2008

<table>
<tr><td>Bibliographic reference</td><td>Heyland, DK; Dodek, P; Muscedere, J. et al. (2008) Randomized trial of combination versus monotherapy for the empiric treatment of ventilator-associated pneumonia. Critical Care Medicine. Vol. 36 (2) pp737-744</td></tr>
<tr><td>Study type</td><td>Multi-centre randomized trial</td></tr>
<tr><td>Study quality</td><td>Low</td></tr>
<tr><td>Number of patients</td><td>n=740 (1 withdrawal of consent subsequently excluded from analysis; 369 randomised to combination therapy and 370 to monotherapy)</td></tr>
<tr><td>Patient characteristics</td><td>740 critically ill adult patients mechanically ventilated (MV) in a participating intensive care unit (ICU) for ≥ 96 hours who developed suspected pneumonia whilst intubated and ventilated.</td></tr>
<tr><td>Intervention</td><td>Initial un-blinded therapy with meropenem (1 gram every 8 hours) and ciprofloxacin (400mg every 12 hours).</td></tr>
<tr><td>Comparison</td><td>Meropenem (1 gram every 8 hours) alone.</td></tr>
<tr><td>Length of follow up</td><td>At 28 days for the primary outcome of the study (28 all-cause mortality)</td></tr>
<tr><td>Location</td><td>28 intensive care units from Canada and the United States</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><th>Clinical outcomes</th><th>Monotherapy</th><th>Combination therapy</th><th>P</th></tr>
<tr><td>Initial use, median days (Inter-Quartile Range)</td><td>3 (2 - 5)</td><td>3 (2 – 5)</td><td>-</td></tr>
<tr><td>Time from randomisation to end of MV alive, median days (IQR)</td><td>8.7 (3.8 to 24.8)</td><td>9.3 (3.8 to 21.6)</td><td>0.79</td></tr>
<tr><td>Discharge from the ICU alive, median days (IQR)</td><td>12.1 (6.4 to 35.2)</td><td>12.8 (6.1 to 27.0)</td><td>0.84</td></tr>
<tr><td>Discharge from hospital alive, median days (IQR)</td><td>45.8 (24.0 to 316.8)</td><td>39.1 (19.7 to undefined)</td><td>0.49</td></tr>
<tr><td>Adequate initial therapy</td><td>85.1%</td><td>93.1%</td><td>0.01</td></tr>
<tr><td colspan="4">No significant difference was found between groups in relation to targeting of therapy once diagnostic cultures received (75.1% vs. 73.7%, P=0.63), antibiotic free days in the first 28 days (10.7 ±7.6 vs. 10.2 ± 7.8, P=0.35) and the relative risk of 28 day mortality 1.05 (95% CI 0.78 to 1.42, P=0.74)[a]
There were similar 14 day mortality rates, ICU discharge and hospital discharge rates between the groups. No difference was noted by the authors in clinical response or microbiological outcomes between the groups.</td></tr>
</table>
<table>
<tr><th>Emergence of resistance</th><th>Monotherapy</th><th>Combination therapy</th><th>P</th></tr>
<tr><td>Acquired resistance to a single antibiotic class[b]</td><td>9.3%</td><td>9.1%</td><td>0.99</td></tr>
<tr><td>Clostridium Difficile toxin isolated from stool</td><td>5.4%</td><td>7.6%</td><td>0.46</td></tr>
</table>
Rates of colonization of sputum with Pseudomonas species, MRSA, Acinetobacter species, vancomycin-resistant enterococci, or any multidrug-resistant organisms (resistant to two or more drug classes) and yeast were not significantly different between groups.
</td></tr>
<tr><td>Source of funding</td><td>Supported by grants from the Canadian Institutes of Health Research and Physicians Services Inc. of Ontario; AstraZeneca Inc.; Bayer Inc.</td></tr>
<tr><td>Comments</td><td>[a] After stratification for diagnostic technique (tracheal aspirate or bronchoalveolar lavage) and APACHE score
[b] Of the 412 patients with a positive enrolment culture (38 / 9.2% overall)</td></tr>
</table>

Evidence table 15: Ishibashi, K; Kuwabara, K; Ishiguro, T et al, 2009

Bibliographic reference	Ishibashi, K; Kuwabara, K; Ishiguro, T. et al. (2009) Short-term intravenous antimicrobial prophylaxis in combination with preoperative oral antibiotics on surgical site infection and Methicillin-Resistant *Staphylococcus Aureus* infection in elective colon cancer surgery: results of a prospective randomized trial. *Surgery Today.* 39. pp1032-1039.
Study type	Prospective randomised controlled trial
Study quality	Moderate
Number of patients	n=283 initially randomised (8 patients subsequently excluded, 136 randomised to group 1 (intravenous (IV) antibiotic for 1 day) and 139 to group 2 (IV antibiotic for 3 days).
Patient characteristics	Adults (aged 25 – 92 years) undergoing elective surgery for colon cancer.
Intervention	All patients received oral preoperative antibiotics (Kanamycin or erythromycin) and mechanical bowel preparation (2-1 polyethylene glycol lavage or magnesium citrate). During surgery all patients were given IV antibiotics (single dose if surgery < 3 hours, second dose if > 3 hours).
Comparison	Comparison was between a single dose of IV antibiotics post operatively 1 hour post-surgery (group 1) and an addition four doses for 2 consecutive days (group 2).
Length of follow up	Daily until discharge and at 1 month in outpatient clinic.
Location	Japan (not further specified)
Outcomes measures and effect size	**Clinical outcomes** / **Group 1 n=136** / **Group 2 n=139** / ***P*** Surgical site infection (overall) / 7 (5.1%) / 9 (6.5%) / 0.80 Incisional site / 5 (3.7%) / 8 (5.8%) / 0.57 Organ / space / 3 (2.2%) / 3 (2.2%) / >0.99 Anastomotic dehiscence / 1 (0.7%) / 1 (0.7%) / >0.99 *No significant difference was reported by antibiotic type used postoperatively (Cefotiam or Cefmetazol)* **Emergence of resistance** / **Group 1 n=136** / **Group 2 n=139** / ***P*** Methicillin-resistant *Staphylococcus Aureus* (MRSA) / 2.2% / 2.9% / >0.99 Surgical site infection (MRSA) / 3 (43%) / 3 (33%) / - Remote infection [a] (MRSA) / 0 / 1 (1.4%) / 0.50
Source of funding	Not reported
Comments	[a] Bloodstream infection

Evidence table 16: Maru, DS-R; Kozal, MJ; Bruce, D et al, 2007

Bibliographic reference	Maru, DS-R; Kozal, MJ; Bruce, D. et al. (2007) Directly administered antiretroviral therapy for HIV-infected drug users does not have an impact on antiretroviral resistance: results from a randomized controlled trial. *Journal of Acquired Immune Deficiency Syndrome* Vol. 46 No. 5 December 15, pp555-563
Study type	Community-based prospective randomised controlled trial
Study quality	Low
Number of patients	n=141. 88 individuals were randomised to receive directly administered antiretroviral therapy (DAART) and 53 to self-administered therapy

	(SAT). Only 74 (84%) of those randomised to DAART actually participated and only 51 (69%) completed the 6 months of intervention.
Patient characteristics	Individuals using drugs, age range not specified only median ages and IQR specified (44.9; 40.9 to 49.7 years for SAT and 42.5; 36.9 to 48.5 years for DAART), who were HIV-seropositive and in receipt of or eligible for highly active antiretroviral therapy (HAART)
Intervention	Directly administered antiretroviral therapy (DAART)
Comparison	Self-administered therapy (SAT)
Length of follow up	Follow-up was for 6 months.
Location	Community-based study in New Haven, CT
Outcomes measures and effect size	

Clinical outcomes	**DAART**	**SAT**	***P***
Virologic success [a]	70.5%	54.7%	0.02
Mean reduction in HIV-1 RNA level (log_{10})	-1.16	-0.29	0.03
Increase in CD4 lymphocyte count (cells/µL)	+58.8	24	0.002

Emergence of resistance	**DAART**	**SAT**	***RR*** [b]***/P***
Adjusted probability of developing 1 new drug related mutation [per person year]	0.49	0.41	1.04; P=0.90
New mutations [per person year]	0.76	0.83	0.99 P=0.99
Probability of developing new major IAS [c] new drug mutation [per person year]	0.33	0.30	1.12 P=0.78

On measures of Genotypic Sensitivity Score and Future Drug Options, the 2 arms also did not differ.

Source of funding	The National Institutes on Drug Abuse (R01 DA13805) funded this study and provided career development awards for F. L. Altice (K24 DA 0170720), S. A. Springer (K23 DA 019381), and R. D. Bruce (K23 DA 022143). D. Smith-Rohrberg Maru receives funding from the National Institutes of Health Medical Science Training Program (GM07205).
Comments	[a] An RNA level reduction ≥1.0 log_{10} or an HIV-1 RNA level <400 copies/mL at the end of six months [b] Adjusted relative risk [c] International Aids Society

Evidence table 17: McCormick, DP; Chonmaitree, T; Pittman, C et al, 2005

Bibliographic reference	Mccormick, DP; Chonmaitree, T; Pittman C. et al. (2005) Non-severe acute otitis media: A clinical trial comparing outcomes of watchful waiting versus immediate antibiotic treatment. *Pediatrics.* June 2005 Vol. 115 No. 6 pp1455-1465.
Study type	Randomised clinical trial
Study quality	Low
Number of patients	n=223 (112 randomised to antibiotics (ABX) and 111 to watchful waiting (WW)).
Patient characteristics	Children aged 6 months to 12 years with diagnosed non-severe acute otitis media (AOM).
Intervention	All parents received educational intervention. Immediate antibiotics, amoxicillin 90mg/kg per day 2 doses daily maximum 1500mg per day, for 10 days, with amoxicillin-clavulanate was used in cases of failure or recurrence. IM ceftriaxone was given to those unable to take oral medication.
Comparison	Watchful waiting (symptomatic medication only)

<table>
<tr><td>Length of follow up</td><td>Follow-up was at days 12 and 30.</td></tr>
<tr><td>Location</td><td>University of Texas Medical Branch pediatric clinic.</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><th>Clinical outcomes</th><th>ABX</th><th>WW</th></tr>
<tr><td>Parent satisfaction score</td><td>44.4</td><td>44</td></tr>
<tr><td>Resolution of AOM (ETG-5 score) at day 12. n (%)</td><td>Age<2yrs: 57 (89)
Age≥2yrs: 41 (95)</td><td>Age<2yrs: 40 (74)
Age≥2yrs: 47 (89)</td></tr>
<tr><td>AOM failure (days 0-12) n (%)</td><td>Age<2yrs: 4(6)
Age≥2yrs: 1(2)</td><td>Age<2yrs: 12(24)
Age≥2yrs: 9(18)</td></tr>
<tr><td>AOM recurrence (days 13-33) n (%)</td><td>Age<2yrs: 11(17)
Age≥2yrs: 9(21)</td><td>Age<2yrs: 10(20)
Age≥2yrs: 3(6)</td></tr>
<tr><td>AOM cure n (%)</td><td>Age<2yrs: 50(77)
Age≥2yrs: 34(77)</td><td>Age<2yrs: 28(56)
Age≥2yrs: 38(76)</td></tr>
<tr><td>Adverse events/quality of life (AOM related):
ABX-related
Extra care
Emergency care
Extra phone calls
Pain medication, n, mean (SD)</td><td>n=111

13
14
1
26
105
3.4 ± 4.0</td><td>n=108

5
22
4
26
102
7.7 ± 7.5*</td></tr>
</table>
AOM resolution: P value was significant for overall difference between ABX and WW groups only for those aged <2yrs (<0.01). The authors reported that children in the immediate antibiotics (ABX) group made faster reported recovery from AOM than did the watchful waiting cohort (P=0.004). At 30 days no significant difference was observed.
The association between clinical outcome and intervention group adjusted for age was statistically significant (P=0.001) mainly due to failure rates.
*P<0.01 all other adverse events and quality of life findings were NS

Emergence of resistance
There was no significant difference in resistant strains of S. pneumoniae at baseline between the ABX and WW groups for ceftriaxone, cefuroxime, clindamycin, erythromycin, levofloxacin, penicillin, trimethoprim, sulfamethoxazole and vancomycin. At day 12 there was greater level of sensitivity to antibiotics in the WW group (P<0.0.2).
</td></tr>
<tr><td>Source of funding</td><td>Study supported by National Center for Research Resources, National Institute for Health and Agency for Healthcare Research and Quality.</td></tr>
<tr><td>Comments</td><td></td></tr>
</table>

Evidence table 18: Moltzahn, F; Haeni, K; Birkhauser, FD et al, 2012

Bibliographic reference	Moltzahn, F; Haeni, K; Birkhauser, FD. et al. (2012) Peri-interventional antibiotic prophylaxis only vs continuous low-dose antibiotic treatment in patients with JJ stents: a prospective randomised controlled trial analysing the effect on urinary tract infections and stent-related symptoms. *BJU International.* Vol. 11. No. 2 pp289-295
Study type	Randomised controlled trial
Study quality	Low
Number of patients	n=95 (44 randomised to peri-interventional antibiotics during stent insertion only [Group A] and 51 randomised to receive continuous low-dose antibiotic treatment [Group B] until stent removal)
Patient characteristics	Adults (aged 18 – 86 years) undergoing temporary JJ stenting due to urolithiasis (temporary tube to hold open the ureter due to kidney stones)
Intervention	All patients received peri-interventional antibiotic prophylaxis (1.2 g amoxicillin/clavulanic acid intravenously) at time of anaesthetic. Those with penicillin allergy received trimethoprim/sulfamethoxazole or

	ciprofloxacin.
Comparison	Amoxicillin/clavulanic acid 625mg once daily
Length of follow up	Follow-up was at 1, 2 and 4 weeks and/or at stent removal.
Location	Not formally stated (Swiss study).

Outcomes measures and effect size

Clinical outcomes	Group A	Group B	*P*
UTI, n/N (%)	4/44 (9)	5/51 (10)	1.000
Stent <2 weeks	1/14 (7)	0/14 (0)	1.000
Stent 2-4 weeks	2/17 (12)	1/12 (8)	1.000
Stent >4 weeks	1/13 (8)	4/25 (16)	0.643
Stent related symptoms, n (%)	43 (98)	49 (96)	-
Drug side-effects, n/N (%)	21/44 (48)	22/51 (43)	[a]
Rash/pruritus, n (%)	0	3 (14)†	[b]
Nausea/diarrhoea, n (%)	7 (33)	13 (59) †	[c]
Fatigue, n (%)	17 (81)	17 (77)	[d]

† Authors state these are significant increases [no P value given]

Emergence of resistance	Group A	Group B
Number of patients		
Stent <2 weeks	0/1	0/0
Stent 2-4 weeks	1/2	-/1
Stent >4 weeks	0/1	1/4

Two additional multi-resistant S. Aureus were found in Group B, although these were at an insignificant bacterial count <10.000 CFU/mL.

Source of funding	Not reported
Comments	[b] 95% CI for Group B – Group A -0.252 to 0.157 [c] 95% CI for Group B – Group A -0.036 to 0.349 [d] 95% CI for Group B – Group A -0.051 to 0.541 95% CI for Group B – Group A -0.292 to 0.244

Evidence table 19: Mountokalakis,T; Skounakis, M; Tselentis, J. 1985

Bibliographic reference	Mountokalakis, T; Skounakis, M; Tselentis, J (1985) Short-term versus prolonged antibiotic prophylaxis in patients with indwelling catheters. *Journal of Urology.* Vol. 134. No.3. pp506-508
Study type	Randomised controlled trial
Study quality	Low
Number of patients	n=78 (24 randomised to short-term antibiotics [Group 1], 28 randomised to prolonged antibiotics [Group 2] and 26 randomised to receive no antibiotic prophylaxis [Group 3]).
Patient characteristics	Newly hospitalised adults with recent stroke aged 58 – 90 years old with indwelling urinary catheters for urinary incontinence.
Intervention	Group 1 were given 3 gram ampicillin intramuscularly (IM) divided into 3 equal doses 1 hour before, at the time and 6 hours post catheterisation. Group 2 received 1 gram ampicillin IM every 8 hours.
Comparison	Group 3 were not given antibiotics.
Length of follow up	At 7 days or when significant bacteriuria was discovered (>10^5 bacteria per ml of urine).
Location	Not stated

Outcomes measures and effect size

Clinical outcomes	Group 1	Group 2	Group 3
Significant bacteriuria, n/N (%)	3/24 (12.5)	12/28 (42.8)	12/26 (46.1)
X^2 test between Group 1 and either group 2 and 3 was significant (X^2 = 5.802, P=0.02 and X^2 = 6.730, P=<0.01)			
Time to diagnosis. Antibiotic prophylaxis delayed acquisition of bacteria (X^2) between groups 1 and 3 on days 5 (5.023, P<0.05), day 6 (7.487, P<0.01)			

	and day 7 (6.731, P<0.01). Also between groups 1 and 2 on days 6 (5.458, P<0.02) and 7 (5.802, P<0.02). No significant difference was found between groups 2 and 3.

Emergence of resistance	Group 1	Group 2	Group 3
Bacterial isolates isolated from each group (resistant)	1/4	12/21	4/15
The mean number of species (± standard error) isolated per case of significant bacteriuria was significantly higher (P<0.05) in Group 2 (1.75 ± 0.13) than in Group 3 (1.25 ± 0.18).			

Source of funding	Not stated
Comments	X^2 is the chi-square test

Evidence table 20: Palmer, LB; Smaldone, GC; Chen, JJ et al, 2008

Bibliographic reference	Palmer, LB; Smaldone, GC; Chen, JJ. et al. (2008) Aerosolized antibiotics and ventilator-associated tracheobronchitis in the intensive care unit. *Critical Care Medical* Vol. 36 No. 7 pp2008-2013
Study type	Double blind randomised placebo controlled trial
Study quality	Moderate
Number of patients	n=43* (19 randomised to receive aerosolised antibiotics (AA) and 24 to receive placebo).
Patient characteristics	Critically ill adults (aged 19 to 92 years) requiring mechanical ventilation (MV) for >3 days and expected to survive at least 14 days.
Intervention	Aerosolised antibiotic choice based upon gram stain of tracheal aspirate secretions (gram positive organisms were treated with vancomycin HCL, 120mg in 2ml normal saline every 8 hours, gram negative organisms were treated with gentamicin-sulfate 80mg in 2ml normal saline every 8 hours) for 14 days, unless extubated earlier.
Comparison	Saline placebo aerosolised
Length of follow up	Follow-up at 14 days
Location	At a single centre (not defined)

Outcomes measures and effect size

Clinical outcomes	AA (n=19)		Placebo (n=24)		
	n (%)	*P Value* [a]	*n (%)*	*P Value* [a]	*P Value* [b]
Treatment day 1	14 (73.6)	_	18 (75)	_	1.00
End of treatment [c]	6 (31.6)	0.007	14 (58.3)	0.28	0.12
Day 14	5 (35.7)	0.06	11 (78.6)	1.00	0.05

[a] McNemar's test compared to baseline;
[b] Fisher's exact test: AA compared with placebo;
[c] end of treatment where discontinued before 14 days due to extubation.

When compared to placebo patients in the AA group were 71% less likely to demonstrate a defined ventilator acquired pneumonia (controlled for age) adjusted odds ratio 0.29 [95% CI 0.13 – 0.66; P=0.006]

White blood cell count [c]	Mean ± SD	P Value [a]	Mean ± SD	P Value [a]	P Value [b]
Day 1	13.6±7.6	_	12.4±4.3	_	0.854
Day 7	10.1±3.2		14.0±7.0		0.087
Day 14	9.2±3.3	0.016	14.9±8.1	NS	0.016

[a] Kendall's correlation test for decreasing WBC count in AA

[b] Wilcoxon rank sum test; NS not significant.

	AA (n=19)	Placebo (n=24)	P Value [a]
Died	4	4	0.999
Tracheostomy	9	13	0.538
Systemic antibiotics [d]	17 at outset 8 additional	15 at outset 17 additional	0.042

[a] Fisher's exact

Emergence of resistance	AA (n=19)	Placebo (n=24)	P Value
End of treatment	0	8	0.0056

Source of funding	Study supported by Nektar Therapeutics.
Comments	*Data from 5 patients was not analysed (4 from the AA arm and one from the placebo arm) due to protocol deviation [c] $X10^3/mm^3$ [d] Additional antibiotics for treatment of new or persistent infection

Evidence table 21: Palmer, LB; Smaldone, GC. 2014

Bibliographic reference	Palmer, LB; Smaldone, GC (2014) Reduction of bacterial resistance with inhaled antibiotics in the intensive care unit. *American Journal of Critical Care Medicine.* Vol.189. No. 10 pp1225-1233
Study type	Double blind placebo controlled study
Study quality	Moderate
Number of patients	n=42 (23 randomised to placebo control and 24 randomised to receive aerosolised antibiotic [AA])*.
Patient characteristics	Adults aged 18 years or older [range 19 to 92 years], who were intubated, mechanically ventilated and expected to survive for at least 14 days.
Intervention	AA selection was based gram stain with gram positive organisms treated with vancomycin HCL, 120mg every 8 hours. Gram negative organisms were treated with gentamycin sulfate, 80mg every 8 hours, or amikacin 400mg every 8 hours.
Comparison	Placebo (2 ml) of normal saline aerosolised.
Length of follow up	Follow-up at 14 days
Location	At a single centre (not defined)
Outcomes measures and effect size	

Clinical outcomes at end of therapy	AA (n=24)	Placebo (n=18)	P Value
CPIS [a]	5.3±2.6	8.6±2.6	0.0008[b]
CPIS w/o culture data	4.9±2.2	6.3±2.0	0.05546[b]
Sputum volume per 4 hour	1.1±1.3	6.3±4.3	<0.001
Systemic white blood count	13.3±1.3	13.9±1.5	0.726
Organisms eradicated [c]	96%	9%	<0.0001
Patients with organisms eradicated	88%	9%	<0.0001
At baseline there were no significant differences between the two groups for these outcomes.			
Total ventilator days	12.9±2.1	13.5±2.1	0.078
Death	6/24	2/18	0.43
No significant difference was seen for nephrotoxicity at follow-up			

Emergence of resistance	AA (n=24)	Placebo (n=18)	P Value

	Patients with new resistant organisms during treatment	2 (13%)	6 (55%)	0.03
Source of funding	Not stated			
Comments	*n= 47 randomised but 5 patients lost to follow-up due to transfers out of ICU and one withdrawal from the study by family, all in the placebo arm. Clinical pulmonary infection score [b] Mann-Whitney test [c] Organisms identified at randomisation			

Evidence table 22: Revankar, S; Kirkpatrick, WR; McAtee, RK et al, 1998

Bibliographic reference	Revankar, S; Kirkpatrick, WR; Mcatee, RK.et al. (1998) A randomized trial of continuous or intermittent therapy with fluconazole for oropharyngeal candidiasis in HIV-infected patients: clinical outcomes and development of fluconazole resistance. *American Journal of Medicine* 105(1) pp7-11
Study type	Randomised controlled trial
Study quality	Low
Number of patients	n=62 (42 randomised to intermittent therapy and 20 randomised to continuous therapy)
Patient characteristics	Patients positive for HIV with a CD4 cell count <350X10^6/L
Intervention	Continuous fluconazole 200mg/day
Comparison	Fluconazole for intermittent episodes of candidiasis only (dose not defined)
Length of follow up	Follow-up was at 3 months
Location	University of Texas Health Science Centre (San Antonio) and the South Texas Veterans Health Care System, Audie Murphy Division (San Antonio.
Outcomes measures and effect size	

Clinical Outcomes	**Continuous (n=16)**	**Intermittent (n=28)**	***P***
Symptomatic relapses	4 (25%)	23 (82%)	-
Total number of relapses	6[a]	112	-
Median annual relapse rate	0	4.1	<0.001[b]
Clinical failure	0	2 (7%)	-
Treatment failure	0	4	0.3

Emergence of resistance	**Continuous (n=16)**	**Intermittent (n=28)**	***P***
Resistant yeasts	9 (56%)	13 (46%)	0.75
Candida -albicans	4 (25%)	7 (25%)	1.0
non-*albicans* yeasts	9 (56%)	10 (36%)	0.31
Clinical resistance requiring increased dose	2 (13%)	5 (18%)	

Source of funding	Study supported by grants from the National Institute of Dental Research, National Institute of Health, and Pfizer. Support was also provided by CHROMagar Candida, Paris (Chromogenic media).
Comments	four of the 6 relapses were associated with interruption of suppressive therapy [b] Wilcoxon rank sum test

Evidence table 23: Stahl, GE; Topf, P; Fleisher, GR et al, 1984

Bibliographic reference	Stahl, GE; Topf, P; Fleisher, GR. et al. (1984) Single-dose treatment of uncomplicated urinary tract infections in children. *Annals of Emergency Medicine.* September part 1 (13) pp705-708
Study type	Randomised controlled trial
Study quality	Low
Number of patients	n=36 ([only 26 completed the study] 18 [10] randomised to the single-dose group and 18 [16] in the conventional therapy group)
Patient characteristics	Girls aged 2 to 17 years with symptoms of lower urinary tract infection (frequency, dysuria, urgency, enuresis, suprapubic pain or haematuria with pyuria (>10 White Blood Cells per power field on unspun specimen) and two sequential urine culture positives for the same organism.
Intervention	Single-dose amoxicillin therapy (50mg/kg orally maximum 3g)
Comparison	Conventional amoxicillin therapy (30mg/kg/day orally in three divided doses for 10 days, maximum per dose 250mg).
Length of follow up	Final follow-up at 3 months
Location	Emergency department or paediatric clinic of Children's Hospital of Philadelphia or St Christopher's Hospital for Children.
Outcomes measures and effect size	**Clinical outcomes** / **Single-dose (n=10)** / **Conventional (n=16)** / ***P* Value** Cure rate / 70% / 75% / NS [c] Relapse rate / 30% / 25% / NS [c] Reinfection rate / 0% / 12% / NS [c] **Emergence of resistance** / **Single-dose** / **Conventional** / ***P* Value** Induction of resistance in relapse patients / 100%[a] (n=3) / 100%[b] (n=4) / <0.05[c]
Source of funding	Not stated
Comments	NS = Not significant [b] Relapse treated with amoxicillin as not resistant [b] Relapse treated with other antibiotic as resistant [c] Fisher's exact test

Evidence table 24: van Zanten, ARH; Oudijk, M; Nohlmans-Paulssen, MKE et al, 2006

Bibliographic reference	Van Zanten, ARH; Oudijk, M; Nohlmans-Paulssen, MKE. et al. (2006) Continuous vs. intermittent cefotaxime administration in patients with chronic obstructive pulmonary disease and respiratory tract infections: pharmacokinetics/pharmacodynamics, bacterial susceptibility and clinical efficacy. *British Journal of Clinical Pharmacology* 63(1) pp100-109
Study type	An non-blinded randomised prospective controlled trial
Study quality	Low
Number of patients	n=93* (47 randomised to the continuous antibiotic [Group I] and 46 randomised to the intermittent antibiotic [Group II])
Patient characteristics	Consecutive hospitalised patients aged ≥18 years (range 34 – 76 years) requiring antibiotics for acute infective exacerbation of chronic obstructive pulmonary disease (COPD) [Gold classes 2 – 4].
Intervention	2g of cefotaxime intravenously over 24 hours plus a loading dose of 1g (over 30 minutes) for 7 days
Comparison	1g of cefotaxime three times daily for 7 days

Length of follow up	Not defined
Location	Hospital setting (not defined)
Outcomes measures and effect size	**Clinical outcomes** / **Group I** / **Group II** / ***P* Value****
	Evaluable patients: 40/47 (85.1%) / 43/46 (93.5%) / -
	Treatment success: 37/40 (92.5%) / 40/43 (93%) / 0.93
	Treatment failure: 3/40 (7.5%) / 3/43 (7%) / -
	Mean duration of treatment (days) (range; median): 9.3±2.6 (1-12; 10) / 9.5±1.5 (4-11; 10) / 0.64
	Emergence of resistance No difference was found in susceptibility between the continuous and intermittent group at baseline or follow-up.
Source of funding	Hoechst Marion Roussel (manufacturer of cefotaxime) provided a restricted research grant for analysing serum cefotaxime concentrations and for assessing MIC values.
Comments	*10 patients subsequently excluded due to death (not due to COPD), protocol breach and alternate diagnosis (squamous cell carcinoma). **Chi-square test

Evidence table 25: van der Wall, E; Verkooyen, RP; Mintjes-De Groot, J et al, 1992

Bibliographic reference	Van Der Wall, E; Verkooyen, RP; Mintjes-De Groot, J, et al. (1992) Prophylactic ciprofloxacin for catheter-associated urinary-tract infection. *The Lancet.* 339, April 18 pp946-951
Study type	Randomised, double blinded placebo-controlled trial
Study quality	Low
Number of patients	n=202* (18 patients subsequently excluded, 61 randomised to placebo arm, 59 randomised to ciprofloxacin 250mg/day and 64 to ciprofloxacin 1000mg/day)
Patient characteristics	Adult (aged range 31-91) hospital patients admitted to two hospitals in the Netherlands for surgery (vaginal repair, hip replacement or colorectal surgery).
Intervention	Ciprofloxacin 250mg (plus placebo) once daily [Group A] or ciprofloxacin 500mg twice daily [Group B] from the second post-operative day until catheter removal.
Comparison	Placebo daily from the second post-operative day until catheter removal.
Length of follow up	Final follow-up ranged from 13 to 102 days.
Location	Two hospitals in the Netherlands.
Outcomes measures and effect size	**Clinical outcomes (ITT [a])** / **Placebo (n=68)** / **Group A (n=66)** / **Group B (n=68)**
	Infectious morbidity: 16 (23.5%)[b] / 5 (7.6%) / 5 (7.4%)
	Side effects: 2 (2.9%) / 1 (1.6%) / 2 (2.9%)
	Therapeutic antibiotics courses: 11 / 2 / 4
	Febrile episodes: - / 4 / 0[c]
	Symptomatic UTI: 12 / 2 / 4
	Asymptomatic UTI: 49 / 57 / 60
	Absolute risk reduction of 15% antibiotic prophylaxis compared to placebo (NNT of 7).

Clinical outcomes at catheter removal		**Placebo (n=57)**	**Ciprofloxacin (n=113)**	**Relative risk (95% CI)**
Pyuria	No	33	101	4.0
	Yes	24	12	(2.1-7.3)
Bacteriuria [d]	No	14	95	4.7
	Yes	43	18	(3.0-7.4)
Bacteriuria [e]	No	17	107	13.2
	Yes	40	6	(6.0-29.3)
Emergence of resistance		**Placebo**	**Group A**	**Group B**
After catheterisation		2/7 (n=57)	2/17 (n=54)	0/15 (n=59)
Pre-catheter removal		7/70 (n=57)	9/13 (n=54)	10/10 (n=59)
At 6 weeks		4/51 (n=54)	11/49 (n=53)	15/77 (n=58)
Number of resistant isolates/total number of isolates				

Source of funding	Supported by the Daikonessen Hospital Research Foundation and Bayer AG, Leverkussen, Germany
Comments	*Of the original 202 randomised 188 were female. [b] Intention to treat analysis [b] Relative Risk (95% CI) versus 250mg ciprofloxacin 3.1 (1.2-8.0); versus 1000mg ciprofloxacin 3.2 (1.2- 8.2) [c] P≤0.023 compared to placebo and 250mg ciprofloxacin group [d] ≥10^3 colony forming units/ml [e] ≥10^5 colony forming units/ml

Evidence table 26: Lesprit et al. (2013) Clinical impact of unsolicited post-prescription antibiotic review in surgical and medical wards: a randomised controlled trial

Bibliographic reference	Lesprit, P; Landelle, C; Brun-Buisson, C (2012) Clinical impact of unsolicited post-prescription antibiotic review in surgical and medical wards: a randomised controlled trial. *Clin Microbiol Infect* 2013; 19: E91–E97
Study type	Randomized, controlled, open trial.
Study quality	Moderate
Number of patients	Analysis included n=753* (376 intervention and 377 controls) out of 855 randomised.
Patient characteristics	Adult patients, identified by a computer generated alert system for all new prescriptions, on a target antibiotic [1] for at least 3 days (5 if over weekend) and did not have excluded conditions [2]. Patients all had mild to moderately severe infection and most common conditions were community acquired and of the respiratory, urinary, skin and soft tissue or digestive tract infections. Half of the antibiotic regimens were initially prescribed intravenously by ward physicians. The majority of prescriptions were of amoxicillin clavulanate, fluoroquinolones and third generation cephalosporins.
Intervention	Post-antibiotic prescription review by an infectious diseases physician (IDP) with either an oral or written recommendation[3] to the prescriber.
Comparison	Usual care from ward physician only.
Length of follow up	Not stated although the total study duration was 6-months.
Location	An 850-bed general university hospital in France.
Outcomes measures and effect size	

Changes in care No (%)	**Control**	**Intervention**	**p value**
Solicited advice (IDP)	30 (8)	11 (2.9)	0.002
Unsolicited advice (IDP)	0 (0)	315 (83.6)	<0.0001

	Antibiotic modified			
	Any change	97 (25.7)	215 (57.1)[6]	<0.0001
	Stopping therapy	15 (0.4)	59 (15.6)	<0.0001
	Shortening duration	24 (63)	65 (17.2)	<0.0001
	De-escalating[4]	9 (0.2)	72 (19.1)	<0.0001
	Oral switch	47 (21.6)	48 (24.1)	0.90
	Other[5]	24 (6.3)	30 (7.9)	0.39
	Duration of therapy Mean (days), IQR	**Control**	**Intervention**	**p value**
	Total antibiotic course	7 (5 – 9)	6 (4 – 9)	<0.0001
	Broad-spectrum	4 (0 – 7)	2 (0 – 5)	0.0003
	Narrow to intermediate	4 (0 – 8)	5 (0 – 7)	0.13
	IV administration	4 (0 – 8)	5 (0 – 7)	0.004
	Oral administration	4 (0 – 7)	4 (0 – 7)	0.84
	Clinical outcomes	**Control**	**Intervention**	**p value**
	Hospital mortality (60 day)	38 (10.1%)	37 (9.8%)	0.91
	ICU admission within 7 days of randomisation	6 (1.6%)	7 (1.9%)	0.78
	New course of antibiotic therapy	25 (6.6%)	17 (4.5%)	0.21
	Antibiotic treatment for relapsing infection	30 (7.9%)	13 (3.4%)	0.01
	Length of stay, days (median, IQR)			
	Overall population	15 (9 – 27)	15 (9 – 25)	0.95
	community acquired	6 (3 – 14)	5 (3 – 10)	0.06

Emergence of resistance

No (%)	**Control**	**Intervention**	**p value**
MRSA[7]	10 (2.6)	11 (2.9)	0.82
ESBLE[8]	17 (4.5)	12 (3.2)	0.34
Total	27 (7.1)	23 (6.1)	0.56

Source of funding	Not stated
Comments	* Study powered to detect a 20% reduction in hospital stay [1] Amoxicillin/clavulanate (intravenous and oral); gentamicin, vancomycin, teicoplanin and linezolid (intravenous and oral), piperacillin /tazobactam, cefotaxime, ceftriaxone, cefepime, ceftazidime, imipenem, ofloxacin (intravenous and oral), ciprofloxacin (intravenous and oral), levofloxacin (intravenous and oral) and moxifloxacin (oral). [2] Acute leukaemia, expected survival <30 days, discontinuation of therapy, discharge and ICU admission or death. [3] Recommendations could be overridden and if this occurred no further recommendations were made in regards to that patient by the IDP [4] Including reducing spectrum covered and combinations [5] Increasing duration, changing doses, switching to a broad spectrum antibiotic [6] Rate of compliance with recommendations was 85% [7] Methicillin resistant staphylococcus aureus [8] Extended spectrum β-lactamase-producing enterobacteria

D.1.2 Additional evidence tables for reducing antimicrobial resistance (de-escalation)

Evidence table 27: Kim, J.W., Chung, J., Choi, S-H. et al. (2012)

<table>
<tr><td>Bibliographic reference</td><td>Kim, J.W., Chung, J., Choi, S-H, et al. 2012. Early use of imipenem/cilastatin and vancomycin followed by de-escalation versus conventional antimicrobials without de-escalation for patients with hospital-acquired pneumonia in a medical ICU: a randomized clinical trial. Critical care. 16 (1) R28</td></tr>
<tr><td>Study type</td><td>Prospective, open-label, randomized intention-to-treat clinical trial</td></tr>
<tr><td>Study quality</td><td>Low</td></tr>
<tr><td>Number of patients</td><td>n=108.</td></tr>
<tr><td>Patient characteristics</td><td>Adults, aged 18 years or over (81% males), who were hospitalised for less than 48 hours and admitted to the intensive care unit (ICU) for hospital acquired pneumonia (HAP)[1]. Patients were excluded if a pathogen was already known, if antimicrobial therapy had been changed in the 48 hours prior to ICU admission, the patient was pregnant or lactating or had a history of HAP in the previous month.</td></tr>
<tr><td>Intervention</td><td>n=55. Administered imipenem /cilastatin (0.5 g every 6 hours) and vancomycin (15mg/Kg) every 12 hours. De-escalation (DE group) was performed at 3 – 5 days based on clinical status and cultures.</td></tr>
<tr><td>Comparison</td><td>n=54. Conventional empiric therapy (non-carbapenem and non vancomycin) at the discretion of the prescribing physician[2]. No de-escalation (non-DE group) was performed and patients were treated for 7 days for non-drug resistant organisms and 14 days for multi-drug resistant organisms.</td></tr>
<tr><td>Length of follow up</td><td>Not specifically defined, however the study reports 28 day and in-patient hospital mortality.</td></tr>
<tr><td>Location</td><td>28 bed medical ICU, Asan Medical Center, Seoul, Korea.</td></tr>
<tr><td>Outcomes measures and effect size</td><td>The primary outcome for the study was adequacy of initial therapy; secondary outcomes were mortality, emergence of multidrug resistant organisms (MDR), duration of treatment and ICU length of stay (LoS).
<table>
<tr><th>Clinical outcomes</th><th>DE</th><th>Non-DE</th><th>P value</th></tr>
<tr><td>Adequacy of initial therapy</td><td>75.9%</td><td>48%</td><td>0.035</td></tr>
<tr><td>Gram +ve organisms</td><td>21/21 (100%)</td><td>2/14 (14.3%)</td><td>< 0.001</td></tr>
<tr><td>Gram –ve organisms</td><td>9/14 (64.3%)</td><td>12/14 (85.7%)</td><td>0.190</td></tr>
<tr><td>Time to adequate antimicrobials[3]</td><td>1.9 [±0.5]</td><td>2.8 [±0.6]</td><td>0.280</td></tr>
<tr><td>Overall hospital mortality</td><td>44.2%</td><td>34.6%</td><td>0.316</td></tr>
<tr><td>14 day mortality</td><td>24.5%</td><td>13%</td><td>0.314</td></tr>
<tr><td>28 day mortality</td><td>44.2%</td><td>25.9%</td><td>0.131</td></tr>
<tr><td>Duration of treatment[3]</td><td>12.5 [±5.8]</td><td>14.1 [±7.3]</td><td>0.222</td></tr>
<tr><td>ICU LoS (survivors)[4]</td><td>21.1 [6-35]</td><td>14.1 [6-19]</td><td>0.464</td></tr>
<tr><td></td><td>Vancomycin</td><td colspan="2">Imipenem /cilastatin</td></tr>
<tr><td>Rate of de-escalation[5]</td><td>30/36 (83.3%)</td><td colspan="2">28/33 (84.8%)</td></tr>
</table>
In 18 patients an MDR was isolated within 1 month of enrolment in the study. Patients with initial MDR culture positive at enrolment were excluded (DE = 24 and Non-DE = 13)
<table>
<tr><th>Emergence of resistance</th><th>DE</th><th>Non-DE</th><th>P value</th></tr>
<tr><td>Emergence of MDR organism</td><td>11 (37.9%)</td><td>7 (16.7%)</td><td>0.043</td></tr>
<tr><td>Time to development[4]</td><td>19.4 [11-30]</td><td>22.7 [9-30]</td><td>0.108</td></tr>
<tr><td>Methicillin-resistant S. aureus[6]</td><td>8 (27.6%)</td><td>4 (9.5%)</td><td>0.059</td></tr>
</table></td></tr>
</table>

Source of funding	The study was partially funded by MSD Korea.
Comments	[1] Hospital acquired pneumonia diagnosis according to the American College of Chest Physicians criteria for HAP. [2] Most commonly this was piperacillin, tazobactam and ciprofloxacin (63.6% of comparison cases) [3] Mean in days [Standard deviation] [4] Mean in days [Inter-quartile range] [5] Number actually de-escalated/ number identified as eligible for de-escalation [6] Non significant differences between DE and Non-DE were found for Gram negative non-Enterobacteriaceae, *S. maltophilia*, imipenem-resistant *A. baumanii* and *P. aeruginosa*, and EBSL-producing *K. pneumonia.*

Evidence table 28: Leone, M., Bechis, C., Baumstarck, K. et al. (2014)

Bibliographic reference	Leone, M., Bechis, C, Baumstarck, K. et al. 2014. De-escalation versus continuation of empirical antimicrobial treatment in severe sepsis: a multicenter non-blinded randomized noninferiority trial. *Intensive care medicine*. 40 (10) Pages 1399-1408
Study type	Multicentre non-blinded randomised non-inferiority trial[1]
Study quality	Low
Number of patients	n=116.
Patient characteristics	Patients (age criteria for entry not defined) with severe sepsis[2] requiring empiric antimicrobial therapy.
Intervention	n=59. Empiric therapy was switched for narrowest spectrum antibiotic possible (median time to de-escalation was 3 days [Inter-quartile range; 2 – 4 days]. Any companion drug (aminoglycoside, fluoroquinolone or macrolide) was also stopped at day 3.
Comparison	n=57. Empiric antibiotic was continued for the entire duration of the treatment, prolonged courses could be de-escalated at 8 – 15 days at the discretion of the treating physician. Companion drugs were stopped at 3 – 5 days.
Length of follow up	90 days
Location	Nine intensive care units (ICU) in France.
Outcomes measures and effect size	The primary outcome of interest of this study was ICU length of stay (LoS). The secondary outcomes of the study were the number of ICU free days, the 90 day mortality rate, the number of ventilator free days[3], the number of catecholamine free days[3], the number of antibiotic free days[3], the number of days of antibiotic therapy in ICU, changes in SOFA score[4], and the number of superinfections requiring antibiotics and *C. diff* infections.

Clinical outcomes	DE	Continuation group	P value
ICU LoS[5]	15.2 [±15.0] 9 [1-79]	11.8 [±12.6] 8 [1-60]	0.71
Number of ICU free days[3,5]	13.2 [±10.6] 18 [0-23]	15.0 [±11.3] 21 [0-25]	0.21
Number of deaths at 90 days[6]	18 (31%)	13 (23%)	0.35
Ventilator free days[3]	18.9 [±11.6] 23 [6-29]	19.3 [±11.8] 26 [6-29]	0.55
Catecholamine free days[3]	22.3 [±10.3] 28 [21-29]	21.6 [±11.2] 28 [16-29]	0.93
Number of antibiotic days[3]	14.1 [±13.4] 9 [7-15]	9.9 [±6.6] 7.5 [6-13]	0.04
Number of companion	2.3 [±0.8]	3.2 [±1.7]	< 0.00

	antibiotic days	2.0 [2.0-3.0]	3.0 [2.8-3.0]	
	Number of antipseudomonal agent free days[3]	23.6 [±9.2] 29 [24-29]	20.1 [±9.6] 24 [15-28]	< 0.001
	Number of carbapenem free days[3]	25.6 [±7.3] 29 [26-29]	23.5 [±8.4] 29 [19-29]	0.17
	Number of anti-MRSA drug free days[3]	25.8 [±7.1] 29 [27-29]	24.1 [±8.4] 29 [21-29]	0.30
	D-SOFA[4] score[7]	3 [0:4]	2 [-1:3]	0.63
	Superinfection episodes requiring antibiotics (ICU)	16 (27%)	6 (11%)	0.03
	No clostridium difficile infections occurred during the study.			
	Secondary post hoc outcomes[8]	**DE**	**Continuation group**	**P value**
	Duration of ICU stay, days[8]	14 [9-31]	15 [8-21]	0.53
	Superinfection	13 (39%)	5 (22%)	0.2
	Duration of ICU stay, days[9]	10 [5-25]	8 [4-16]	0.71
	Antibiotics for *P. aeruginosa*[3, 10], days	12 [5-22]	6 [3-12]	0.03
	Treatment escalation[3]	8 (14%)	5 (8.8%)	0.41
	This study did not measure the effect of de-escalation on local ecology. However the authors state that they collected samples from patients at inclusion and day 8, and did not find any significant differences in either of the groups (data not reported).			
Source of funding	No source of funding was declared, authors made declarations of interest.			
Comments	[1] A study which compares an intervention to an active treatment in order to demonstrate that it is not clinically worse with regards to a specific outcome. [2] A systemic inflammatory response syndrome and suspected infection with at least 1 organ failure. [3] From inclusion to day 28. [4] Sequential organ failure assessment score [5] Mean in days [Standard deviation], followed by medians [inter-quartile range] [6] The 90-day mortality rate did not differ (Hazard Ratio: 1.31 [95% CI: 0.64 – 2.67], p=0.49. Results remained non-significant following adjustment for the simplified acute physiology (SAPS) II score, age and treatment group. [7] Median score in 66 patients with an ICU stay more than 7 days. [8] Multivariate analyses performed as the groups were uneven for lung infection (used as an independent variable), age, SAPS II and chronic arterial hypertension at baseline. [9] In 93 patients with risk factors for MDR bacteria carriage [10] The total number of patients with P. aeruginosa was not given			

Evidence table 29: Micek, ST., Ward, S., Fraser, VJ. et al. (2014)

Bibliographic reference	Micek, ST., Ward, S., Fraser, VJ. et al. 2014. A randomized controlled trial of an antibiotic discontinuation policy for clinically suspected ventilator-associated pneumonia. Chest. 125 (5) Pages 1791-1799
Study type	Prospective randomised controlled clinical trial
Study quality	Low
Number of patients	n=290.
Patient characteristics	Adult patients (aged >18 years) admitted to a medical intensive care unit

	(ICU) during a 14 month study period and treated for ventilator associated pneumonia (VAP) with antibiotics. Patients were excluded if they had transferred from another hospital or unit. Entry to the study was on the clinical judgement of the treating physician as to the presence of VAP.
Intervention	n=150. Duration of antibiotic therapy was determined according to a formalized antibiotic discontinuation policy (discontinuation group). An investigator offered recommendations, based on clinical findings or patient condition[1], for patients during patient care rounds based upon the policy[2].
Comparison	n=140. Duration of antibiotic therapy was determined by the clinical judgement of the treating ICU physician.
Length of follow up	Until hospital discharge or until patient death.
Location	A medical ICU (single centre) in the Barnes-Jewish Hospital, St Louis, MO.
Outcomes measures and effect size	The primary outcome of the study was the duration of antibiotic treatment for VAP. The secondary outcomes were hospital mortality, lengths of ICU and hospital stay, duration of mechanical ventilation and occurrence of secondary episodes of VAP during the same ICU stay.

Clinical outcomes	Discontinuation group	Conventional antibiotic group	P value
Number (%) of patients at high risk[3] of VAP	99 (66%)	101 (72.1%)	0.259
Non-infectious etiologies	8.7%	6.4%	0.472
Initial adequate antimicrobial treatment	93.3%	93.6%	0.935
Overall days of antibiotic treatment for VAP	6.0 [±4.9]	8.0 [±5.6]	0.001
Days of Gram –ve antibiotic treatment	5.8 [±4.7]	7.1 [±5.1]	0.023
Days of Gram +ve antibiotic treatment	2.3 [±3.2]	4.8 [±4.4]	0.001
Secondary episodes of VAP	26 (17.3%)	27 (19.3%)	0.667
Number of MRSA	11	13	-
Number of P. aeruginosa	7	8	-
Number of candida or Aspergillus species	4	4	-
Number of other Gram –ve bacterial species	4	2	-
Hospital mortality	48 (32%)	52 (37.1%)	0.357
Hospital LoS, days[4]	15.7 [±18.2]	15.4 [±15.9]	0.865
ICU LoS, days[4]	6.8 [±6.1]	7.0 [±7.3]	0.798
Duration of ventilation, days[4]	5.4 [±5.7]	5.7 [±7.1]	0.649
Subsequent HAI[5]	56 (37.3%)	46 (32.9%)	0.425

Source of funding	Study was part funded by the Barnes-Jewish Hospital Foundation and an unrestricted grant from Elan Pharmaceuticals.
Comments	[1] Non-infectious etiology identified, signs and symptoms suggesting active infection had resolved (temperature ≤38.3°C, circulating leukocyte count < 10,000/μL [10X10^9/L] or decreased by >25% from peak value,

	improvement or lack of progression on chest radiograph, absence of purulent sputum, and PaO_2/FiO_2 ratio >250. All criteria had to be met for an antibiotic discontinuation recommendation to be made. [2] Recommendations could be overridden by treating physicians [3] Likelihood based on a modified version of the American College of Chest Physicians criteria. [4] Mean days [Standard deviation] [5] Healthcare acquired infection

Evidence table 30: Singh, N., Rogers, P., Atwood, CW. et al. (2000)

Bibliographic reference	Singh, N., Rogers, P., Atwood, CW. et al. 2000. Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. A proposed solution for indiscriminate antibiotic prescription. American journal of respiratory and critical care medicine. 162 (2 Pt 1) Pages 505-511
Study type	Randomised, un-blinded, controlled trial
Study quality	Low
Number of patients	n=81[1].
Patient characteristics	Patients (age 18 years and over) with a clinical pulmonary infection score (CPIS) ≤ 6[2], were included in the study. Exclusion criteria were patients with HIV, patients with cytotoxic chemotherapy induced neutropenia, use of antibiotics (other than for surgical prophylaxis) and allergy to fluoroquinolones.
Intervention	n=39. Ciprofloxacin 400 mg intravenously every 8 hours for 3 days. Other antibiotics were not allowed. Patients were re-evaluated and CPIS recalculated at day 3 and included clinical and microbiological findings and patient progress. If the CPIS at 3 days was ≤ 6 then ciprofloxacin was discontinued due to the low likelihood of pneumonia, providing there was no other infection. If the CPIS was > 6 the ciprofloxacin was continued or antimicrobial therapy modified based on microbiology results.
Comparison	n=42. Choice, number and duration of antibiotic were at the discretion of the treating physician[3].
Length of follow up	Not explicitly stated, however mortality was assessed at 30 days
Location	The surgical and medical ICUs of a tertiary care university affiliated Veterans Affairs Medical Center.
Outcomes measures and effect size	The primary outcomes of this study were mortality, length of ICU stay, emergence of antimicrobial resistance or superinfection.

Clinical outcomes	Experimental group	Standard therapy group	P value
Number of deaths at 3 days (%)	0/39 (0%)	3/42 (7%)	>0.05
Number of deaths at 14 days (%)	3/39 (8%)	9/42 (21%)	>0.05
Number of deaths at 30 days (%)	5/39 (13%)	13/42 (31%)	0.06
Complete resolution of pulmonary infiltrates[4]	16/39 (41%)	9/42 (21%)	>0.05
Number of patients with CPIS > 6 at 3 days (%)	8/39 (21%)	9/39 (23%)	>0.05
Extra-pulmonary infection	7/39 (18%)	6/39 (15%)	>0.05
Antibiotic continuation > 3 days	11/39 (28%)	38/39 (97%)	0.0001
Antibiotic continuation in those with CPIS ≤6 at day 3[5]	0/25 (0%)	24/25 (96%)	0.0001

	<table><tr><td>Duration of antibiotic therapy[6]</td><td>3 [3]</td><td>9.8 [4-20]</td><td>0.0001</td></tr><tr><td>ICU LoS[7], days mean / median [range]</td><td>9.4/ 4 1-47</td><td>14.7/ 9 1-91</td><td>0.04</td></tr></table> <table><tr><th>Emergence of resistance and/or superinfection</th><th>Experimental group</th><th>Standard therapy group</th><th>P value</th></tr><tr><td>Resistance and/or superinfection in those surviving at least 7 days</td><td>5/37 (15%)</td><td>14/37 (35%)</td><td>0.017</td></tr><tr><td>Resistance and/or superinfection in all study patients</td><td>5/39 (13%)</td><td>14/42 (33%)</td><td>0.025</td></tr></table> Mortality at 30 days was significantly associated with patients with a CPIS > 6 at 3 days compared to those with a CPIS score of ≤6 at 3 days (47% compared to 16%, p=0.018).
Source of funding	
Comments	[1] Please note that this study did not achieve its desired sample size of 88 in each group (sample target size of 176). Please see footnote[3]. [2] Patients with a CPIS > 6 were treated with antibiotics for 10-21 days, In a pilot study by the authors a CPIS score of greater than 6 was associated with the exclusion of acute lung injury, pulmonary oedema, atelectasis, or contusion as causes of pulmonary infiltrates in ICU. [3] A trend was noted in this un-blinded study, by the authors, towards physicians prescribing fewer antibiotics and shorter durations in patients randomised to standard therapy. The study was terminated early following analysis. [4] Non significant results were also found for partial resolution, unchanged and worsening illness. [5] In patients without extra-pulmonary infection [6] Mean days [range] [7] Excluding patients who died, mean ICU length of stay was 8.7 days in the experimental group, compared to 14.7 days in the standard therapy group.

Evidence table 31: Oosterheert, JJ., Bonten, MJM., Schneider, MME. et al. (2006)

Bibliographic reference	Oosterheert, JJ., Bonten, MJM., Schneider, MME, et al. (2006) Effectiveness of early switch from intravenous to oral antibiotics in severe community acquired pneumonia: multicentre randomised trial. BMJ. 7th November
Study type	Multicentre open label randomised controlled trial
Study quality	Low
Number of patients	n=265[1] in the Intention to treat analysis, n=229 in a per protocol analysis
Patient characteristics	Adults aged 18 years or over, with severe community acquired pneumonia (CAP) admitted to general hospital wards (not requiring intensive care unit (ICU) therapy). Excluded were patients with cystic fibrosis, those requiring ICU care, history of colonisation with Gram negative bacteria, malfunction of the gastrointestinal tract, life expectancy <1 month, concomitant infection requiring antimicrobials and severe immunosuppression.
Intervention	n=132 in an intention to treat analysis (n=108 in per protocol analysis). Clinically stable patients[2], were switched from intravenous (IV) to oral antibiotics on day 3 after admission to hospital. Total duration of antibiotics was 10 days.
Comparison	n=133 in an intention to treat analysis (n=121 in per protocol analysis). A

<table>
<tr><td></td><td>standard regimen of 7 days IV antibiotic therapy, any additional therapy after 7 days was at the discretion of the treating physician according to Dutch treatment guidelines.</td></tr>
<tr><td>Length of follow up</td><td>Follow-up was at 28 days.</td></tr>
<tr><td>Location</td><td>Two university medical centres and 5 teaching hospitals in the Netherlands.</td></tr>
<tr><td>Outcomes measures and effect size</td><td>The primary outcome of the study was clinical cure[3]. The secondary outcome was hospital length of stay (LoS).

Intention to treat analysis
<table>
<tr><th>Clinical outcomes</th><th>Intervention (n=132)</th><th>Control (n=133)</th><th>Mean Difference [95% CI]</th></tr>
<tr><td>Clinical cure</td><td>110 (83%)</td><td>113 (85%)</td><td>2% [-7% - 10%]</td></tr>
<tr><td>Death after day 3</td><td>5 (4%)</td><td>8 (6%)</td><td>2% [-3% - 8%]</td></tr>
<tr><td>Clinical failure</td><td>22 (17%)</td><td>20 (15%)</td><td>-2% [-10% - 7%]</td></tr>
<tr><td>Hospital LoS, days[4]</td><td>9.6 (5.0)</td><td>11.5 (4.9)</td><td>1.9 (0.6 – 3.2)</td></tr>
<tr><td>Duration of IV therapy[4]</td><td>3.6 (1.5)</td><td>7.0 (2.0)</td><td>3.4 (2.8 – 3.9)</td></tr>
</table>
Per protocol analysis
<table>
<tr><th>Clinical outcomes</th><th>Intervention (n=132)</th><th>Control (n=133)</th><th>Mean Difference [95% CI]</th></tr>
<tr><td>Clinical cure</td><td>93 (86%)</td><td>101 (83%)</td><td>-3% [-12% - 7%]</td></tr>
<tr><td>Death after day 3</td><td>1 (1%)</td><td>8 (7%)</td><td>5% [0% - 12%]</td></tr>
<tr><td>Clinical failure</td><td>15 (14%)</td><td>20 (17%)</td><td>3% [-7% - 12%]</td></tr>
<tr><td>Hospital LoS, days[4]</td><td>9.0 (4.7)</td><td>11.3 (4.7)</td><td>2.3 (1.0 – 3.6)</td></tr>
<tr><td>Duration of IV therapy[4]</td><td>3.3 (1.1)</td><td>7.5 (2.0)</td><td>4.2 (3.7 – 4.6)</td></tr>
</table>
No data was presented on the emergence of resistance. IV therapy was in most cases amoxicillin or amoxicillin/clavulanic acid (58%) or a cephalosporin (20%) in line with Dutch treatment guidelines.</td></tr>
<tr><td>Source of funding</td><td>The study was funded by a grant from the Dutch Health Insurance Council.</td></tr>
<tr><td>Comments</td><td>[1] Please note that this study failed to recruit to its sample target size (n=500)
[2] Respiratory rate <25/min, O_2 saturation >90% or arterial oxygen pressure >55 mm Hg, haemodynamically stable, > 1°C decrease in temperature in case of fever, absence of mental confusion and the ability to take oral therapy.
[3] Clinical cure was defined as discharged in good health without signs and symptoms of pneumonia and no treatment failure during follow-up.
[4] Mean days (Standard deviation)</td></tr>
</table>

D.1.3 Decision making

Evidence table 32: Butler et al 2012

Bibliographic reference	Butler (2012) Effectiveness of multifaceted educational programme to reduce antibiotic dispensing in primary care: practice based randomised controlled trial
Study type	RCT (randomised using dynamic block allocation to achieve balance between groups of practices for potential confounders of previous rate of antibiotic dispensing, practice size and proportion of clinicians in the practice registered for the study)

	Study aim; to evaluate the effectiveness of a multifaceted flexible educational programme aimed at reducing antibiotic dispensing at the practice level in primary care
Study quality	
Number of studies	
Participant characteristics	General medical practices in Wales (2007, 2008); following discussion 70 of 212 practices contacted agreed to participate (2 of these ineligible/withdrew before randomisation) The previous year's antibiotic dispensing rate for the 68 practices randomised was about 15% lower than the Welsh average
Intervention	Stemming the Tide of Antibiotic Resistance (STAR) educational programme, 7 parts; Part 1, Online – clinicians asked to make judgements on 4 case scenarios. Reflected on antibiotic resistance, their decisions regarding antibiotic prescribing, provide with summaries of research evidence and guidelines, videos giving range of options Part 2, Online – clinicians reflected on decisions to prescribe antibiotics for 4 patients, other clinicians in the study could see the summaries Part 3, Face-to-face – a facilitator in a practice based seminar presented, and invited interpretation of, 7-year trends for antibiotic dispensing and resistance trends in all Wales, local area level, and the actual practice. The aim – to encourage prescribers to interpret data from their practice and consider appropriate responses Part 4, Online – repeated questions on 4 case scenarios from part 1, compared responses of other clinicians with their own. Four video scenarios were used to demonstrate the skills of "Lifting the lid" (identifying the main concerns and expectations of the patient), "Information exchange" (using a strategy from motivational interviewing to share information about the pros and cons of antibiotic use, prognosis, treatment and reconsulting), and "Wrap-Up" (acknowledging the patient's concerns, summarising the medical situation, clarifying reasons to reconsult, checking back with the patient) – these interactive invited clinicians to identify evidence of "good practice in an antibiotic consultation". Perspectives from patients, clinicians, and expert colleagues on the consultations were linked to supporting research evidence and guidelines Part 5, Clinical practice with reflection – with the principles of context bound learning, clinicians described 3 consultations in which they used the new consultation skills Part 6, Online – ongoing active web forum provided updates on emerging evidence, educators in the STAR study team could respond to queries, feedback and comments Part 7, Online – optional booster module (N=76 attended), 6-8months after initial training completion, reminded clinicians of previously outlined consultation skills, video of a consultation for a common infection – asked to identify key strategies used. Clinicians sent snapshot of their practice's antibiotic dispensing from 2 recent winter months compared with corresponding months before the programme started
Comparison	Not exposed to learning programme, provided care as usual
Length of follow up	Follow-up period started for each practice in the intervention group from the month after their practice based seminar (May to Oct 2007), and for next 12 months
Location	UK
Outcomes measures and effect size	Compared the two groups' annual rates of total oral antibiotic dispensing for all causes per 1000 practice patients within practices in the year after intervention, using analysis of covariance with the previous year's prescribing as a covariate (log transformed to produce approx. normally distributed data)

N=127/139 clinicians completed the programme
N=117/154 clinicians in the control practices

Primary outcome;
Rate of dispensing oral antibiotics for any cause over one year for the whole practice population

Secondary outcome;
Average hospital admission rates for specified complications between the two groups for the year

Results;
Antibiotic dispensing;

Intervention practices; reduced oral antibiotic dispensing by 14.1 items per 1000 registered patients
Control practices; increased oral antibiotic dispensing by 12.1 items per 1000 registered patients
Overall difference; 26.1 items per 1000 registered patients

In the practices where >67% of clinicians participated;
Intervention practices; average reduction in the follow-up year 17.7 items per 1000 registered patients
Remainder of intervention practices; average increase in the follow-up year 2.6 items per 1000 registered patients

	Mean at baseline		Mean at follow-up		% reduction, intervention relative to control (95% CI)[#]	P value
Outcome	Control	Intervention	Control	Intervention		
All antimicrobials*	669.0	678.1	681.1	664.0	4.2 (0.6 to 7.7)	0.02
All broad spectrum penicillins*	254.3	252.6	249.6	238.9	4.7 (-1.6 to 10.7)	0.14
Amoxicillin*	215.5	215.8	211.5	203.9	4.7 (-1.5 to 10.6)	0.13
Co-amoxiclav*	36.0	34.6	36.3	33.7	7.3 (-5.1 to 7.3)	0.23
Phenomethylpenicillin*	45.8	53.3	47.3	49.5	7.3 (0.4 to 13.7)	0.04
Cephalosporins*	53.7	50.0	55.6	49.5	2.3 (-8.0 to 11.6)	0.65
Macrolides *	73.9	76.4	76.7	73.7	7.7 (1.1 to 13.8)	0.02
Quinolones*	22.0	20.9	23.7	20.8	8.3 (-2.9 to 18.5)	0.14
Penicillinase-resistant penicillins	67.8	76.3	67.5	76.2	-3.4 (-12.3 to 4.8)	0.43
Trimethoprim	65.5	63.2	70.6	66.6	4.3 (-2.4 to 8.9)	0.24
Tetracyclines	57.0	57.3	60.3	58.5	4.7 (-1.5 to 10.6)	0.22
Hospital admissions[~]	8.7	7.7	8.0	7.5	-1.9 (-13.2 to 8.2)	0.72

*annual no of dispensed units for oral antibiotics per 1000 registered patients

	#difference in means in intervention group and control group as percentage of mean in control group ˜annual no of hospital episodes for possible respiratory tract infections and complications of common infections per 1000 registered patients **Re-consultation rates for respiratory tract infections**;

	Intervention N=20*	Control N=17*	Median difference (95%CI)	P value
Within 7days	2.66 (1.88 to 4.25)	3.35 (2.16 to 4.31)	-0.65 (-1.69 to 0.55)	0.446
Within 14days	5.10 (4.70 to 7.92)	6.43 (4.04 to 7.84)	-1.33 (-2.12 to 0.74)	0.411
Within 31days	9.06 (7.53 to 12.62)	11.38 (7.39 to 14.05)	-2.32 (-4.76 to 1.95)	0.503

	*values in each group refer to subset of intervention practices for which data on re-consultation were available.
Source of funding	UK Medical Research Council, National Institute for Health and Social Care Research
Comments	General practice as the unit of randomisation and analysis Main analysis was intention to treat (2 practices withdrew after randomisation)

Evidence table 33: Camins et al 2009

Bibliographic reference	Camins (2009) The impact of an antimicrobial utilization program on antimicrobial use at a large teaching hospital: a randomized controlled trial
Study type	RCT (No details reported of randomisation) Study aim, to determine the impact of an AUT on antimicrobial use at a teaching hospital
Study quality	
Number of studies	
Participant characteristics	953-bed urban teaching hospital 12 internal medicine teams, randomised monthly, 6 to each arm Inclusion; - prescribed selected antibiotics (piperacillin-tazobactam, levofloxacin, or vancomycin)
Intervention	N=390 Antimicrobial utilisation strategy; - Academic detailing by the antimicrobial utilization team (AUT) - AUT – infectious diseases physician, infectious diseases pharmacist - Provided structured verbal feedback to prescribing physicians on appropriateness of antimicrobial use AUT reviewed all prescriptions, to determine if the criteria for appropriate antimicrobial use were met, recommendations made for alternative therapy where needed, not communicated to the control group unless failure to do so could jeopardise the patient
Comparison	N=394 Antimicrobial utilisation strategy; - Indication-based guidelines for prescription of broad spectrum antimicrobials
Length of follow up	10-month study period (gives 60 team-months in each arm)
Location	USA
Outcomes measures and	Initial antibiotic use - <72hours of starting therapy – initiated for empiric coverage whole microbiologic results pending or for definitive therapy in which a pathogen

effect size

was already known

Empiric antimicrobial use – occurred with 72houts of initiation of therapy while microbiologic blood culture results were pending, or antimicrobial use in situations after 72hours of initiation when microbiologic cultures did not yield a pathogen

Definitive (therapeutic) antimicrobial use – at a time when microbiologic culture results and susceptibility data were available

End antimicrobial usage – final choice of regimen for the indication being treated – includes definitive use in which a pathogen was isolated or empiric use in which no pathogen was ever isolated or cultures were never obtained

Primary outcomes;

- proportion of appropriate prescriptions for empiric therapy
- proportion of appropriate prescriptions for definitive therapy
- proportion of appropriate end antimicrobial use

Secondary outcomes;

- volume of inappropriate antimicrobial use in daily defined doses (DDD)
- duration of inappropriate antimicrobial use in days
- hospital length of stay
- clinical outcome of in-hospital mortality

Results;

Appropriateness of antibiotic use;

	Intervention	Control	Risk ratio (95%CI)	P value
Appropriate initial antimicrobial use (<72hrs)	305/390 (78%)	229/394 (58%)	1.35 (1.22 to 1.49)	<0.001
Appropriate empiric antimicrobial use	242/294 (82%)	211/291 (73%)	1.14 (1.04 to 1.24)	0.005
Appropriate definitive antimicrobial use	92/112 (82%)	60/138 (43%)	1.89 (1.53 to 2.33)	<0.001
Appropriate end antimicrobial usage	367/390 (94%)	277/394 970%)	1.34 (1.25 to 1.43)	<0.001

Inappropriate antibiotic usage;

Median days of inappropriate use (range); intervention 2.0 (1 to 16), control 5.0 (1 to 20), p<0.001

Predictors for appropriate end antimicrobial usage (N=784), multivariate analysis

AUT intervention with infectious disease consultation; aRR 2.28 (95%CI, 1.64 to 3.19), p<0.001

AUT intervention without infectious disease consultation; aRR 1.37 (95%CI, 1.27 to 1.48), p<0.001

Infectious diseases consultation (alone); aRR 1.31 (95%CI, 1.14 to 1.51), p<0.001

Length of stay;

- median length of stay (range); intervention 7days (1 to 50), control 8days (2 to 86 days), p=0.03

In-hospital mortality;

- intervention N=11/390 (3%), control N=18/194 (5%), p=0.18

Source of funding

Grants from the Emory Medical Care Foundation and National Institutes of Health

Comments

Assuming a baseline proportion of inappropriate use for vancomycin (30%),

	levofloxacin (50%) and piperacillin/tazobactam (50%), 96 in team-months in each treatment arm would allow for a detection of a 6% reduction in suboptimal use (vancomycin), 11% (levofloxacin), 18% (piperacillin/tazobactam

Evidence table 34: Christakis et al 2001

Bibliographic reference	Christakis (2001) A randomized controlled trial of point-of-care evidence to improve the antibiotic prescribing practices for otitis media in children
Study type	RCT (Stratified randomisation using an electronic number generator, providers in 3 strata (N=29 residents, N=2 nurses, N=7 physicians)) Study aim, to test whether pertinent, timely, and relevant evidence to providers at the point of care could change their prescribing practices for otitis media
Study quality	
Number of studies	
Participant characteristics	38 providers caring for patients at an outpatient teaching clinic – included 1339 visits for otitis media
Intervention	6-month run-in period using prescription writer Evidence-based prompts On-line prescription writer developed to interface with the existing computerised patient flow manager - pop-up screens based on choice of antibiotic, indication and duration - first screen, 5-line summary of the evidence – at the bottom were options to see more information
Comparison	6-month run-in period using prescription writer No evidence-based prompts
Length of follow up	8 month study period
Location	USA
Outcomes measures and effect size	488 visits for otitis media during baseline 851 visits in the intervention period Primary outcome; - reduced duration of therapy below the 10-day course typically used **Results**; Baseline, 50.7% prescriptions written for <10days After intervention, 69.7% prescriptions written for <10days

<10days of antibiotics	Intervention N=537 visits (N=12 providers)	Control N=423 visits (N=16 providers)
Change in mean (before vs after) (SE)	44.43% (4.24%)	10.48% (5.25%)
P value	0.000	0.057

P value for the difference 0.000

No antibiotics for otitis media	Intervention N=751 visits (N=17 providers)	Control N=574 visits (N=18 providers)
Change in mean (before vs after) (SE)	-4.33% (5.15%)	-16.81% (5.09%)
P value	0.399	0.003

	P value for the difference 0.095 (baseline was summer, intervention autumn and winter)
Source of funding	Unclear (Packard Foundation thanked for supporting the project)
Comments	Noted that the small sample size that made it impossible to ensure complete comparability of the 2 groups at the start of the trial – did control for provider baseline prescribing practice The outcomes were expressed as a mean of provider behaviour, with varying work schedules there were differences in the numbers of otitis media visits between providers. All analyses were conducted using weights, in which each provider's actions contributed information to the analyses according to the precision with which the mean was estimated

Evidence table 35: Dranitsaris et al 2001

Bibliographic reference	Dranitsaris (2001) A randomized trial to measure the optimal role of the pharmacist in promoting evidence-based antibiotic use in acute care hospitals
Study type	RCT (stratified by hospital, randomised on a one-to-one basis via a computer generated list. The unit pharmacist and central pharmacy were aware of allocation, other medical personnel blinded) Study aim, to evaluate the optimal role of the pharmacist as an agent for promoting evidence-based antibiotic use in the acute care setting
Study quality	
Number of studies	
Participant characteristics	Two hospital sites Cefotaxime prescriptions that were written on units that were serviced by a clinical pharmacist (restricted antibiotics have to be approved by the infectious disease service – cefotaxime had recently had the restricted use label used) Cefotaxime prescription alone or with another antibiotic (patients could be enrolled >1 if cefotaxime was prescribed on two separate occasions) Inclusion; - Adults with infections requiring IV antibiotics Considered well distributed between the groups for age, sex, previous antibiotic therapy and site of infection. Not balanced for underlying disease, risk factors for infection and diagnosis
Intervention	N=162 Physician promoting and educational outreach by pharmacist – reviewed cefotaxime prescription to see if it was consistent with institutional guidelines – if not contacted physicians for therapeutic modification via a verbal reminder followed by educational outreach with physicians who had not modified therapy
Comparison	N=147 Non-intervention group
Length of follow up	6-month study
Location	Canada
Outcomes measures and effect size	Primary outcome; - Proportion of cefotaxime prescriptions that were consistent with hospital guidelines with respect to indication and dosage Clinical response; resolution of all signs and symptoms without treatment modification or switched to an oral antibiotic because of an adequate response

	Results; Cefotaxime prescriptions meeting guidelines; Criteria | Non-intervention (%) | Intervention (%) | P value Indication | 117/147 (80%) | 132/162 (81%) | 0.67 Dosage | 126/147 (86%) | 152/162 (94%) | 0.018 Overall | 102/147 (69%) | 122/162 (75%) | 0.24 Mean duration of therapy in days (SD) | 4.8 (4.6) | 4.3 (3.1) | 0.28 Multivariate analysis of appropriate prescribing | OR (95%CI) | P value Intervention vs non-intervention | 1.45 (0.79 to 2.68) | 0.23 Staff physician vs resident | 4.86 (1.42 to 15.58) | 0.012 Duration of therapy (days) | 1.11 (1.01 to 1.21) | 0.029 Patient age (yrs) | 1.04 (1.02 to 1.06) | 0.001 Renal insufficiency | 4.79 (1.88 to 12.18) | 0.001 Immunosuppression | 3.12 91.04 to 9.33) | 0.042
Source of funding	Not reported
Comments	Assuming an alpha of 5%, power of 80%, probability of appropriate prescribing with the intervention at 75% and without at 60% (absolute difference 15%) needed a sample size of 300

Evidence table 36: Fine et al 2003

Bibliographic reference	Fine (2003) Implementation of an evidence-based guideline to reduce duration of intravenous antibiotic therapy and length of stay for patients hospitalized with community-acquired pneumonia: a randomized controlled trial
Study type	Cluster RCT (randomisation stratified on practice type and group size/patient volume. Physicians and research nurses not blinded, patients not informed of physician treatment assignment) Study aim, to determine whether implementation of an evidence-based guideline would reduce duration of IV antibiotic therapy and length of stay for those hospitalised with pneumonia
Study quality	
Number of studies	
Participant characteristics	Seven hospital sites; - Physician groups with no admission in 1996 and non-pulmonary and non-infectious disease specialist groups with <2 pneumonia admissions per physician were excluded - Eligible patients, Feb 1998 to March 1999, community acquired pneumonia, >18years There were no significant differences in the physicians in the intervention and control groups with regard to age, sex, and medical speciality There were no significant differences in the patients in the intervention and control groups with regard to age, sex, ethnicity, nursing home residency and comorbid conditions
Intervention	N=283 patients managed by 277 physicians (57 groups) Both intervention and control groups received educational mailing of the medical practice guideline and hospital's utilisation management director's description of

	the rationale for the guideline Educational mailing to physicians (included letter from hospital's utilisation manager and a written version of the guideline), daily assessment of patient stability and multifaceted guideline intervention; Guideline intervention; - One of 3 site-specific detail sheets promoting the recommended actions (conversion to oral therapy, conversion and hospital discharge, discharge only) - Research nurse contacted the patient's physician to note that the guideline criteria had been met, to indicate that the detail sheet had been added, to take a verbal order for oral antibiotics
Comparison	N=325 patients managed by 268 physicians (59 groups) Educational mailing to physicians (included letter from hospital's utilisation manager and a written version of the guideline)
Length of follow up	
Location	USA
Outcomes measures and effect size	Primary outcomes; - Duration of IV antibiotics, length of hospital stay Results;

Outcome	Intervention Median (IQR)	Control Median (IQR)	HR (95%CI)	P value
Duration of IV therapy (days)	3.0 (2.0 to 5.0)	4.0 (2.0 to 6.0)	1.23 (1.00 to1.52)	0.06
Length of hospital stay (days)	5.0 (3.0 to 7.0)	5.0 (3.0 to 8.0)	1.16 (0.97 to1.38)	0.11

Source of funding	Agency for Healthcare Research and Quality, National Institute of Allergy and Infectious Diseases
Comments	Designed with 80% power to detect a 1-day decrease in length of stay from an assumed baseline of 7.2days, sample size adjusted for clustering on physician group assumed an average of 3.5patients per group All analysis based on ITT

Evidence table 37: Gerber et al 2012

Bibliographic reference	Gerber (2013) Effect of an outpatient antimicrobial stewardship intervention on broad-spectrum antibiotic prescribing by primary care paediatricians
Study type	Cluster RCT (block randomised practices (clusters) by location (urban, suburban, rural) and volume (encounters per year) Study aim, to evaluate the effect of an antimicrobial stewardship intervention on antibiotic prescribing for paediatric outpatients
Study quality	
Number of studies	
Participant characteristics	18 paediatric primary care practices (N=162 physicians) June 2010 to June 2011
Intervention	9 practices Clinical education; - 1-hour clinical education session by a member of the study team to outline study goals, provide updates on prescribing guidelines, and present practice

	specific prescribing data regarding these guidelines - Personalised audit and feedback of guideline-based antibiotic prescribing rates for the individual, the individual's practice and the network of enrolled practices. Feedback reports were personalised, private and delivered via email and mail
Comparison	9 practices Aware of participation in the study – no education or prescribing feedback
Length of follow up	12 month study period
Location	USA
Outcomes measures and effect size	Primary outcomes; - Change in broad-spectrum antibiotic prescribing for acute sinusitis, streptococcal pharyngitis and pneumonia - Change in antibiotic prescribing for viral infections Baseline taken for the 20months before the intervention Data obtained from electronic health record used by all practice sites **Results**; Antibiotic prescribing for any indication; - Intervention group; deceased from 26.8% to 14.3% (absolute difference 12.5%) - Control group; deceased from 28.4% to 22.6% (absolute difference 5.8%) - Difference of differences 6.7%; relative changes in trajectories of prescribing before and during the intervention (p=0.01) Antibiotic prescribing for pneumonia; - Intervention group; deceased from 15.7% to 4.2% - Control group; deceased from 17.1% to 16.3% - Difference of differences 10.7%; relative changes in trajectories of prescribing before and during the intervention (p=0.001) Antibiotic prescribing for acute sinusitis; - Intervention group; deceased from 38.9% to 18.8% - Control group; deceased from 40.0% to 33.9% - Difference of differences 14.0%; relative changes in trajectories of prescribing before and during the intervention (p=0.12) Antibiotic prescribing for streptococcal pharyngitis; - Intervention group; deceased from 4.4% to 3.4% - Control group; deceased from 5.6% to 3.5% - Difference of differences -1.7%; relative changes in trajectories of prescribing before and during the intervention (p=0.82) Antibiotic prescribing for viral infections; - Intervention group; deceased from 7.9% to 7.7% - Control group; deceased from 6.4% to 4.5% - Difference of differences -1.7%; relative changes in trajectories of prescribing before and during the intervention (p=0.93)
Source of funding	Agency for Healthcare Research and Quality
Comments	Unit of observation was the clinician, was randomised at practice level to avoid intrapractice contamination of the intervention. Power calculations, performed at cluster level suggested adequate power (>90%)

	to detect 10% point improvement in prescribing from the intervention.

Evidence table 38: Gjelstad et al 2013

Bibliographic reference	Gjelstad (2013) Improving antibiotic prescribing in acute respiratory tract infections: cluster randomised trial from Norwegian general practice (prescription peer academic detailing (Rx-PAD) study)
Study type	Cluster RCT Study aim, to assess the effects of a multifaceted educational intervention in general practice aiming to reduce antibiotic prescription rates for acute respiratory tract infections and to reduce the use of broad spectrum antibiotics
Study quality	
Number of studies	
Participant characteristics	N=79 groups (N=382 GPs) from existing continuing medical education groups
Intervention	N=39 continuing education groups (N=202 GPs)(about 10% of Norway's GPs) Specially trained GPs acting as academic detailers (all had the same training); - Each detailer responsible for 3 continuing education groups - Frist group meeting – presented the content of the national guidelines regarding appropriate use of antibiotics for acute respiratory infections, with recent research evidence - Participants encouraged to use delayed prescribing - Generated individual report to be sent to each GP showing prescription rates, distribution of different antibiotics for acute respiratory tract infection compared with corresponding averages from participating GPs – these were discussed at the second group meeting (group meetings Dec2005 to March 2006) - Regional one-day seminars with more in-depth teaching at the end of the intervention (Apr and May2006)
Comparison	N=41 continuing education groups (N=232 GPs) Difference intervention targeting prescribing practice for older patients, covering 13 criteria for potentially inappropriate drugs (not including antibiotics) - The intervention was based on the same procedures as for the antibiotic intervention – two group visits by the academic detailer, individual prescription reports and a one day seminar
Length of follow up	
Location	Norway
Outcomes measures and effect size	Outcomes; - Prescription rates - Proportion of non-penicillin V antibiotics Data from datasets that included total number of encounters with patients and all the GP antibiotic prescriptions for acute respiratory tract infections **Results**; Changes in rates of antibiotic prescriptions

Outcome	Intervention (N=39)	Control (N=40)
Mean (95%CI) proportion of acute respiratory tract infection episodes with antibiotic prescription		
Before intervention	31.7 (29.4 to 34.0)	32.7 (30.2 to 35.2)
After intervention	30.4 (27.9 to 32.8)	34.2 (31.5 to 37.0)

Change	-1.29 (-2.43 to -0.16), -4.1% (relative)	1.49 (0.58 to 2.40), 4.6% (relative)
Mean (95%CI) proportion of penicillin V		
Before intervention	45.0 (40.8 to 49.2)	45.2 (40.4 to 50.1)
After intervention	53.8 (49.2 to 58.3)	43.2 (38.1 to 48.2)
Change	8.74 (5.71 to 11.8), 19.4% (relative)	-2.03 (-3.75 to -0.30), -4.5% (relative)
Mean (95%CI) proportion of penicillins with extended spectrum		
Before intervention	11.4 (9.50 to 13.3)	11.8 (9.40 to 14.2)
After intervention	10.8 (8.38 to 13.2)	11.3 (9.19 to 13.3)
Change	-0.58 (-2.12 to-0.96), -5.1% (relative)	-0.55 (-1.73 to 0.64), -4.7% (relative)
Mean (95%CI) proportion of macrolides and lincosamides		
Before intervention	27.0 (24.0 to 29.9)	26.0 (23.0 to 29.0)
After intervention	23.7 (21.1 to 26.3)	28.9 (25.6 to 32.2)
Change	-3.28 (-5.40 to -1.16), -12.1% (relative)	2.92 (1.29 to 4.55), 11.2% (relative)
Mean (95%CI) proportion of tetracyclines		
Before intervention	15.4 (24.0 to 29.9)	15.7 (12.8 to 18.5)
After intervention	10.5 (8.18 to 12.9)	15.3 (12.4 to 18.1)
Change	-4.86 (-6.68 to -3.05), -31.6% (relative)	-0.39 (-1.55 to 0.76), -2.5% (relative)
Mean (95%CI) proportion of all other antibiotics in anatomical therapeutic chemical classification		
Before intervention	1.23 (0.74 to 1.71)	1.32 (0.85 to 1.78)
After intervention	1.21 (0.76 to 1.66)	1.36 (0.93 to 1.80)
Change	-0.02 (-0.40 to 0.37), -1.6% (relative)	0.05 (-0.33 to 0.42), 3.8% (relative)

After the intervention, adjusted OR for prescribing an antibiotic for acute respiratory tract infections 0.72 (95%CI; 0.61 to 0.84)

After the intervention, adjusted OR for prescribing a non-penicillin V antibiotic when an antibiotic was used was 0.64 (95%CI; 0.49 to 0.82)

Effect of intervention on independent categories associated with antibiotic prescribing;

(only type of acute respiratory tract infection reported in this ET)

Type of acute respiratory tract infection	No. of acute respiratory tract infection episodes after intervention	OR (95%CI) Antibiotic prescription rate	OR (95%CI) Proportion of non-penicillin V

	Upper respiratory tract infections and respiratory symptoms	71 791	0.68 (0.58 to 0.80)	0.64 (0.49 to 0.83)
	Acute tonsillitis	6710	0.79 (0.57 to 1.09)	1.19 (0.84 to 1.70)
	Acute sinusitis	10 131	0.97 (0.74 to 1.29)	0.53 (0.37 to 0.76)
	Acute bronchitis	12 543	0.66 (0.51 to 0.86)	0.50 (0.35 to 0.70)
	Pneumonia	8440	1.13 (0.87 to 1.46)	0.57 (0.41 to 0.80)
	Acute otitis media and ear pain	11 821	0.86 (0.69 to 1.09)	0.73 (0.50 to 1.07)
	Other respiratory tract infections	11 822	0.64 (0.49 to 0.82)	0.55 (0.37 to 0.80)
Source of funding	Norwegian Ministry of Health, the Norwegian Medical Association, the Research Council of Norway			
Comments	Power calculation based on what was considered to be a clinically significant reduction in total antibiotic prescribing rates. The sample size calculation was adjusted for cluster effects within the continuing medical education groups. Estimated a required intervention sample of 31 medical education groups and an equal number of controls to detect a 33% reduction in antibiotic prescribing rate with 80% power level			

Evidence table 39: Lesprit 2012

Bibliographic reference	Lesprit (2012) Clinical impact of unsolicited post-prescription antibiotic review in surgical and medical wards: a randomized controlled trial
Study type	RCT (open, computer-generated randomisation list, maintained independently of the infectious disease physician, allocation concealment – patient's physician and infectious disease physician involved after randomisation) Study aim, to evaluate the clinical impact of an unsolicited post-prescription review of selected antibiotic prescriptions in addition to other components of an antimicrobial stewardship programme
Study quality	
Number of studies	
Participant characteristics	General university hospital (6month study period) Inclusion; - Surgical and medical wards (71% of total hospital antibiotic prescription) - 15 selected antibiotics of intermediate or broad spectrum (47% of total antibiotic prescriptions of surgical and medical wards) - Treated with one of the targeted antibiotics for ≥3days (up to 5days if initiated in bank holiday periods) Exclusion; - If infectious disease physician advice had been requested within the first 3days of initiating therapy for the infectious episode considered - Have acute leukaemia - Expected survival <30days At baseline 2 groups similar in clinical and demographic characteristics, most prescriptions for respiratory, urinary, skin and soft tissue or digestive tract infections – no differences in this distribution between 2 groups (overall hospital

<table>
<tr><td></td><td>consumption prior to the study 650DDDs/1000 hospital days – in the low range of antibiotic consumption among French university hospitals in the Paris area)</td></tr>
<tr><td>Intervention</td><td>N=424
Post-prescription review by a single infectious disease physician – in addition to other components of the antimicrobial stewardship programme
- Provided oral recommendation to modify the antibiotic regimen when deemed appropriate – when could not be given directly recommendations were written in the medical chart
- Recommendations could be overridden – not further attempt was made if recommendations were not followed</td></tr>
<tr><td>Comparison</td><td>N=430
No prescription review
- Antibiotic management and re-evaluation by ward physician
- Could request advice from the infectious disease physician as needed</td></tr>
<tr><td>Length of follow up</td><td></td></tr>
<tr><td>Location</td><td>France</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Primary outcome;
- Length of hospital stay
Secondary outcome;
- In-hospital mortality
- ICU admission
- New course of antibiotic
- Relapse of the infection

Secondary exclusion of 102 patients;
Intervention, N=346/424 in analysis (N=48 did not receive intervention)
Control, N=377/430 in analysis

Infectious disease physician advice sought for N=30 (8%) of prescriptions in the control group
N=315/376 in the intervention group had infectious disease physician review

Results;
Duration of antibiotic therapy;
<table>
<tr><td>Median duration, days (IQR)</td><td>Control, N=377</td><td>Intervention, N=376</td><td>P value</td></tr>
<tr><td>Total antibiotic course</td><td>7 (5 to 9)</td><td>6 (4 to 9)</td><td><0.0001</td></tr>
<tr><td>Broad-spectrum antibiotic</td><td>4 (0 to 7)</td><td>2 (0 to 5)</td><td>0.0003</td></tr>
<tr><td>Narrow to intermediate spectrum antibiotic</td><td>4 (0 to 8)</td><td>5 (0 to 7)</td><td>0.13</td></tr>
<tr><td>Intravenous administration</td><td>4 (0 to 8)</td><td>3 (0 to 6)</td><td>0.004</td></tr>
<tr><td>Oral therapy</td><td>4 (0 to 7)</td><td>4 (0 to 7)</td><td>0.84</td></tr>
</table>
Clinical outcomes;
<table>
<tr><td></td><td>Control, N=377</td><td>Intervention, N=376</td><td>P value</td></tr>
<tr><td>Length of stay, days, median (IQR) – overall</td><td>15 (9 to 27)</td><td>15 (9 to 25)</td><td>0.95</td></tr>
<tr><td>Length of stay, days, median (IQR) – community acquired infection</td><td>6 (3 to 14)[#]</td><td>5 (3 to 10)[~]</td><td>0.06</td></tr>
<tr><td>60day in-hospital mortality</td><td>38</td><td>37 (9.8%)</td><td>0.91</td></tr>
</table></td></tr>
</table>

		(10.1%)		
	ICU admission within 7days of randomisation, N(%)	6 (1.6%)	7 (1.9%)	0.78
	New course of antibiotic therapy, N(%)	25 (6.6%)	17 (4.5%)	0.21
	Antibiotic treatment for relapsing infection, N(%)	30 (7.9%)	13 (3.4%)	0.01
	#N=260 ˜N=249			
Source of funding	Not reported			
Comments	Hypothesised that the intervention might result in a 20% reduction in hospitalisation Sample size estimated on previous observations that mean length of stay for patients treated with one of the targeted antibiotics was 15±7days, to detect a 20% reduction needed 506 (253 in each group)(80%)			

Evidence table 40: Linder 2009

Bibliographic reference	Linder (2009) Documentation-based clinical decision support to improve antibiotic prescribing for acute respiratory infections in primary care: a cluster randomised controlled trial
Study type	Cluster RCT (matched pairs randomised simultaneously, one to intervention, one to usual care) Study aim, to evaluate a decision support system (ARI Smart Form) in primary care clinics
Study quality	
Number of studies	
Participant characteristics	27 primary care clinics that use longitudinal medical records , matched on basis of size (excepting one clinic) Groups were similar with regard to patient characteristic of age, sex, ethnicity, language, income
Intervention	N=13 intervention practices (116 006 visits by 62 505 patients to 262 clinicians) ARI Smart Form – a longitudinal medical record that is launched from the notes page of an electronic health record (previously reported results of this toll included usability testing and pilot testing) – Nov 2005 to May2006 6 components; - Clinical information, patient data display, diagnosis section, presentation of treatment options with integrated decision support, printing of patient handouts and access to supporting medical literature Provides decision support via; - Antibiotic prescribing and antibiotic choices based on CDC and ACP (American College of Physicians) recommendations - Provides diagnostic decision support - Has medication prescribing alerts regarding potential medication interactions or patient allergies Visit to introduce the intervention, monthly reminder emails sent
Comparison	N=14 control practices (98 894 visits by 49 315 patients to 181 clinicians) Usual care
Length of follow up	30 day revisit rate

Location	USA
Outcomes measures and effect size	(antibiotic use defined as the prescription of an orally administered antibiotic agent within 3 days of an acute respiratory tract infection visit Acute respiratory infections visits identified using International Classification of Diseases Clinical Modification) Primary outcome; - Antibiotic prescribing rate for acute respiratory infection visits (based on electronic prescribing using the electronic record, using an intention-to-intervene analysis) Secondary outcome; - Antibiotic prescribing for antibiotic appropriate diagnoses, non-antibiotic appropriate diagnoses and individual acute respiratory diagnoses, 30-day revisit rate Data from longitudinal medical records Results; Antibiotic prescribing; - Antibiotics prescribed for acute respiratory infections; control group 4316/10007 (43%) of visits; intervention group 4601/11954 (39%) of visits; OR (95%CI) 0.8 (0.6 to 1.2), p=0.30 - Antibiotic appropriate acute respiratory infections; OR 0.8 (95%CI) 0.6 to 1.4 - Antibiotics prescribed for non-acute respiratory infections visits; control group 4727/88887 (5%) of visits; intervention group 5957/104052 (6%) of visits; OR (95%CI) 1.1 (0.9 to 1.3), p=0.30
Source of funding	Agency for Healthcare Research and Quality, National Heart, Lung and Blood Institute
Comments	Assuming a baseline antibiotic prescribing rate for acute respiratory infections of 35%, alpha of 0.05, 1798 visits in each group for an 80% power to detect a 7% absolute reduction in the antibiotic prescribing rate Intent-to-intervene analysis

Evidence table 41: McGregor 2006

Bibliographic reference	McGregor (2006) Impact of a computerised clinical decision support system on reducing inappropriate antimicrobial use: a randomised controlled trial
Study type	RCT (randomised according to their medical record number, even numbers to control arm, odd numbers to intervention arm, patients and healthcare providers blinded to randomisation) Study aim, to evaluate a web-based application designed to assist existing antimicrobial management teams to optimise patient antimicrobial therapy and minimise inappropriate and inadequate use
Study quality	
Number of studies	
Participant characteristics	Patients admitted to wards managed by the antimicrobial management team in a tertiary-care referral centre (May to August 2004) No significant differences between the intervention and control arms in age, sex, chronic disease score or whether they were admitted to medicine, surgery or other services A comparison of antimicrobials prescribed to ≥20 patients indicated no difference in the frequency of individual antimicrobial prescriptions between the 2 trial arms

<table>
<tr><td>Intervention</td><td>N=2237 patient admissions (N=1315, 58.8% received an antimicrobial)
Standard care by antimicrobial management team supplemented by web-based clinical decision support system (PharmWatch);
- Viewed alert list of patients who may require a change in current therapy – criteria for alerts based on the patient's antimicrobial use and microbiological results – 32 alerts created
- Accessing alerts could view lab results, medications, admission, discharge and transfer information in the system
- If change recommended – completed and printed a an intervention form that described the problem and recommended a change – verbally transmitted, or if not possible form was temporarily placed in the patient's chart</td></tr>
<tr><td>Comparison</td><td>N=2270 patient admissions (N=1325, 58.4% received an antimicrobial)
Standard care by antimicrobial management team;
Antimicrobial management team; infectious disease attending physician and clinical pharmacist ;
- Review list of all patient receiving antimicrobials on previous 24 hours
- Identifying those receiving the 23 restricted antimicrobials – charts reviewed, changes recommended
- Only intervened on those receiving restricted antimicrobials – not limited to make changes only to restricted antimicrobials
- Blinded from receiving system alerts on patients in the control arm

In both arms the primary treating team was responsible for making changes to therapy</td></tr>
<tr><td>Length of follow up</td><td>3-month study period</td></tr>
<tr><td>Location</td><td>USA</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Primary outcome;
- Antimicrobial costs (not reported in this ET)
Additional outcomes;
- Mortality
- Length of hospitalisation
- Frequency of testing for C. difficile (not reported in this ET)
- Time spent by team in antimicrobial utilisation (not reported in this ET)
Data from hospital Cerner pharmacy database

Results;
Intervention – intervened in 359 (16.0%) of the 570 (25.5%) patients with system alerts
Control – intervened in 180 (7.9%) of patients

In-hospital mortality , length of stay (days);
<table>
<tr><td>outcome</td><td>Intervention</td><td>Control</td><td>P value</td></tr>
<tr><td>In-hospital mortality (N(%))</td><td>73 (3.26%)</td><td>67 (2.95%)</td><td>0.55</td></tr>
<tr><td>Length of stay, days (median (IQR))</td><td>3.84 (2.12 to 7.57)</td><td>3.99 (2.19 to 7.57)</td><td>0.38</td></tr>
</table></td></tr>
<tr><td>Source of funding</td><td>National Institutes of Health grant and Maryland Industrial Partnerships grant</td></tr>
<tr><td>Comments</td><td>This study period was initially to interim analysis but stopped after this period and system implemented in all patient wards managed by the antimicrobial management team</td></tr>
</table>

Evidence table 42: Seager 2006

Bibliographic reference	Seager (2006) A randomised controlled trial of clinical outreach education to rationalise antibiotic prescribing for acute dental pain in the primary care setting
Study type	Cluster RCT (practices stratified prior to randomisation by level of antibiotic prescribing – randomisation via computer programme, practices assigned to 1 of 3 groups) Study aim, to assess the change in prescribing habits as a result of active patient-medicated and practitioner-mediated programmes
Study quality	
Number of studies	
Participant characteristics	General dental practitioners in 4 health authority areas in Wales The characteristics of the dental practitioners who returned questionnaires were similar in the different arms of the study Presenting complaints and findings similar across the 3 groups; excepting patients having a symptom of spreading infection; 19.0% (control), 23.1% (guideline), 24.5% (intervention), between intervention and control p=0.03
Intervention	2 groups – guideline and intervention N=20 (N=451 questionnaires) Guideline; - Educational material via post – guidelines for the management of acute dental pain, laminated page of summary of recommendations and patient information leaflets N=27 (N=556 questionnaires) Intervention; - Educational material via post – as for guideline group - Academic detailing visit (pharmacist who had been involved in the guideline development) – discussed the content of the guidelines and encourage the rationale use of antibiotics and analgesics in acute dental pain
Comparison	N=23 (N=490 questionnaires) Control – no intervention
Length of follow up	
Location	UK
Outcomes measures and effect size	Outcomes; - Number of prescriptions issues - Number of inappropriate prescriptions (considered to be inappropriate if the patient did not have symptoms indicative of spreading infection) Data collection via questionnaire – practitioners asked to complete if an >16years presented with acute dental pain N=27 practitioners dropped out after randomisation Patient satisfaction questionnaire, aimed to recruit 10% of patients – obtaining patient consent considered time consuming by practitioners, slow return rate, this section of the study discontinued – not reported in this ET)

Results;

All antibiotic prescriptions;

	Patients prescribed antibiotics		Patients prescribed antibiotics inappropriately	
	%	OR (95% CI)	%	OR (95% CI)
Control group (N=490)	32%	1	18%	1
Guideline group (N=451)	29%	0.83 (0.55 to 1.21)	15%	0.82 (0.53 to 1.29)
Intervention group (N=556)	23%	0.63 (0.41 to 0.95)	7%	0.33 (0.21 to 0.54)

Multivariate multilevel analysis;

(patient characteristics; age, gender, registration status – practitioner characteristics; gender, post-graduate qualification, number of years since qualification, population to whole time equivalents ratio)

		OR (95%CI)	P value
Prescribing	Intervention vs control	0.59 (0.57 to 0.93)	0.022
Prescribing	Guideline vs control	0.81 (0.50 to 1.30)	0.40
Age	Difference of 10 years	0.82 (076 to 0.98)	<0.0001

Multivariate multilevel analysis (without those variables for which the evidence of an association was weakest);

(patient characteristics; age, registration status – practitioner characteristics; post-graduate qualification)

		OR (95%CI)	P value
Prescribing	Intervention vs control	0.62 (0.40 to 0.97)	0.033
Prescribing	Guideline vs control	0.83 (0.55 to 1.35)	0.47
Age	Difference of 10 years	0.82 (076 to 0.98)	<0.0001

Source of funding	NHS National R&D Programme on Primary Dental Care
Comments	Cluster sampling, practice (not practitioner) was the unit of randomisation, 30 practitioners into each arm providing date on 30 patients from each practitioner, 90% power to detect a change of one third in the prescribing rate, from 28% to 18%

Evidence table 43: Shojania 1998

Bibliographic reference	Shojania (1998) Reducing vancomycin use utilizing a computer guideline
Study type	RCT (randomisation via even and odd numbers) Study aim, to determine whether the computer intervention would reduce vancomycin ordering
Study quality	
Number of studies	
Participant characteristics	N=396 physicians, tertiary-care hospital, June 1996 to March 1997 Distribution of physicians between departments balanced between intervention and control No significant differences between group physicians with regard to length of stay of their patients or the services on which patients received their care
Intervention	N=198

<table>
<tr><td></td><td>Showing computerised guidelines for vancomyicn ordering at the time of prescribing and after 72hours of therapy;
- Clinician in the intervention group requested vancomycin, initial screen contained an adaption of the indications for vancomycin use
- Asked for indication for continuing therapy after 72hours</td></tr>
<tr><td>Comparison</td><td>N=198
Control;
- Usual screen computer for ordering
- Asked at 72hours to renew or discontinue therapy</td></tr>
<tr><td>Length of follow up</td><td></td></tr>
<tr><td>Location</td><td>USA</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Primary outcome;
- Number of vancomycin prescriptions
- Duration of therapy
Secondary outcome;
- Utilisation of vancomycin in the hospital (not reported in this ET)
Data from computer log containing all the vancomycin prescriptions

Results;
Vancomycin use;
<table>
<tr><td></td><td>Control (N=174)</td><td>Intervention (N=174)</td><td>P value</td></tr>
<tr><td>Patients per physician prescribed vancomycin; mean (SD)</td><td>10.3±15.1</td><td>7.4±11.4</td><td>0.02</td></tr>
<tr><td>Patients per physician prescribed vancomycin; median (IQR)</td><td>4.0 (1.0 to 12)</td><td>3.0 (1.0 to 9.0)</td><td></td></tr>
<tr><td>Vancomycin days per physician; mean (SD)</td><td>41.2±76.7</td><td>26.5±47.6</td><td>0.05</td></tr>
<tr><td>Vancomycin days per physician; median (IQR)</td><td>11 (3.3 to 44)</td><td>7.5 (2.8 to 32)</td><td></td></tr>
<tr><td>Duration of therapy; mean (SD)</td><td>2.0±1.1</td><td>1.8±1.1</td><td>0.05</td></tr>
<tr><td>Duration of therapy; median (IQR)</td><td>1.8 (1.4 to 2.4)</td><td>1.7 (1.2 to 2.2)</td><td></td></tr>
</table>
Piecewise linear regression analysis of the percentage of patients who received vancomycin ≥once – showed that both the slope (p=0.04) and vertical intercept (p=0.01) changed significantly (note the pre-period was Sept to June, the intervention period was June to March)</td></tr>
<tr><td>Source of funding</td><td>Not reported</td></tr>
<tr><td>Comments</td><td>The authors note the possibility that physicians in the intervention group could learn about the intervention from those in the study group
Results for the numbers of orders and ordering rates reported as means (SD) as well as medians (IQR) as results non-normal and the expectation that far outliers would have an influence on the overall amount of vancomycin used</td></tr>
</table>

Evidence table 44: Solomon 2001

Bibliographic reference	Solomon (2001) academic detailing to improve use of broad-spectrum antibiotics at an academic medical center
Study type	RCT (block randomisation, interns/residents were not aware their ordering patterns were being studied) Study aim, to determine whether one-on-one education by clinical specialists on a

	patient-specific basis (academic detailing) could reduce excessive use of broad-spectrum antibiotics
Study quality	
Number of studies	
Participant characteristics	Medical-surgical service, one hospital Patient characteristics in both sets of services were similar and did not differ between baseline and study periods Study period Jan 1999 to May 1999 (18weeks, baseline 4 weeks prior)
Intervention	Intervention prompted by prescription for levofloxacin or ceftazidime – the hospital infectious diseases division had developed guidelines for first-line antibiotic therapy – these were disseminated to all house officers All orders for these drugs reviewed by a research assistant In the intervention levofloxacin or ceftazidime orders considered to be unnecessary prompted academic detailers to review fill medical record and contact the intern/resident Educational intervention; - Academic detailing (clinician educators, infectious diseases physicians, specially trained clinical pharmacist) - Presented information directly(in person or via phone) to intern/resident on a case-relevant basis, stressing microbiologic data, local resistance patterns and clinical literature - Provided copy of guidelines and made suggestions for alternative regimes Final drug choice down to interns/residents
Comparison	Control
Length of follow up	
Location	USA
Outcomes measures and effect size	Primary outcome; - Average number of days of unnecessary levofloxacin or ceftazidime administration during each 2week interval Secondary outcomes; - Length of admission, mortality, rehospitalisation (not reported in this ET), ICU transfer (not reported in this ET) Prescribing data taken from the hospital's computerised pharmacy records N=278 unnecessary prescriptions in N=260 patients; indications for treatment or presumed sources of infection ere similar between the intervention and control groups **Results**; Baseline, number of days of unnecessary target antibiotic use per 2 week interval; - Intervention (mean ± SD) 8.5±7.8; control 7.6±4.7; p=0.80 Study period, number of days of unnecessary target antibiotic use per 2 week interval; - Intervention (mean ± SD) 5.5±2.1; control 8.8±42.2; p<0.001 - Multivariate analysis (accounting for repeated measures of target antibiotics and baseline prescribing) showed unnecessary use reduced by 41% for intervention compared with controls (95%CI, 44% to 78%), p<0.001 Secondary outcomes; Outcome | Intervention (N=2624) | Cont

	Average length of admission, days, mean±SD	4.8±6.0	4.8±5.5
	Death during admission, %	2.3	2.2
Source of funding	Brigham and Women's Hospital, Arthritis Foundation Investigator Award		
Comments	Analyses ITT Several services had unusually heavy prescribing during certain 2week blocks – to examine these analyses done after removing these outliers , results were nearly identical, so analyses using all data points presented		

Evidence table 45: Spurling 2013

Bibliographic reference	Spurling (2013) Delayed antibiotics for respiratory infections (Cochrane)
Study type	SR Study aim, to evaluate the use of delayed antibiotics compared to immediate or no antibiotics as a prescribing strategy for acute respiratory tract infections
Study quality	
Number of studies	Overall review; N=10 studies, N=3157 participants
Participant characteristics	RCTs Inclusion; - Patients of all ages defined as having acute respiratory tract infections
Intervention	Delayed antibiotic use; - A strategy involving the use or advice to use antibiotics more than 48hours after the initial consultation
Comparison	Immediate antibiotic use; - The immediate use of a prescription of oral antibiotics given at the initial consultation No antibiotic use; - No prescription of antibiotics at the initial consultation
Length of follow up	
Location	
Outcomes measures and effect size	Primary outcomes; - Clinical outcomes for sore throat, acute otitis media, bronchitis and common cold - Antibiotic use - Patient satisfaction (where measured on a 4 to 6 point Likert scale) - Antibiotic resistance Secondary outcomes; - Adverse effects of antibiotics - Complications of disease (not reported in this ET) - Re-consultation - Use of alternative therapies (not reported in this ET) Meta-analysis for antibiotic use not completed due to heterogeneity of included study results, likely owing to difference antibiotic indications for different clinical presentations.

Results;

Study summary;

Arroll (2002)	Adults and children	Common cold	Delayed antibiotics (given prescription and instructed to fill within 72hours) compared with immediate antibiotics
Dowell (2001)	Adults and children	Cough	Delayed antibiotics (prescription left at reception and instructed to pick up after 1week delay) compared with immediate antibiotics
Little (1997)	Adults and children	Sore throat	Delayed antibiotics (prescription left at reception and instructed to pick it up after 72hours) compared with immediate antibiotics compared with no antibiotics
Little (2001)	Children 6months to 10years	Otitis media	Delayed antibiotics (72hours, parents advised to use antibiotics if child had significant otalgia or fever after 72hours, or if discharge lasted 10days or more) compared with immediate antibiotics
Little (2005)	Adults and children >3years	Cough and ≥1 symptom/sign localising to lower respiratory tract	Delayed antibiotics (prescription left at reception and instructed to pick up after 14days) compared with immediate antibiotics compared with no antibiotics
Spiro (2006)	Children 6months to 12years	Acute otitis media	Delayed antibiotics (given prescription which was to expire after 72hours) compared with immediate antibiotics

Studies excluded from this Cochrane;

- Chao (2008), no antibiotics compared with delayed prescribing
- El-Daher (1991), study designed to consider relapse rates, no antibiotic use outcomes
- Gerber (1990), study designed to consider relapse rates, no antibiotic use outcomes
- Pichichero (1987), study designed to consider relapse rates, no antibiotic use outcomes

Antibiotic use;

Prescription at time of visit

Reference	Delayed antibiotics	Immediate antibiotics	OR (95%CI)
Arroll (2002)	N=32/67 (47.8%)	N=55/67 (82.1%)	0.20 (0.09 to 0.44)
Spiro (2006)	N=50/132 (37.9%)	N=116/133 (87.2%)	0.09 (0.05 to 0.17)

Return for prescription

Reference	Delayed antibiotics	Immediate antibiotics	OR (95%CI)
Dowell (2001)	N=43/95 (45.3%)	N=92/93 (98.9%)	0.00 (0.00 to 0.07)
Little (1997)	N=55/176 (31.3%)	N=210/211 (99.5%)	0.00 (0.00 to 0.02)
Little (2001)	N=36/150 (42%)	N=132/151 (87.4%)	0.05 (0.02 to 0.08)
Little (2005)	N=39/197 (19.8%)	N=185/193 (95.9%)	0.01 (0.00 to 0.02)

Clinical outcomes;

Reference	Outcomes	Delayed antibiotics	Immediate antibiotics	OR (95%CI)
Little (2001)	Acute otitis media, pain, day3	N=28/111	N=15/101	1.93 (0.96 to 3.88)
Little (2001)	Acute otitis media, pain, day7	N=3/111	N=0/101	6.55 (0.33 to 128.35)
Spiro (2006)	Acute otitis media, pain, days4 to 6	N=85/132	N=89/133	0.89 (0.54 to 1.48)
Spiro (2006)	Acute otitis media, fever, days4 to 6	N=42/132	N=46/133	0.88 (0.53 to 1.47)
Arroll (2002)	Common cold, pain, day3	N=13/61	N=9/58	1.47 (0.58 to 3.77)
Arroll (2002)	Common cold, pain, day7	N=1/61	N=3/58	0.31 (0.03 to 3.03)
Arroll (2002)	Common cold, fever, day3	N=5/67	N=6/62	0.75 (0.22 to 2.60)
Arroll (2002)	Common cold, fever, day7	N=3/67	N=4/62	0.68 (0.15 to 3.17)
Arroll (2002)	Common cold, cough, day3	N=54/67	N=51/62	0.90 (0.37 to 2.18)
Arroll (2002)	Common cold, cough, day7	N=41/61	N=43/58	0.72 (0.32 to 1.58)

Reference	Outcomes	Delayed antibiotics	Immediate antibiotics	Mean difference (95%CI)
Little (2001)	Acute otitis media, pain severity, day3 (mean (SD))	N=111 2.56 (2.14)	N=102 1.81 (1.44)	0.75 (0.26 to 1.24)
Little (2001)	Acute otitis media, pain severity, day7 (mean (SD))	N=111 1.17 (0.75)	N=101 1.05 (0.38)	0.12 (-0.04 to 0.28)
Arroll (2002)	Common cold, fever severity, day1 (mean (SD))	N=67 36.74 (0.65)	N=61 36.87 (0.68)	-0.13 (-0.36 to 0.10)
Arroll (2002)	Common cold, fever severity, day3 (mean (SD))	N=61 36.15 (0.73)	N=58 36.39 (0.58)	-0.24 (-0.48 to 0.00)
Arroll (2002)	Common cold, fever severity, day7 (mean (SD))	N=59 36 (0.77)	N=60 36.32 (0.58)	-0.32 (-0.57 to -0.07)

Adverse events;

Reference	Outcomes	Delayed antibiotics	Immediate antibiotics	OR (95%CI)
Little (1997)	Vomiting	N=15/179 (8.4%)	N=18/215 (8.4%)	1.00 (0.49 to 2.05)
Spiro (2006)	Vomiting	N=15/132 (11.4%)	N=15/133 (11.3%)	1.01 (0.47 to 2.16)
Arroll (2002)	Diarrhoea	N=11/67 (16.4%)	N=12/62 (19.4%)	0.82 (0.33 to 2.02)
Little (1997)	Diarrhoea	N=23/179	N=23/215	1.23 (0.67 to

		(12.9%)	(10.7%)	2.28)
Little (2001)	Diarrhoea	N=14/150 (9.3%)	N=25/135 (18.5%)	0.45 (0.22 to 0.91)
Spiro (2006)	Diarrhoea	N=10/132 (7.6%)	N=31/133 (23.3%)	0.27 (0.13 to 0.58)
Little (1997)	Rash	N=11/180 (6.1%)	N=14/215 (6.5%)	0.93 (0.41 to 2.11)
Little (2001)	Rash	N=8/150 (5.3%)	N=6/135 (4.4%)	1.21 (0.41 to 3.58)
Little (1997)	Stomach ache	N=48/180 (26.7%)	N=66/215 (30.7%)	0.82 (0.53 to 1.27)

Patient satisfaction;

Meta-analysis;

Patient satisfied;

Reference	Delayed antibiotics	Immediate antibiotics	OR (95%CI)
Prescription at time of visit			
Arroll (2002)	N=64/67	N=55/67	1.47 (0.09 to 0.44)
Return for prescription			
Dowell (2001)	N=71/73	N=75/75	0.19 (0.01 to 4.01)
Little (1997)	N=165/177	N=202/211	0.61 (0.25 to 1.49)
Little (2001)	N=115/150	N=123/135	0.32 (0.16 to 0.65)
Little (2005)	N=147/190	N=166/194	0.58 (0.34 to 0.97)
Total	N=657	N=677	0.52 (0.35 to 0.76)

Source of funding	
Comments	

Evidence table 46: Aabenhus et al (2014), point-of-care

Bibliographic reference	Aabenhus (2014) Biomarkers as point-of-care tests to guide prescription of antibiotics in patients with acute respiratory infections in primary care (Cochrane)
Study type	Systematic review and meta-analysis Study aim; to assess the benefits and harms of point-of-care biomarker tests of infection to guide antibiotic treatment in patients presenting with symptoms of acute respiratory infections in primary care settings, regardless of age
Study quality	Consideration of the overall quality of the evidence according to GRADE is moderate
Number of studies	6 RCTs and cluster RCTs, N=3284 participants
Participant characteristics	RCTs Primary care patients, all ages, with symptoms from, or a diagnosis of an acute respiratory infection at study entry; - Symptoms were defined as cough, discoloured/increased sputum, fever, runny nose, respiratory distress, feeling unwell, or combinations of focal and systemic symptoms having a duration of less than 4weeks - Diagnoses included lower or upper respiratory tract infection, pneumonia, bronchitis, acute exacerbations of chronic obstructive pulmonary disease or asthma, pharyngitis, tonsillitis, laryngitis, rhinosinusitis, common cold, acute otitis media or influenza - Studies of biomarkers point-of-care

Intervention	Point-of-care biomarkers (available for general use) of infection to guide antibiotic treatment for acute respiratory tract infection in primary care settings
Comparison	Standard care
Length of follow up	
Location	
Outcomes measures and effect size	Primary outcomes: - number of patients given an antibiotic prescription at the index consultation and at 28days follow-up - number of patients with substantial improvement at day 7 - total mortality at 28days follow-up Secondary outcomes; - number of patients in need of reconsultation at 28days follow-up - number of patients in need of a hospital admission at 28days follow-up - duration of acute respiratory infection - number of satisfied patients - number of patients with substantial improvement at 28days follow-up Tested for subgroup effects – preplanned subgroup analysis; cluster-RCT vs individual RCTs; type of point-of-care test; trials with low risk of bias vs trials with high risk of bias. Unit of analysis was the individual patient, for cluster RCT adjusted the unit of analysis by calculating the design effect to modify sample sizes and inflate confidence intervals (CIs) accordingly. Investigated heterogeneity using I^2 with a cut-off value of 40% to indicate important inconsistency. **Included studies**;

Reference	Participants	CRP
Andreeva (2013), cluster RCT – sample size modified	8 GP offices, Russia Included: >18years lower respiratory tract infection/acute cough (including acute bronchitis, pneumonia, infectious exacerbations of COPD or asthma for <28days N=179	Single point-of-care measurement, Afinion test system (Axis-Shield, Norway) <20mg/L – antibiotics not usually needed >50mg/L – antibiotic prescribing could be indicated, taking into account the duration of illness
Cals (2009), cluster RCT	20 primary care practices, the Netherlands >18years Suspected lower respiratory tract infection (cough <4weeks and 1 focal and 1 systemic symptom or sign)	Single point-of-care measurement <20mg/L – bacterial infection considered highly unlikely, prescribing discouraged 20 to 99mg/L – delayed prescribing recommended >100mg/L – bacterial infection considered likely, immediate antibiotic prescribing recommended
Cals (2010), RCT	11 primary care practices, The Netherlands Included:	Single point-of-care measurement <20mg/L – antibiotic prescribing

	>18years lower respiratory tract infection (cough<4weeks) and specified signs/symptoms rhinosinusitis (<4weeks) and specified sign/symptoms	discouraged 20 to 99mg/L – consider delayed prescribing >100mg/L – immediate antibiotic prescribing recommended
Diederichsen (2000), RCT	35 primary care practices, Denmark Included: Respiratory infection (no further details)	<10mg/L – normal <50mg/L – seldom a result of bacterial infection

Studies included in the Cochrane review, excluded in this ET;

- Little (2013) – interventions based on training, not relevant
- Melbye (1995) – not in English

Results;

	CRP	Control	RR (95%CI)
Antibiotics prescribed at index consultation			
Andreeva (2013)*	N=18/49	N=22/38	0.63 (0.40 to 1.00)
Cals (2009)*	N=20/65	N=31/59	0.59 (0.38 to 0.91)
Cals (2010)	N=56/129	N=73/129	0.77 (0.60 to 0.98)
Diederichsen (2000)	N=179/414	N=184/398	0.94 (0.80 to 1.09)
Total	N=657	N=624	0.77 (0.62 to 0.95)
Antibiotics prescribed within 28days			
Andreeva (2013)*	N=20/49	N=27/38	0.57 (0.39 to 0.85)
Cals (2009)*	N=29/65	N=34/59	0.77 (0.55 to 1.10)
Cals (2010)	N=68/129	N=84/129	0.81 (0.66 to 1.00)
Substantially improved at day7			
Cals (2010)	N=27/118	N=31/125	1.03 (0.89 to 1.18)
Diederichsen (2000)	N=251/407	N=252/394	1.12 (0.93 to 1.34)
Re-consultations within 28days			
Andreeva (2013)*	N=3/93	N=3/72	0.77 (0.16 to 3.72)
Cals (2009)*	N=66/188	N=51/169	1.16 (0.86 to 1.57)
Cals (2010)	N=33/129	N=23/129	1.43 (0.89 to 2.30)
Clinical recovery day28			
Andreeva (2013)*	N=60/64	N=48/51	0.94 (0.69 to 1.28)
Cals (2009)*	N=76/102	N=69/91	1.05 (0.64 to 1.73)

*cluster-randomised, modified sample size

Patient satisfaction			
Cals (2009)*	N=159/227	N=136/204	0.90 (0.68 to 1.19)
Cals (2010)	N=90/118	N=79/125	0.64 (0.43 to 0.96)
Total	N=345	N=329	0.79 (0.57 to 1.08)

Source of funding	
Comments	

Table 47: Baer et al (2013), point-of-care

Bibliographic reference	Baer (2013) Procalcitonin guidance to reduce antibiotic treatment of lower respiratory tract infection in children and adolescents (ProPAED): a randomised controlled trial
Study type	RCT (pre-specified computer-generated 1:1 randomisation, allocation concealed via web-based online patient registration) Study aim, to investigate whether PCT guided treatment can reduce antibiotic prescribing rate and duration of treatment in lower respiratory tract infection presenting to an emergency department (using cut-off ranges established in adults)
Study quality	
Number of studies	
Participant characteristics	January 2009 to February 2010 Inclusion; - 1month to 18years - Presenting with lower respiratory tract infection for <14days (presence of fever and ≥1 symptom (cough, sputum production, pleuritic pain, poor feeding) and ≥1 sign (tachypnoea, dyspnoea, wheezing, late inspiratory cackles, bronchial breathing, pleural rub) in the emergency department of two hospital - Regardless of antibiotic treatment history Exclusion; - Severe immunosuppression, immunosuppressive treatment, neutropenia, cystic fibrosis, acute croup, hospital stay within previous 14days, other serious infection Baseline characteristics of randomised patients were similar in both groups
Intervention	N=168 Serum PCT measured by B.R.A.H.M.S. PCT sensitive Kryptor; rapid sensitive assay, assay time <30minutes PCT based decision categories, likelihood of needing antibiotic treatment for bacterial lower respiratory tract infection (based on previous trials in adults with lower respiratory tract infection); - Definitely; >0.5µg/L - Probably; 0.26 to 0.5µg/L - Probably not; 0.1 to 0.25µg/L - Definitely not; <0.1µg/L PCT measurement and clinical re-evaluation on days 3 and 5
Comparison	N=169 Control – antibiotic treatment initiated based on physician assessment and clinical guidelines for a duration of 7 to 10days for uncomplicated community-acquired pneumonia and ≥14days for complicated community-acquired pneumonia
Length of follow	

up

Location Switzerland

Outcomes measures and effect size

Primary outcome;
- Antibiotic prescribing rate

Secondary outcome;
- Duration of treatment
- Side effects
- Hospitalisation
- Serious AEs, complications, disease specific failure
- Impairment of daily activities (not reported in this ET)

Rate difference and OR by logistic regression (model included an interaction term between therapeutic group and diagnosis (CAP vs non-CAP) to obtain estimate effects of PCT in the two pre-specified subgroups

N=167/168 intervention and N=162/169 control completed 14day interview

Results;

Antibiotic prescribing;

Received antibiotics;
- PCT group N=104/168 (62%); control group N=93/156 (56%)
- For receiving antibiotics within 14days of randomisation PCT vs control, 1.26 (0.81 to 1.95)

Subgroups:

Non-community-acquired pneumonia	**PCT group N=60**	**Control group N=62**	**Rate difference, % (95%CI)**	**OR (95%CI)**	**Mean difference (95%CI)**
Antibiotic prescription (within 14days), N (%)	N=60 27 (45%)	N=60 10 (17%)	28 (12 to 43)	4.09 (1.80 to 9.93)	
Duration of antibiotics (days), mean (median, IQR)	N=59 2.4 (0; 0 to 5)	N=60 1.6 (0; 0 to 0)			0.8 (-0.5 to 2.0)
Antibiotic side effects, N (%)	N=54 14 (26%)	N=58 6 (10%)	16 (1 to 30)	3.03 (1.11 to 9.22)	
Duration of side effects (days), mean (median, IQR)	N=54 1.0 (0; 0 to 0.8)	N=58 0.5 (0; 0 to 0)			0.5 (-0.2 to 1.2)
Hospitalisation, N (%)	N=60 37 (62%)	N=60 32 (53%)	8 (-9 to 25)	1.41 (0.68 to 2.93)	
Duration of hospitalisation, mean (median, IQR)	N=60 2.5 (2; 0 to 4)	N=60 2.3 (2; 0 to 4)			0.3 (-0.8 to 1.2)
Safety, N (%)	N=60 15 (25%)	N=60 13 (22%)	3 (-12 to 18)	1.21 (0.52 to 2.85)	
Community-acquired pneumonia	**PCT group N=108**	**Control N=107**			

	Antibiotic prescription (within 14days), N (%)	N=108 77 (71%)	N=105 83 (79%)	-8 (-19 to 4)	0.66 (0.35 to 1.23)	
	Duration of antibiotics (days), mean (median, IQR)	N=-108 5.7 (5; 0 to 9)	N=104 9.1 (10; 4.5 to 12.3)			-3.4 (-4.9 to -1.7)
	Antibiotic side effects, N (%)	N=90 42 (47%)	N=91 51 (56%)	-9 (-23 to 5)	0.69 (0.38 to 1.23)	
	Duration of side effects (days), mean (median, IQR)	N=90 1.7 (0; 0 to 2)	N=91 1.8 (1; 0 to 3)			-0.1 (-0.9 to 0.6)
	Hospitalisation, N (%)	N=108 67 (62%)	N=107 68 (64%)	-2 (-14 to 11)	0.94 (0.54 to 1.63)	
	Duration of hospitalisation, mean (median, IQR)	N=107 2.6 (2; 0 to 4)	N=104 2.9 (2; 0 to 5)			-0.3 (-1.1 to 0.5)
	Safety, N(%)	N=108 23 (21%)	N=107 20 (19%)	2 (-9 to 13)	1.14 (0.58 to 2.24)	
	Combined safety endpoint; SAE, complications of lower respiratory tract infection, disease specific failure) Combined safety endpoint; - Rate difference PCT vs control, 2% (95%CI; -6 to 11), OR 1.16 (95%CI; 0.69 to 1.97)					
Source of funding	The Division of Infectious Diseases and Vaccines, University Children's Hospital, Basel, Switzerland Procalcitonin test kits and platform were provided by B.R.A.H.M.S.					
Comments	Sample size assumed PCT guidance would reduce prescribing from 90% to 60% (community-acquired pneumonia) and from 30% to 15% (non-community-acquired pneumonia), 64 (CAP) and 242 (non-CAP) had to be included for 80% power, assuming 20% would have CAP, total sample size 320 to give 93% power to detect a decrease in antibiotic prescribing from 42% (control) to 24% (PCT) for all patients Intention to treat analysis					

Table 48: Esposito et al (2011), point-of-care

Bibliographic reference	Esposito (2011) Procalcitonin measuremetns for guiding antibiotic treatment on pediatric pneumonia
Study type	RCT (randomisation by previously prepared computer-generated randomisation list and sealed envelope) Study aim, to evaluate the use of an algorithm based on a PCT cut-off value to guide the management of antibiotic therapy in hospitalised children with uncomplicated community-acquired pneumonia
Study quality	
Number of studies	
Participant characteristics	Consecutive children who were hospitalised with community-acquired pneumonia in 1 hospital, Oct 2008 to Sept 2010 Inclusion; - >1month to <14years, diagnosis of community-acquired pneumonia made on

	clinical signs and symptoms (history of fever/cough, tachypnoea, dyspnoea/respiratory distress, breathing with grunting/wheezingsounds with rales) and confirmed by chest radiography, no demonstrable complications Exclusion; - Antibiotics in the 10days before admission - Underlying chronic disease, severe malnutrition, other concurrent infections PCT and control groups comparable in terms of gender, mean age, race, mean number of respiratory infections in their history, number of antibiotic course in last 6months, urban residence, number of siblings, duration of breast-feeding, exposure to cigarette smoke, child-care attendance, history of allergy, previous hospitalisations, previous vaccinations against pneumococcal infections and influenza.
Intervention	N=155 Procalcitonin-guided treatment; - Initially <0.25ng/mL – no antibiotics, if increased to ≥0.25ng/mL given antibiotics - Initially ≥0.25ng/mL – immediate antibiotics, treated until <0.25ng/mL, resumed antibiotics only if PCT levels subsequently increased PCT using rapid and sensitive immunoassay (KryptornPCT, Brahms) PCT on admission or within 6hours – results available 60minutes later PCT every 2days until discharge Untreated children showing no reduction in signs/symptoms after 3days could be treated regardless of PCT level.
Comparison	N=155 Control; - Treatment guided by Italian Society of Pediatrics guidelines – antibiotic monotherapy chosen on the basis of age if mild, combined beta-lactam and macrolide therapy if severe - Duration as recommended by Italian Society of Pediatrics guidelines
Length of follow up	Follow-up 14 and 28days after admission or in the case of any new episode of fever
Location	Italy
Outcomes measures and effect size	Outcomes; - Antibiotic use - Adverse events All clinically reassessed daily Follow-up visits evaluated by a blinded researcher N=5/160 (PCT group), N=4/159 (control) lost to follow-up **Results**; **Antibiotic use**; - N=24 (15.5%) in PCT group never given antibiotics (N=21 mild, N=3 severe). No respiratory problems during follow-up, considered cured at control visits - N=131 (84.5%) in PCT group given antibiotics, N=2 (1.5%) discontinued after 2days, N=6 (4.6%) after 4days, N=49 (37.4%) after 6days, N=61 (46.6%) after 8days, N=10 had >8days of antibiotics. For N=3 (2.3%) discontinuation at 4days was followed by increase in PCT ≥0.25ng/mL – resumed antibiotics stopped on day 10 when PCT levels had returned to <0.25ng/mL - N=155 (100%) in control group given antibiotics for ≥7days, N=128 (82.6%) for 10days, N=39 (25.2%) for 12days, N=21 (13.5%) for 14days

	Between group difference for rate and duration of antibiotic exposure, p<0.05 Adverse events; - PCT group 25.2%, control group 3.9%, p<0.05 - Most frequent, diarrhoea
Source of funding	Italian ministry of health
Comments	90% power, 76 patients in each group necessary to detect a 15% lower antibiotic use, considering that 100% of children with community-acquired pneumonia were treated with antibiotics – planned to analyse in subgroups (mild, severe) so doubled the number in each group Not ITT analysis

Table 49: Gonzales et al (2008), point-of-care

Bibliographic reference	Gonzales (2008) C-reactive protein testing does not decrease antibiotic use for acute cough illness when compared to a clinical algorithm
Study type	RCT (randomisation using a random-number generator, by data coordinating centre staff) Study aim, to consider the incremental effect of point-of-care CRP testing with a clinical algorithm on antibiotic prescribing and chest x-ray ordering rates compared to the clinical algorithm alone
Study quality	
Number of studies	
Participant characteristics	Emergency department, Nov 2005 to March 2006 Inclusion; - ≥18years, new cough present ≤21days, ≥1 acute respiratory infection symptom (fever, sore throat, night sweats, body aches, nasal or chest congestion, shortness of breath) - Availability for a telephone follow-up interview in 2-4weeks Exclusion; - Symptoms or signs requiring urgent evaluation, cystic fibrosis, immunodeficiency - Inability to provide informed consent No differences between CRP and control groups in sociodemographic characteristics, comorbidities, illness features, principal diagnosis Staff given 1.5hr educational seminar that reviewed evidence-based recommendations for evaluation and treatment of acute cough and community-acquired pneumonia, current evidence on CRP levels as adjuncts in the diagnosis of pneumonia
Intervention	N=69 CRP; - Fingerstick, whole blood specimen (QuikRead CRP, Orion Corporation, Orion Diagnostics, Finland) - Result placed in patient's chart before being seen by a clinician - Management algorithm in medical chart that provided recommendations for chest x-ray and antibiotic treatment of adults with acute cough CRP categorised as; - Normal, <10mg/mL - Indeterminate, 10 to 99mg/mL - High, >100mg/mL

Comparison	N=62 Control; - Management algorithm in medical chart that provided recommendations for chest x-ray and antibiotic treatment of adults with acute cough
Length of follow up	
Location	USA
Outcomes measures and effect size	Primary outcome; - Antibiotic prescription, from medical record abstraction Secondary outcomes; - Chest x-ray ordering - Total visit duration (difference between the time of triage and time of emergency department discharge, not included in this ET) N=131/139 completed their emergency department visit (N=8 left before being evaluated by emergency physician) **Results**; **Antibiotic treatment**; - CRP group (N=69), 37% (95%CI, 26% to 48%) - Control (N=62), 31% (95%CI, 19% to 43%) - P=0.46 **Length of stay**, median (IQR); - CRP group (N=69), 283 (95%CI, 200 to 362) - Control (N=62), 285 (95%CI, 208 to 369) - P=0.73
Source of funding	Translating Research into Practice initiative, sponsored by the Agency for Healthcare Research and Quality and the Health Services Research and Development Service of the Department of Veterans Affairs
Comments	Sample size calculation abed on hypothesis that CRP testing would have a prescription rate of 30%, compared with 50% without, estimated a requirement for 103 subjects in each arm

Table 50: Manzour et al (2010), point-of-care

Bibliographic reference	Manzano (2010) Impact of procalcitonin on the management of children aged 1 to 36 months presenting with fever without source: a randomised controlled trial
Study type	RCT (computer-generated block randomisation, envelopes containing PCT+, PCT-, attending physician drew next available numbered, sealed envelope) Study aim, to evaluate the impact of PCT measurement on antibiotic prescription and on hospitalisation rate
Study quality	
Number of studies	
Participant characteristics	Emergency department, tertiary, urban paediatric centre (Nov 2006 to Nov 2007) Inclusion; - Presenting to paediatric emergency department with fever without source - 1 to 36months with rectal temperature >38ºC - No identified source of infection after history, physical examination, blood test and bladder catheterisation or suprapublic aspiration Exclusion; - Acquired or congenital immunodeficiency

<table>
<tr><td></td><td>- Already treated with antibiotics

Prior to the study staff physicians received an oral presentation on PCT and serious bacterial infection and an email with 2 recent articles highly relevant to this study

Groups similar in mean age, triage level, mean temperature duration, mean maximal temperature, median pretest VAS for serious bacterial infection</td></tr>
<tr><td>Intervention</td><td>N=192
PCT;
- PCT measurement received with other requested tests, usually within 1hour
- Decision to treat with antibiotics or hospitalise left to attending physician
PCT results accompanied by interpretation;
- <0.5ng/mL, low risk of bacterial infection
- ≥0.5ng/mL, moderate risk
- ≥2ng/mL, high risk

PCT, individual semiquantitative test PCT-Q</td></tr>
<tr><td>Comparison</td><td>N=192
Control;
- Other requested tests without PCT results, usually within 1hour
- Decision to treat with antibiotics or hospitalise left to attending physician</td></tr>
<tr><td>Length of follow up</td><td></td></tr>
<tr><td>Location</td><td>Canada</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Primary outcome;
- Difference in prescription of antibiotics
Secondary outcome;
- Difference in hospitalisation rate

Results;
Antibiotic use;
<table>
<tr><td></td><td>PCT group</td><td>Control</td><td>% difference (95% CI)</td></tr>
<tr><td>All children</td><td>N=48/192 (25%)</td><td>N=54/192 (28%)</td><td>-3 (-12 to 6)</td></tr>
<tr><td>(if all those with PCT ≥0.5ng/mL had antibiotics</td><td>N=79/192 (41%)</td><td>N=54/192 (28%)</td><td>13 (4 to 22))</td></tr>
<tr><td>Children without bacterial infection or neutropenia *</td><td>N=14/158 (9%)</td><td>N=16/154 (10%)</td><td>-2 (-8 to 5)</td></tr>
</table>
*identified in the emergency department

Hospitalisation rate;
<table>
<tr><td></td><td>PCT group</td><td>Control</td><td>% change (95% CI)</td></tr>
<tr><td>All children</td><td>N=50/192 (26%)</td><td>N=48/192 (25%)</td><td>1 (-8 to 10)</td></tr>
<tr><td>Children without bacterial infection or neutropenia *</td><td>N=16/158 (10%)</td><td>N=11/154 (7%)</td><td>3 (-3 to 10)</td></tr>
</table>
*identified in the emergency department</td></tr>
<tr><td>Source of</td><td>Not reported. Received 200 PCT-Q free from Brahms</td></tr>
</table>

funding	
Comments	ITT analysis As primary outcome unknown, power80%, calculated to lie between 335 and 419 patients, assuming PCT sensitivity 93%, specificity 74%, serious bacterial infection prevalence 5%

Table 51: Schuetz et al (2013), point-of-care

Bibliographic reference	Schuetz (2013) Procalcitonin to initiate or discontinue antibiotics in acute respiratory infections (Cochrane)
Study type	Individual patient data mate-analysis Study aim; to assess the safety and efficacy of using procalcitonin for starting or stopping antibiotics over a large range of patients with varying severity of acute respiratory tract infections and from different clinical settings
Study quality	Consideration of the overall quality of the evidence according to GRADE is moderate
Number of studies	14 RCTs, N=4211 participants (ITT population)
Participant characteristics	RCTs Adults, with a clinical diagnosis of acute respiratory infection; - lower acute respiratory infection; including community-acquired pneumonia, hospital-acquired pneumonia, ventilator-associated pneumonia, acute bronchitis, exacerbation of asthma or COPD - upper respiratory infection; including common cold, rhinosinusitis, pharyngitis, tonsillitis, otitis media Exclusion; - paediatric participants - used procalcitonin to escalate antibiotic therapy Baseline characteristics of included patients were similar in the procalcitonin and control groups with respect to important prognostic features
Intervention	Strategy to initiate or discontinue antibiotic therapy based on procalcitonin cut-off ranges
Comparison	Control arm without procalcitonin measurements, including antibiotic management based on usual care or guidelines
Length of follow up	Follow-up time of 30days
Location	
Outcomes measures and effect size	Primary outcomes: - All-cause mortality - Setting-specific treatment failure (not reported in this ET) Secondary outcomes; - Antibiotic use (initiation of antibiotics, duration of antibiotics, total exposure to antibiotics (total amount of antibiotic days divided by total number of patients) - Length of hospital stay - Length of ICU stay (not reported in this ET) - Number of days with restricted activities (not reported in this ET) Multivariable hierarchial logistic regression for co-primary endpoints Fitted corresponding linear (continuous) and logistic (binary) regression models for secondary endpoints Pre-specified analyses stratified by clinical setting to investigate consistency of results across heterogeneous patient populations in terms of disease severity

Tested for subgroup effects – added clinical setting and diagnosis in turn to the regression model together with the corresponding interaction term with the procalcitonin group as a fixed-effects model

Assessed the heterogeneity by estimating I^2

Results;

Included studies;

Reference	Study type, nos.	Infection	Type of algorithm and procalcitonin cut-off used (µg/L)	Primary endpoint, follow-up
Briel (2008) Switzerland	Primary care, multicentre N=458	Upper and lower acute respiratory infection	Initiation and duration Recommendation against AB <0.25 (<0.1) Recommendation for AB >0.25 (>0.5)	Days with restricted activities 1mth
Burkhardt (2010) Germany	Primary care, multicentre N=550	Upper and lower acute respiratory infection	Initiation Recommendation against AB <0.25 Recommendation for AB >0.25	Days restricted activities 1mth
Christ-Cain (2004) Switzerland	Emergency dept., single-centre N=243	Lower acute respiratory infection with x-ray confirmation	Initiation Recommendation against AB <0.25 (<0.1) Recommendation for AB >0.25 (>0.5)	Antibiotic use 2wks
Christ-Cain (2006) Switzerland	Emergency dept., medical ward, single-centre N=302	Community-acquired pneumonia with x-ray confirmation	Initiation and duration Recommendation against AB <0.25 (<0.1) Recommendation for AB >0.25 (>0.5)	Antibiotic use 6wks
Stolz (2007) Switzerland	Emergency dept., medical ward, single-centre N=208	Exacerbated COPD	Initiation and duration Recommendation against AB <0.25 (<0.1) Recommendation for AB >0.25 (>0.5)	Antibiotic use 2 to 3wks
Kristoffersen (2009) Denmark	Emergency dept., medical ward, multicentre N=210	Lower acute respiratory infection without x-ray confirmation	Initiation and duration Recommendation against AB <0.25 Recommendation for AB >0.25 (>0.5)	Antibiotic use Hospital stay
Long (2009) China	Emergency dept., outpatients, single-centre N=127	Community-acquired pneumonia with x-ray confirmation	Initiation and duration Recommendation against AB <0.25 Recommendation for AB >0.25	Antibiotic use 1mth
Schuetz	Emergency	Lower acute	Initiation and	Antibiotic

(2009) Switzerland	dept., medical ward, centre N=1359	respiratory infection with x-ray confirmation	duration Recommendation against AB <0.25 (<0.1) Recommendation for AB >0.25 (>0.5)	use 1mth
Long (2011) China	Emergency dept., outpatients, single-centre N=156	Community-acquired pneumonia with x-ray confirmation	Initiation and duration Recommendation against AB <0.25 Recommendation for AB >0.25	Antibiotic use 1mth
Nobre (2008) Switzerland	Medical ICU, single-centre N=52	Suspected severe sepsis or septic shock	Duration Recommendation against AB <0.5 (<0.25) or >80% drop Recommendation for AB >0.5 (>1.0)	Antibiotic use 1mth
Schroeder (2009) Germany	Surgical ICU, single-centre N=8	Severe sepsis following abdominal surgery	Duration Recommendation against AB <1 or >65% drop over 3days	Antibiotic use Hospital stay
Hochreiter (2009) Germany	Surgical ICU, single-centre N=43	Suspected bacterial infections and >1 SIRS criteria	Duration Recommendation against AB <1 or >65% drop over 3days	Antibiotic use Hospital stay
Stolz (2010) Switzerland, USA	Medical ICU, multicentre N=101	Clinically diagnosed ventilator-associated pneumonia	Duration Recommendation against AB <0.5 (<0.25) or 80% drop For AB >0.5 (>1.0)	Antibiotic-free days alive 1mth
Bouadma (2010) France	Medical ICU, multicentre N=394	Suspected bacterial infections during ICU stay	Initiation and duration Recommendation against AB <0.5 (<0.25) For AB >0.5 (>1.0)	All-cause mortality 2mths

Adherence to algorithms was variable; 47% to 91%

Primary endpoint – mortality;

	Procalcitonin	**Control**	**Adjusted OR (95%CI)***	**P value**
Overall	N=2085	N=2126		
Mortality, No (%)	118 (5.7%)	134 (6.3%)	0.94 (0.71 to 1.23)	0.754
Primary care	N=507	N=501		
Mortality, No (%)	0	1 (0.2%)	-	
Emergency department	N=1291	N=1314		

Mortality, No (%)	61 (4.7%)	59 (4.5%)	1.03 (0.7 to 1.5)	0.895
Upper acute respiratory infection	N=282	N=267		
Mortality, No (%)	0	1 (0.4%)	-	
Community-acquired pneumonia	N=999	N=1028		
Mortality, No (%)	92 (9.2%)	111 (10.8%)	0.89 (0.64 to 1.23)	0.471
Acute bronchitis	N=249	N=282		
Mortality, No (%)	0	2 (0.8%)	-	
Exacerbation of COPD	N=288	N=296		
Mortality, No (%)	9 (3.1%)	8 (2.7%)	1.15 (0.43 to 3.09)	0.774

*multivariate hierarchial regression with outcome of interest as the dependent variable, procalcitonin group, age and diagnosis as independent variables, trial as a random-effects

Secondary endpoint – antibiotic use;

	Procalcitonin	**Control**	**Adjusted OR or difference (95%CI)***	**P value of the regression model**
Overall	N=2085	N=2126		
Initiation of antibiotics, No. (%)	1341 (64%)	1778 (84%)	0.24 (0.20 to 0.29)	<0.001
Duration (days), median (IQR)	7 (4 to 10)	10 (7 to 13)	-2.75 (-3.12 to -2.39)	<0.001
Total exposure (days), median (IQR)	4 (0 to 8)	8 (5 to 12)	-3.47 (-3.78 to -3.17)	<0.001
Primary care	N=507	N=501		
Initiation of antibiotics, No. (%)	116 (23%)	316 (63%)	0.10 (0.07 to 0.14)	<0.001
Duration (days), median (IQR)	7 (5 to 8)	7 (6 to 8)	-0.6 (-1.17 to -0.03)	0.04
Total exposure (days), median (IQR)	0 (0 to 0)	6 (0 to 7)	-3.06 (-3.48 to -2.65)	<0.001
Emergency department	N=1291	N=1314		
Initiation of antibiotics, No. (%)	939 (73%)	1151 (88%)	0.34 (0.28 to 0.43)	<0.001
Duration (days), median (IQR)	7 (4 to 10)	10 (7 to 12)	-3.7 (-4.09 to -3.31)	<0.001
Total exposure (days), median (IQR)	5 (0 to 8)	9 (5 to 12)	-2.96 (-3.38 to -2.54)	<0.001
Upper acute respiratory infection	N=282	N=267		
Initiation of antibiotics, No. (%)	43 (15%)	129 (48%)	0.14 (0.09 to 0.22)	<0.001
Duration (days), median (IQR)	7 (5 to 8)	7 (6 to 7)	-1.16 (-2.08 to -0.24)	0.013
Total exposure (days),	0 (0 to 0)	0 (0 to	-2.64 (-3.16	<0.001

	median (IQR)		7)	to -2.11)	
	Community-acquired pneumonia	N=999	N=1028		
	Initiation of antibiotics, No. (%)	898 (90%)	1019 (99%)	0.07 (0.03 to 0.14)	<0.001
	Duration (days), median (IQR)	7 (5 to 10)	10 (8 to 14)	-3.34 (-3.79 to -2.88)	<0.001
	Total exposure (days), median (IQR)	6 (4 to 10)	10 (8 to 14)	-3.98 (-4.44 to -3.52)	<0.001
	Acute bronchitis	N=249	N=282		
	Initiation of antibiotics, No. (%)	61 (24%)	185 (66%)	0.15 (0.10 to 0.23)	<0.001
	Duration (days), median (IQR)	7 (4 to 9)	7 (5 to 8)	-0.38 (-1.21 to 0.46)	0.375
	Total exposure (days), median (IQR)	0 (0 to 0)	5 (0 to 7)	-3.06 (-3.69 to -2.43)	<0.001
	Exacerbation of COPD	N=288	N=296		
	Initiation of antibiotics, No. (%)	137 (48%)	216 (73%)	0.32 (0.23 to 0.46)	<0.001
	Duration (days), median (IQR)	6 (3 to 9)	8 (6 to 10)	-1.58 (-2.33 to -0.82)	<0.001
	Total exposure (days), median (IQR)	0 (0 to 6)	7 (0 to 10)	-3.03 (-3.76 to -2.3)	<0.001
	*multivariable hierarchial model adjusted for age and diagnosis and trial as a random-effect Duration – total days of antibiotic therapy in patients in whom antibiotics were initiated Total exposure – total days of antibiotic therapy in all randomised patients				
Source of funding					
Comments	Assumed those lost to follow-up did not experience an event – included a complete case analysis (excluding those lost to follow-up) or an analysis assuming that patients lost to follow-up experienced an event would change the primary outcome results in sensitivity analysis				

D.1.4 Barriers to decision making

Evidence table 52: Abbo L et al 2013

Bibliographic reference	Abbo, L., Lo, K., Sinkowitz-Cochran, R. et al (2013) Antimicrobial Stewardship Programs in Florida's Acute Care Facilities
Study type	Cross-sectional study
Study quality	Poor
Number of respondents	82 participants with a response rate of 39%
Participant characteristics	Primary roles: physician or medical director (21), pharmacist (20), pharmacy director (14), infection control professional (16), and Other (11)
Intervention	N/A
Comparison	N/A
Length of follow up	N/A
Location	Acute care facilities in Florida, USA.
Results	Perceived Barriers to establish or Sustain Antimicrobial Stewardship Programs*

		No. (%) of respondents		
		Current ASP	ASP planned within 12 months	No ASP planned
	Inadequate time for ASP activities	27 (68)	10 (63)	12 (60)
	Personnel shortages	27 (68)	9 (56)	14 (70)
	Inadequate funding for activities or personnel	24 (60)	11 (69)	12 (60)
	Lower priority than other clinical initiatives	20 (50)	7 (44)	6 (30)
	Inadequate IT support	16 (40)	3 (19)	7 (35)
	Opposition from prescribers	16 (40)	5 (31)	6 (30)
	Paucity of data on improved outcomes with ASPs	10 (25)	3 (19)	3 (15)
	Multiple ID groups within the facility	8 (20)	3 (19)	3 (15)
	Financial support for ASP activities	25 (56)	9 (53)	15 (75)
Source of funding	Bureau of Epidemiology of the Florida Department of Health			
Comments	* There were no significant differences in the responses according to whether an ASP was present, facility type, or number of beds.			

Evidence table 53: Bannan A et al 2009

Bibliographic reference	Bannan, A., Buono, E., Mclaws, ML. et al. (2009) A survey of medical staff attitudes to antibiotic approval and stewardship programme. *Internal Medicine Journal*. 39 pp 662-668
Study type	Cross-sectional study
Study quality	Poor
Number of respondents	256 respondents with and a response rate of 56%
Participant characteristics	Clinicians: Junior clinical staff (90), specialists (82 (8 blank questionnaires)), senior staff (74), pharmacists (18)
Intervention	N/A
Comparison	N/A
Length of follow up	N/A
Location	Concord hospital, Sydney, New South Wales, Australia.
Results	Key findings: • 10% (95% CI: 6-16%) believed the antimicrobial restriction policy (ARP) did not value their intuition and experience. • 33% (95% CI: 26-41%) believed the ARP policy was time-consuming and detracted from other clinical duties • 19% (95% CI: 13-25%) felt that the ARP policy was an infringement on their autonomy
Source of funding	Not reported
Comments	Sampling method and survey design not fully discused

Evidence table 54: Broom A et al 2014

Bibliographic reference	Broom, A., Broom, J. and Kirkby, E. (2014) Cultures of resistance? A Bourdieusian analysis of doctors' antibiotic prescribing. *Social Science & Medicine* 110 pp81-88
Study type	Qualitative: Semi-structured interviews
Study quality	Moderate
Number of respondents	30 participants
Participant characteristics	Doctors who prescribe antibiotics: emergency medicine (3), general medicine (4), geriatrics (3), intensive care (2), obstetrics and gynaecology (3), oncology (2), orthopaedics (2), paediatrics (1), renal medicine (2), sexual health (1), surgery (2), urology (1) and infectious diseases (4).
Intervention	N/A
Comparison	N/A
Length of follow up	N/A
Location	Queensland, Australia.
Results	The following key themes were identified: • Everyday sensitivity toward resistance ○ Relative to other day-to day clinical considerations, antibiotic resistance was of limited concern at the bedside. • Risk, fear and uncertainty ○ Overtreatment – utilising broad spectrum, prescribing prophylactic antibiotics, or beginning antibiotics, or beginning antibiotics without a clear rationale was viewed as more favourable than the potential for adverse immediate patient outcomes. ○ Social risks including peer-based and hierarchical reputational consequences associated with “not doing enough”. “I would probably tend to over treat rather than under treat.” “Safety for us is not making a mistake…where a patient has a bad outcome…miss-prescribing [antibiotics] is more of a [broader] issue.” • Benevolence and the emotional prerogative ○ Emotional and relational pressures to “do everything possible” for a patient/family. *“…giving antibiotics sometimes is to keep the family happy…”* • Hierarchies and the localisation of antibiotic prescribing ○ Doctors’ prescribing practices appeared to be governed by micro-social peer networks and hierarchies.
Source of funding	Not reported
Comments	

Evidence table 55: Charani E et al 2013

Bibliographic reference	Charani, E., Castro-Sanchez, N., Sevdalis, N, et al. (2013) Understanding the Determinants of Antimicrobial Prescribing Within Hospitals: The Role of "Prescribing Etiquette". *Clinical Infectious Diseases.* 57, pp 188-196
Study type	Qualitative: Semi-structured interviews
Study quality	Moderate
Number of respondents	39 participants
Participant characteristics	Healthcare professionals from 4 hospitals of the Imperial College Healthcare NHS Trust: doctors (10), pharmacists (10), and nurses and midwives (19)
Intervention	N/A

Comparison	N/A
Length of follow up	N/A
Location	London, England.
Results	The analysis identified 3 key themes: • Decision-making autonomy o Senior doctors rely on their own professional judgement and the need to freely choose what they judge to be the most appropriate when prescribing antimicrobials. *"…all the pharmacists know that doctor's just going to do what he wants so that's quite difficult…"* o There is a clear shared view of "non-interference" when it comes to doctors judging or intervening in the antimicrobial prescribing behaviour of their colleagues *"I think doctor to doctor, it's very difficult for clinician to clinician, especially different specialities to go and criticize one another"* • Limitations of evidence-based policies o Doctors rely on their own clinical knowledge and experience to guide their antimicrobial prescribing practice and frequently consider their patients to be "outside" the boundaries of local evidence-based treatment policies for infection. *"I'm a clinician and have some degree of independent practice; protocols are quite constrictive and restrictive for individual patient use."* • A culture of hierarchy o The practice of prescribing is primarily performed by junior doctors at the coalface, but it is the seniors who decide what needs to be prescribed. *"Consultants. Those are the people who we listen to. It's partly because we know the hierarchy, from the doctor's side of things"*
Source of funding	National Institute for Health Research and the United Kingdom Clinical Research Council.
Comments	

Evidence table 56: Cortoos P et al 2008

Bibliographic reference	Cortoos, P., De Witte, K., Peetermans,WE., et.al, (2008) Opposing expectations and suboptimal use of a local antibiotic hospital guideline: a qualitative study. *Journal of Antimicrobial Chemotherapy*. 62, pp 189-195
Study type	Qualitative: Focus groups
Study quality	Poorly reported
Number of respondents	22 participants took part in 5 focus groups
Participant characteristics	Physicians from a 1,900 bed tertiary care teaching hospital: Internal medicine residents (7), Surgery residents (6), Internal medicine staff (6), and Surgery Staff (3)
Intervention	N/A
Comparison	N/A
Length of follow up	N/A
Location	Leuven, Belgium.
Results	2 relevant key themes were: • Social influence o Internal medicine and surgical residents emphasised the importance of supervisors as role models; because supervisors practice strongly determined the subsequent prescribing behaviour of residents.

	• Organisational constraints ○ The pressure of work was mentioned by residents as a cause of not being able to consult guidelines.
Source of funding	Faculty of Pharmaceutical Sciences, Katholieke Universiteti Leuven, Belgium.
Comments	

Evidence table 57: De Souza V et al 2006

Bibliographic reference	De Souza, V., Mac Farlane, A., Murphy, A. W., et al. (2006) A qualitative study of factors influencing antimicrobial prescbring by non-consultant hospital doctors. *Journal of Antimicrobial Chemotherapy*. 58 pp 840-843
Study type	Qualitative: Semi-structured Interviews
Study quality	Poorly reported
Number of respondents	22 participants
Participant characteristics	Non-consultant hospital doctors from a 500 bed university teaching hospital: Interns, senior house officers, registrars, and specialist registrars.
Intervention	N/A
Comparison	N/A
Length of follow up	N/A
Location	Galway, Ireland.
Results	From the analysis 4 key findings are relevant: • Instructions from seniors ○ The most significant influence on prescribing practices was the opinion of more senior colleagues in the team. *"…In practice senior colleagues are getting it from more seniors and in so the practice is going into the different generations"* • Team preferences and prescribing practices ○ Individual teams had patterns of prescribing and standard ways of doing things with which new team members had to become familiar. *"There were quite a lot of differences in what was acceptable and what wasn't acceptable (in different teams?)"* • Developing individual experience and prescribing practices ○ Decisions made at the stage of registrar or senior registrar tended to emphasise the doctors' individual assessment of the patient and application of their individual tacit knowledge base. *"Whereas at the start you just did what you were told without question because you had so little experience, but now…you can question it a bit more…"* • On education and training ○ Participants felt that undergraduate left interns insufficiently trained to make autonomous antimicrobial prescribing decisions. *"What you learned in lectures was not real; because lectures is more theory-how the antibiotic works, the mechanism really. The lectures is not practice"*
Source of funding	Not reported
Comments	

Evidence table 58: Doron S et al 2013

Bibliographic reference	Doron, S., Nadkarni, L., Price, LL., et al (2013) A Nationwide Survey of Antimicrobial Stewardship Practices. *Clinical Therapeutics* 35 (6) pp 758-765
Study type	Cross-sectional study

Study quality	Poor
Number of respondents	406 participants with a response rate of 7%
Participant characteristics	Hospital pharmacists who are members of the Yankee Alliance or the Premier Health Care Alliance, and hospital pharmacy directors (purchased list of contacts). Pharmacy director (201), clinical pharmacist/other (135) and ID pharmacist/physician.
Intervention	N/A
Comparison	N/A
Length of follow up	N/A
Location	USA
Results	Barriers to implementation of an antimicrobial stewardship programme (ASP): • Of those respondents working in hospitals that they claimed did not have an ASP, common barriers to implementation were: ○ 69.4% staffing constraints ○ 32.8% insufficient staff buy-in ○ 22.2% not high on the list of priorities ○ 42.8% too many other things on the table • Respondents from nonteaching and smaller hospitals were more likely to report that an organised programme had not been proposed (P = 0.02 and P = 0.01, respectively)
Source of funding	Merck Sharp & Dohme Corp: Investigator-Initiated Studies Program.
Comments	The principal objective of the survey was to identify factors associated with the presence of a programme.

Evidence table 59: Hart A et al 2006

Bibliographic reference	Hart, A.M., Pepper, G.A. and Gonzales, R. (2006) Balancing acts: Deciding for or against antibiotics in acute respiratory infections. *Journal of Family Practice*. 55(4), pp320-325
Study type	Qualitative: Semi-structured interviews
Study quality	Very poorly reported
Number of respondents	21 Participants
Participant characteristics	Primary care clinicians: Nurse practitioners (4) and 17 doctors.
Intervention	N/A
Comparison	N/A
Length of follow up	N/A
Location	A small Western community in the USA.
Results	Two main concepts were identified by the analysis: • Individual best practice ○ Ultimately, each clinician made a decision based on what he or she believed was best for the patient. ○ 57% (21) of participants cited research based findings as their main source of evidence for their clinical practice. However, some of these clinicians were unfamiliar with the research based evidence they claimed to use. • Perceived patient/parent satisfaction ○ Each clinician had ideas about what constituted best practice; however, each was also concerned about maintaining good patient relationships and often

	saw these 2 concepts at odds.
Source of funding	National Institutes of Health, National Institute for Nursing Research grant
Comments	The researcher was a clinician in the same community and this may have impacted the results. Differences were also seen between salaried and fee-for-service clinicians.

Evidence table 60: Heritage J et al 2010

Bibliographic reference	Heritage, J., Elliott, M. N., Stivers, T, et al. (2010) Reducing inappropriate antibiotics prescribing: The role of online commentary on physical examination findings. *Patient Education and Counseling* 81 pp 119-125
Study type	A nested cross-sectional study
Study quality	Poor
Number of respondents	522 paediatrician encounters clustered within 38 paediatricians (participation rate 64%)
Participant characteristics	Paediatricians in 27 community paediatric practices in Los Angeles County.
Intervention	N/A
Comparison	N/A
Length of follow up	N/A
Location	Los Angeles, USA.
Results	<table><tr><td>Variable</td><td>Change in probability of parent questioning Rx plan (%)</td><td>95% CI</td></tr><tr><td>Any problem online commentary</td><td>13[#]</td><td>0% - 26%</td></tr></table> <table><tr><td>Predictor variable</td><td>Change in probability of MD inappropriately prescribing. 9BASE RATE = 16%) (%)</td><td>95% CI</td></tr><tr><td>Any problem online commentary^</td><td>27*</td><td>2% - 52%</td></tr><tr><td>Physician perceives parents as expecting antibiotics</td><td>26**</td><td>13% - 48%</td></tr></table>
Source of funding	Robert Wood Johnson Foundation and the Agency for Healthcare Research and Quality.
Comments	[*] P < .05 for increase or decrease in probability of the outcome *** P< .001 for increase or decrease in probability of the outcome [#] For viral cases ^ relative to only no problem online commentary

Evidence table 61: Hersh A et al 2009

Bibliographic reference	Hersh, A. L., Beekmann, Susan E, et al (2009). Antimicrobial stewardship programs in pediatrics. Infection control and hospital epidemiology : the official journal of the Society of Hospital Epidemiologists of America 30 (12) PAGES 1211-1217
Study type	Cross sectional study
Study quality	Poor

Number of participants	246 surveyed, 147 responded (60%)
Participant characteristics	paediatric infectious disease consultants
Intervention	N/A
Comparison	N/A
Length of follow up	N/A
Location	North America
Results	The authors concluded the prevalence of ASPs is limited in paediatrics (51% reported having or planning ASP). Many programs were not monitoring important end points associated with ASPs, including cost and number of antibiotic-days. The major barriers to implementation of an ASP were • lack of resources, including funding, time, and personnel (noted by more than 50% of respondents). • Regardless of the presence of an ASP, respondents perceived antibiotic resistance as a more significant problem nationally than at their local hospital. The authors concluded the prevalence of ASPs in paediatrics is limited, and opportunities exist to improve current programs.
Source of funding	Centers for Disease Control and Prevention (grant U50 CI000358); National Institute of Child Health and Development (grant T32HD044331 to A.L.H.).
Comments	Details of the survey Research question, study design, format, piloting and instructions are not clearly reported.

Evidence table 62: Johannsson B et al 2011

Bibliographic reference	Johannsson, B., Beekmann, SE.et al (2011).Improving antimicrobial stewardship the evolution of programmatic strategies and barriers. Epidemiologists of America 32 (4) PAGES 367-374
Study type	Cross sectional study
Study quality	Poor
Number of participants	1,044 invited to participate, 522 (50%) responded
Participant characteristics	Infectious diseases physician members of the Infectious Diseases Society of America Emerging Infections Network (IDSA EIN)
Intervention	N/A
Comparison	N/A
Length of follow up	N/A
Location	America
Results	Seventy-three percent of respondents reported that their institutions had or were planning an ASP. The authors noted a shift from formulary restriction alone to use of a set of tailored strategies designed to provide information and feedback to prescribers, particularly in community hospitals. Major barriers to implementing a program (ranked in order) where: • Lack of funding and lack of personnel • Other higher-priority clinical initiatives • Administration not aware of value of ASP • Opposition from prescribers • Lack of information technology support and/or inability to get data • Other speciality's antagonized by ASP • Multiple infectious disease groups within the facility

	The authors concluded that the lack of funding remains a key barrier for ASPs, and administrators need additional cost savings data in order to support ASPs.
Source of funding	Centres for disease control and prevention and Robert Wood Johnson Foundation and the Agency for Healthcare Research and Quality
Comments	Details of the survey Research question, study design, format, piloting and instructions are not clearly reported.

Evidence table 63: Kumar S et al 2003

Bibliographic reference	Kumar, S., Little, P., Britten N (2003).Why do general practitioners prescribe antibiotics for sore throat? Grounded theory interview study. BMJ 326 PAGES 1-6
Study type	Qualitative: Semi-structured interviews
Study quality	Poor
Number of participants	40 general practitioners
Participant characteristics	General practitioners
Intervention	N/A
Comparison	N/A
Length of follow up	N/A
Location	England
Results	Key themes identified included: Decision making: The presence of adverse social factors lowered general practitioners' threshold for prescribing antibiotics for sore throat. • Clinical experience, length of service and research evidence: o Doctors prescribing responded to external pressures (policy and research) acting over the long term and to daily pressures of clinical general practice (running late as a duty doctor). *"…it's too much to go through the detailed process of saying sore throats are caused by viruses and they will get better anyhow…"* o GPs identified specific clinical contexts and groups of patients where the decision to prescribe was guided by context and experience and not patient's symptoms, policy or evidence. *"..you know some people will not be satisfied unless they get their antibiotic and I know who these people are..."* • Antimicrobial resistance: o GPs were sceptical that prescribing penicillin for sore throat contributed greatly to antimicrobial resistance. *"I don't think GPs contribute in any significant way, not really, and I think we are being targeted unfairly"* • Maintaining doctor-patient relationships: o Prescribing antibiotics for sore throat was acknowledged as relevant but not the most important factor in maintaining the doctor-patient relationship.
Source of funding	National primary care development award from the Department of Health
Comments	It is not clear if the participants were GPs in England or from the wider UK. The principal researcher introduced him-self as a clinical general practice researcher and this may have influenced some responses.

Evidence table 64: Schouten J et al 2007

Bibliographic reference	Schouten, J.A., Hulscher, Marlies E.J. L, et al. (2007). Barriers to optimal antibiotic use for community-acquired pneumonia at hospitals: a qualitative study. Quality & safety in health care, 16 (2) PAGES 143-149
Study type	Qualitative: Semi-structured interviews
Study quality	Moderate
Number of participants	Invitational letters were sent to 12 residents, 6 specialists, 3 microbiologists and 3 clinical pharmacists
Participant characteristics	Eighteen care providers (9 residents, 6 consultants, 2 microbiologists and 1 clinical pharmacist).
Intervention	N/A
Comparison	N/A
Length of follow up	N/A
Location	Secondary care hospitals, Netherlands
Results	Relevant barrier identified: • The authors found non-adherence to guidelines for empirical antibiotic therapy was mainly attributable to physician's negative attitude towards the guideline. Intervention • Interventions aimed at improving physician's attitude to guideline rather than improving physician's knowledge is suggested by the authors. • The authors suggest involving local specialists to develop local guidelines based on evidence.
Source of funding	Not reported
Comments	Limited to antibiotic treatment for community-acquired pneumonia

Evidence table 65: Simpson S et al 2007

Bibliographic reference	Simpson, S. A., Wood, Fiona et al (2007). General practitioners' perceptions of antimicrobial resistance: a qualitative study. The Journal of antimicrobial chemotherapy, 59 (2) PAGES 292-296
Study type	Qualitative: Semi-structured interviews
Study quality	Poor
Number of participants	32 GP practices were approached
Participant characteristics	40 GP's across 23 practices
Intervention	N/A
Comparison	N/A
Length of follow up	N/A
Location	Wales
Results	The authors found most GPs were concerned about the broad issue of antimicrobial resistance and agreed that it was a growing problem. • Many said they infrequently encountered its consequences in their everyday practice and some questioned the evidence linking their prescribing decisions to resistance and poorer outcomes for their patients. • They felt conflicted by their apparent inability to influence the problem in the face of many other competing demands. Interventions

	• More information from their microbiological colleagues about resistance patterns locally • Undergraduate and graduate education about antimicrobial prescribing and resistance should be enhanced. • A heightened awareness of antimicrobial resistance locally may cause them to prescribe more second line agents.
Source of funding	Department of general practice, Cardiff university
Comments	

Evidence table 66: Teo C et al 2013

Bibliographic reference	Teo, C.K., Baysari, M. T.et al (2013).Understanding compliance to an antibiotic prescribing policy: Perspectives of policymakers and prescribers. Journal of Pharmacy Practice and Research 43 (1) PAGES 32-36
Study type	Qualitative: Semi-structured interviews
Study quality	Moderate
Number of participants	20
Participant characteristics	5 antimicrobial stewardship committee members (policymakers) and 15 prescribers
Intervention	N/A
Comparison	N/A
Length of follow up	N/A
Location	Sydney hospital, Australia
Results	This study identified several barriers to compliance with the antibiotic prescribing policy, such as poor knowledge of policy specifics and medical hierarchies. • Prescribers considered inapplicability of the antibiotic prescribing policy as an important barrier (professional judgement and medical hierarchy). • Antimicrobial stewardship committee members identified lack of knowledge as the main barrier to compliance with the antibiotic prescribing policy. • Antimicrobial stewardship committee members attributed non-compliance to the policy to prescriber autonomy and personal experience. • Organisational hierarchies were frequently reported as a barrier by both participant groups. The study concludes: Involving prescribers in policy development, giving them feedback about their prescribing, and improving existing collaboration and decision support platforms may further improve judicious antibiotic use.
Source of funding	NH & MRC program grant
Comments	A study from one Australian hospital. Involved both prescribers and policymakers

Evidence table 67: Wigton R et al 2008

Bibliographic reference	Wigton, R. S., Darr, Carol A.et al (2008). How do community practitioners decide whether to prescribe antibiotics for acute respiratory tract infections? Journal of general internal medicine 23 (10) PAGES 1615-1620
Study type	Cross-sectional study: Paper case vignette study using a fractional factorial design
Study quality	Poor
Number of participants	One hundred one community practitioners and eight faculty members
Participant characteristics	There were 58 physicians, 18 physician assistants, and 23 nurse practitioners. Twenty-three practiced in an internal medicine practice, 40 in family practice, 30 in

	paediatrics, and 7 in “other.” Additionally eight general internist faculty members at the University of Nebraska College of Medicine and at the University of California San Francisco
Intervention	N/A
Comparison	N/A
Length of follow up	N/A
Location	Colorado, USA
Results	The study asked community practitioners to estimate how likely they would be to prescribe antibiotics in each of 20 cases of Acute Respiratory Tract Infection. The study then compared practitioners’ weights with those of a panel of eight faculty physicians who evaluated the cases following the *Centers for Disease Control and Prevention* (CDC) guideline rather than their own judgments. • Practitioners prescribed antibiotics in 44.5% of cases, over twice the percentage treated by the panel using the CDC guidelines (20%). • In deciding to prescribe antibiotic treatment, practitioners gave little or no weight to patient factors such as whether the patients wanted antibiotics. • Practitioners were most strongly influenced by duration of illness. The effect of duration was strongest when accompanied by fever or productive cough; the authors suggest that these situations would be important areas for practitioner education and further clinical studies.
Source of funding	Agency for Health Care Research and Quality. Minimizing Antibiotic Resistance in Colorado (MARC) Project
Comments	Descriptions of clinical findings and patient factors may have lacked the force they would have in patient encounters as the decisions were made in response to paper case vignettes limited to nine features and not actual patients.

Evidence table 68: Wood F et al 2007

Bibliographic reference	Wood, F, Simpson, Sharon et al (2007). Socially responsible antibiotic choices in primary care: a qualitative study of GPs' decisions to prescribe broad-spectrum and fluroquinolone antibiotics.Family practice 24 (5) PAGES 427-434
Study type	Qualitative: Semi-structured interviews
Study quality	Poor
Number of participants	40 GPs
Participant characteristics	26 GPs from practices known to be high prescribers of fluroquinolone antibiotics and 14 from average fluroquinolone prescribing practices
Intervention	N/A
Comparison	N/A
Length of follow up	N/A
Location	Wales
Results	The study looked at GP surgeries with differing levels of prescribing broad-spectrum antibiotics (fluroquinolone). • GPs from high fluroquinolone prescribing practices were more likely to prioritize patients' immediate needs, • GPs from average prescribing practices were more likely to consider longer term issues. • GPs from both high and average fluroquinolone prescribing practices justified their antibiotic choices on the basis of a desire to do their best for their patients and society. Choosing to prescribe powerful, broad-spectrum antibiotics such as fluroquinolones, as well as choosing to keep these agents in reserve, was justified on the basis of social responsibility. Strategies to change fluroquinolone and

	broad-spectrum antibiotic prescribing will need to take into account clinicians' perceptions of social responsibility
Source of funding	Department of general practice, Cardiff university
Comments	

D.1.5 Timely adoption and diffusion of a new antimicrobial

Evidence table 69: McNulty *et al*. (2011)

Bibliographic reference	McNulty, CAM; Lasseter, GM; Charlett, AM. et al. (2011) Does laboratory antibiotic susceptibility reporting influence primary care prescribing in urinary tract infection and other infections? *J Antimicrob Chemother* 2011; 66: 1396–1404
Study type	Prospective interrupted time series design To determine whether a change in urine antibiotic susceptibility reporting from co-amoxiclav to cefalexin to community clinicians served by Southmead General Hospital led to a change in antibiotic prescribing.
Study quality	Low
Number of studies	The study included general practices served by the Southmead Microbiology Laboratory (Southmead), North Bristol Trust, Bristol, England. Practices were excluded from the study if they were involved in research regarding UTI prescribing during the data collection period.
Participant characteristics	Not stated
Intervention	One of the routinely reported antibiotic susceptibilities for primary care UTI reports was changed: susceptibility to cefalexin was reported in place of susceptibility to co-amoxiclav. Routine reporting of amoxicillin, nitrofurantoin and trimethoprim remained unchanged. An audit determined that Cefalexin was not reported in the pre-intervention period, but was included on all reports during the intervention. Co-amoxiclav was reported on 69% of reports pre-intervention and on 2% of reports during the intervention period.
Comparison	Was pre-intervention period (commencement of data collection [MIQUEST data] June 2005, start of intervention period July 2006).
Length of follow up	Start of intervention period July 2006 until end of data collection (February 2008).
Location	General practices served by the Southmead Microbiology Laboratory (Southmead, UK)
Outcomes measures and effect size	Resistance rates of primary care *E. coli* urine isolates to trimethoprim and amoxicillin did not change during the study period (trimethoprim 28.2% before and 29.8% during; amoxicillin 43.2% before and 43.4% after).

Intervention period compared to control period.	Estimated OR[1] [95% Confidence Interval]	P value
Survey results for: Cefalexin Co-amoxiclav	 9.88 [3.00 – 32.51] 0.30 [0.16 – 0.57]	 <0.001 <0.001
MIQUEST query for: Cefalexin Co-amoxiclav	 1.5 [1.18 – 1.95] 0.75 [0.58 – 0.97]	 =0.001 =0.03
MIQUEST query for second prescriptions[2, 3, 4, 5] Cefalexin Co-amoxiclav	 2.18 [1.44 – 3.30] 2.44 [2.01 – 2.97]	 <0.001 <0.001

	MIQUEST query for : Ciprofloxacin[6, 7]	0.66 [0.485 – 0.897]	=0.008
	PACT data for:		
	Cefalexin	1.20 [1.12 – 1.30]	<0.001
	Co-amoxiclav	0.92 [0.89 – 0.96]	<0.001
	All oral Cephalosporin's	1.04 [1.00 – 1.09]	=0.05
	Nitrofurantoin	1.12 [1.06 – 1.19]	<0.001

MIQUEST query - After the intervention was removed, cefalexin prescriptions returned to pre-intervention levels, regardless of whether it was for initial or 'second' prescriptions [OR 1.186 (P=0.2) and 1.042 (P=0.8), respectively].

PACT data – After the intervention was removed, nitrofurantoin prescribing was still raised OR 1.20; 95% CI 1.11–1.30, P<0.001.

Source of funding	This study was supported by a grant from the British Society for Antimicrobial Chemotherapy
Comments	[1] Odds ratio is the ratio of two odds (odds in the intervention group versus the odds in the control group) these were estimated through multivariable cox regression. [2] A second antibiotic prescription within 4 weeks [3] Changes were found not to be related to seasonal factors. [4] There was a significant interaction between the intervention and second prescription for cefalexin but no such interaction for co-amoxiclav. [5] There was no significant increase in initial antibiotic prescriptions (OR 1.22; 95% CI 0.892–1.672, P=0.2). [6] After, but not during the intervention, prescribing of cefradine decreased (OR 0.73; 95% CI 0.60–0.89, P=0.002), and [7] prescribing of nitrofurantoin increased (OR 1.20; 95% CI 1.02–1.41, P=0.03).

D.2 GRADE profiles and forest plots

D.2.1 Reducing antimicrobial resistance.

Prophylaxis studies

GRADE profile 1: Continuous versus intermittent antimicrobials for candida

Author(s): Goldman 2005; Revankar 1998
Date: 2014-08-20
Question: Continuous versus intermittent (episodes) fluconazole for candida
Settings: Community

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continuous prophylaxis	Control	Relative (95% CI)	Absolute		
Emergence of resistance (follow-up 3 - 24 months; assessed with: Proportion of people in whom the final isolate was resistant)												
2[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	52/126 (41.3%)	84/246 (34.1%)	RR 1.22 (0.93 to 1.59)	75 more per 1000 (from 24 fewer to 201 more)	⊕OOO VERY LOW	CRITICAL
								0%		-		
Fungal infection (follow-up 3 - 24 months; assessed with: Number of individuals with candida infections)												
2[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	15/126 (11.9%)	39/246 (15.9%)	RR 0.66 (0.15 to 2.85)	54 fewer per 1000 (from 135 fewer to 293 more)	⊕OOO VERY LOW	CRITICAL
								0%		-		
Mortality related to fungal infection (follow-up median 24 years; assessed with: Number of deaths in each group)												
1[4]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	3/413 (0.73%)	1/416 (0.24%)	RR 3.02 (0.32 to 28.93)	5 more per 1000 (from 2 fewer to 67 more)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
CD4*T cell count at last study measurement (follow-up median 24 years; assessed with: Median cells/mm^3)												
1[4]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	108/329 (32.8%)	151/333 (45.3%)	RR 0.72 (0.6 to 0.88)	127 fewer per 1000 (from 54 fewer to 181 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Laboratory anomalies (follow-up median 24 years; assessed with: Number of individuals with a platelet count <50,000 platelets/mm^3)												
1[4]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	8/327 (2.4%)	1/334 (0.3%)	RR 8.17 (1.03 to 64.97)	21 more per 1000 (from 0 more to 192 more)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		

[1] Goldman 2005; Revankar 1998
[2] High risk of performance and attrition bias, unknown /unclear risk of selection and detection bias in Goldman study; Unknown/unclear risk of performance, attrition, selection and detection bias in Revankar study.

[3] Low n even in pooled analysis
[4] High risk of performance and attrition bias, unknown /unclear risk of selection and detection bias
[5] High risk of performance and attrition bias, unknown/unclear risk of selection and detection bias in Goldman study

GRADE profile 2. Short-course versus longer course antimicrobial prophylaxis in surgery

Author(s): Chardin (2009); Hasselgren (1984); Hemsell (1984); Hemsell (1985); Ishibashi (2009)
Date: 2014-08-15
Question: Short-course prophylaxis vs longer-course prophylaxis for surgery
Settings: Hospital

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short-course prophylaxis	Longer-course prophylaxis	Relative (95% CI)	Absolute		
Emergence of resistance (assessed with: Number of individuals with resistance after prophylaxis (placebo versus antibiotics))												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	1/66 (1.5%)[4]	0/121 (0%)	RR 5.46 (0.23 to 132.24)	-	⊕⊕OO LOW	CRITICAL
								0%		-		
Emergence of resistance (follow-up 30 days; measured with: Percentage of streptococci resistant to amoxicillin)												
1[5]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[7]	none	42	39	Percentage of 3 day course with resistance at day 30, 7.7% [95% CI 3.4 to 15.3] and 7% [95% CI 1.1 to 8.3] for 7 day course		⊕⊕OO LOW	CRITICAL
Emergence of resistance (assessed with: Pairs of resistant isolates before and after prophylaxis)												
1[8]	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	serious[10]	none	4/109 (3.7%)	9/75 (12%)	RR 0.31 (0.1 to 0.96)	83 fewer per 1000 (from 5 fewer to 108 fewer)	⊕⊕OO LOW	CRITICAL
								0%		-		
Emergence of resistance (follow-up 3 - 6 weeks; measured with: Comparison of entry and exit study culture MIC for same bacterial species)												
1[11]	randomised trials	serious[12]	no serious inconsistency	no serious indirectness	serious[13]	none	58	54	MIC concentrations at entry and exit compared, no inter-group differences found.		⊕⊕OO LOW	CRITICAL
Emergence of resistance (follow-up mean 1 months; assessed with: Number of participants in whom resistant organisms noted)												
1[14]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[15]	none	3/136 (2.2%)	4/139 (2.9%)	RR 0.77 (0.17 to 3.36)	7 fewer per 1000 (from 24 fewer to 68 more)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Clinical outcomes (assessed with: Number of individuals with wound infections (placebo versus treated))												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	11/66 (16.7%)[4]	5/121 (4.1%)	RR 4.03 (1.46 to 111.11)	125 more per 1000 (from 19 more to 1000 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
Clinical outcomes (assessed with: Number of individuals with wound infections (short course versus longer course)[16])												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	2/52 (3.8%)[4]	3/69 (4.3%)	RR 0.88 (0.15 to 5.1)	5 fewer per 1000 (from 37 fewer to 178 more)	⊕⊕OO	CRITICAL

								0%		-	LOW	
Clinical outcome (follow-up 30 days; measured with: Pain intensity score; Better indicated by lower values)												
1[5]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[7]	none	42	39	Pain intensity score (100mm VAS) 3 days 3.5 [3 to 6] and 7 days 4.0 [2 to 6]		⊕⊕OO LOW	CRITICAL
Clinical outcome (follow-up 30 days; measured with: Analgesia (total paracetamol) taken mg; Better indicated by lower values)												
1[5]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[7]	none	42	39	3 days course 5000mg [1600 to 9000] vs. 7 days course 4000mg [1000 to 6000]		⊕⊕OO LOW	CRITICAL
Clinical outcome (assessed with: Febrile morbidity (n in the 1 and 2 dose groups))												
1[8]	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	serious[10]	none	10/50 (20%)	6/50 (12%)[17]	RR 1.67 (0.66 to 4.24)	80 more per 1000 (from 41 fewer to 389 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
Clinical outcome (assessed with: Major infection (n in the 1 and 3 dose groups))												
1[8]	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	serious[10]	none	2/50 (4%)	6/50 (12%)[17]	RR 0.33 (0.07 to 1.57)	80 fewer per 1000 (from 112 fewer to 68 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
Hospital and healthcare utilisation (measured with: Hospital stay (days) for those with febrile morbidity ; Better indicated by lower values)												
1[8]	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	serious[10]	none	1 dose group n=20 2 dose group n=12 3 dose group n=12		1 dose group LoS 5.8±1.7 2 dose group LoS 7.1±4.2 3 dose group LoS 5.3±0.8		⊕⊕OO LOW	IMPORTANT
Hospital and healthcare utilisation (measured with: Hospital stay (days) for those with major infection; Better indicated by lower values)												
1[8]	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	serious[10]	none	1 dose group n=4 2 dose group n=12 3 dose group n=4		1 dose group LoS 8.0±1.4 2 dose group LoS 11.7±4.4 3 dose group LoS 8.5±3.5		⊕⊕OO LOW	IMPORTANT
Clinical outcome (follow-up 3 - 6 weeks; assessed with: Febrile morbidity)												
1[11]	randomised trials	serious[12]	no serious inconsistency	no serious indirectness	serious[13]	none	10/58 (17.2%)	11/54 (20.4%)	RR 0.93 (0.44 to 1.97)	14 fewer per 1000 (from 114 fewer to 198 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
Clinical outcome (follow-up 3 - 6 weeks; assessed with: Pelvic cellulitis)												
1[11]	randomised trials	serious[12]	no serious inconsistency	no serious indirectness	serious[13]	none	1/58 (1.7%)	2/54 (3.7%)	RR 0.47 (0.04 to 4.99)	20 fewer per 1000 (from 36 fewer to 148 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
Unintended consequences (follow-up 3 - 6 weeks; assessed with: Adverse drug reaction)												
1[11]	randomised trials	serious[12]	no serious inconsistency	no serious indirectness	serious[13]	none	0/58 (0%)	1/54 (1.9%)	RR 0.31 (0.01 to 7.47)	13 fewer per 1000 (from 18 fewer to 120 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
Hospital and healthcare utilisation (follow-up 3 - 6 weeks; measured with: Mean hospital stay; Better indicated by lower values)												
1[11]	randomised	serious[12]	no serious	no serious	serious[13]	none	58	54	1 dose group LoS 4.6		⊕⊕OO	IMPORTANT

	trials		inconsistency	indirectness					2 dose group LoS 4.9		LOW	
Clinical outcome (follow-up mean 1 months; assessed with: Surgical site infection[18])												
1[14]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[15]	none	7/136 (5.1%)	9/139 (6.5%)	RR 0.79 (0.30 to 2.07)	14 fewer per 1000 (from 45 fewer to 69 more)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		

[1] Hasselgren 1984
[2] Unknown/unclear risk of selection, attrition bias and detection bias
[3] Low n (=211)
[4] Intervention in this case was placebo versus control (short and long course of antibiotics)
[5] Chardin 2009
[6] High risk of attrition bias, unclear risk of detection bias
[7] Low n (=81)
[8] Hemsell 1985
[9] Unknown/unclear risk of selection, performance, attrition and detection bias
[10] Low n (=150)
[11] Hemsell 1984
[12] Unknown / unclear risk of attrition and detection bias
[13] Low n (=116)
[14] Ishibashi 2009
[15] Low n (=283)
[16] No difference between the treated groups for additional antibiotics, debridement, dehiscence or graft infection, excision or revision.
[17] Incidence of febrile morbidity was equal in the 2 and 3 dose groups, and the incidence of major infection was the same in the 1 and 3 dose groups
[18] No significant difference between groups for anastomotic dehiscence

GRADE profile 3: Short-course versus longer course antimicrobial prophylaxis of UTI

Author(s): Moltzhan (2012); Mountokalakis (1985)
Date: 2014-08-20
Question: Short-course prophylaxis vs longer course prophylaxis for urinary tract infection
Settings: Hospital

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Short-course prophylaxis**	**Longer course prophylaxis**	**Relative (95% CI)**	**Absolute**		
Emergence of resistance (follow-up 1 - 4 weeks[1]; assessed with: Number of patients who developed resistant infection)												
1[2]	randomised trials	serious[3]	serious[4]	no serious indirectness	serious[5]	none	1/44 (2.3%)	1/51 (2%)	RR 1.16 (0.07 to 17.99)	3 more per 1000 (from 18 fewer to 333 more)	⊕OOO VERY LOW	CRITICAL
								0%		-		
Emergence of resistance (follow-up mean 7 days; assessed with: Number of resistant isolates)												
1[6]	randomised	serious[7]	serious[8]	no serious	serious[9]	none	1/4 [10]	12/21	RR 0.44	320 fewer per 1000	⊕OOO	CRITICAL

	trials			indirectness				(57.1%)	(0.89 to 2.49)	(from 526 fewer to 851 more)	VERY LOW	
								0%		-		
Clinical outcomes (follow-up 1 - 4 weeks[1]; assessed with: Number of stent related symptoms)												
1[2]	randomised trials	serious[3]	serious[4]	no serious indirectness	serious[5]	none	43/44 (97.7%)	49/51 (96.1%)	RR 1.02 (0.95 to 1.09)	19 more per 1000 (from 48 fewer to 86 more)	⊕OOO VERY LOW	CRITICAL
								0%		-		
Clinical outcomes (follow-up 1 - 4 weeks[1]; assessed with: Number of urinary tract infections developed)												
1[2]	randomised trials	serious[3]	serious[4]	no serious indirectness	serious[5]	none	4/44 (9.1%)	5/51 (9.8%)	RR 0.93 (0.27 to 3.24)	7 fewer per 1000 (from 72 fewer to 220 more)	⊕OOO VERY LOW	CRITICAL
								0%		-		
Clinical outcomes (follow-up mean 7 days; assessed with: Significant bacteriuria (>10[5] bacteria per ml of urine))												
1[6]	randomised trials	serious[7]	serious[8]	no serious indirectness	serious[9]	none	3/24 (12.5%)	12/28 (42.9%)	RR 0.29 (0.09 to 0.91)	304 fewer per 1000 (from 39 fewer to 390 fewer)	⊕OOO VERY LOW	CRITICAL
								0%		-		
Unintended consequences (follow-up 1 - 4 weeks[1]; assessed with: Drug side-effects in each group)												
1[2]	randomised trials	serious[3]	serious[4]	no serious indirectness	serious[5]	none	21/44 (47.7%)	22/51 (43.1%)	RR 1.11 (0.71 to 1.72)	47 more per 1000 (from 125 fewer to 311 more)	⊕OOO VERY LOW	CRITICAL
								0%		-		

[1] and/or at stent removal
[2] Moltzhan 2012
[3] Unclear/unknown risk of selection, performance, attrition and detection bias
[4] Conflicts with Mountokalakis 1985
[5] Low n (=95)
[6] Mountokalakis 1985
[7] Unknown/unclear risk of selection, performance and detection bias
[8] Findings conflict with Moltzhan 2012
[9] Low n (=78)
[10] Intervention (short course) also a placebo group 4/26 resistant isolates developed

GRADE profile 4: Low dose versus higher dose antimicrobials for prophylaxis of UTI

Author(s): van der Wall (1992)
Date: 2014-08-20
Question: Low dose ciprofloxacin (250mg OD) vs higher dose ciprofloxacin (500mg BD) for urinary tract infection
Settings: Hospital

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Low dose ciprofloxacin (250mg OD)**	**Higher dose ciprofloxacin (500mg BD)**	**Relative (95% CI)**	**Absolute**		
Emergence of resistance (follow-up 13 - 102 days; assessed with: number of resistant isolates (by group) compared to the total number of isolates)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	11/49 (22.4%)	15/77 (19.5%)	RR 1.15 (0.58 to	29 more per 1000 (from 82 fewer to	⊕⊕OO	CRITICAL

									2.3)[4]	253 more)	LOW	
								0%		-		
Clinical outcome (follow-up 13 - 102 days; assessed with: Infectious morbidity)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	5/66 (7.6%)	5/68 (7.4%)	RR 1.03 (0.31 to 3.39)[4]	2 more per 1000 (from 51 fewer to 176 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
Clinical outcome (follow-up 13 - 102 days; assessed with: Infectious morbidity)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	5/66 (7.6%)	16/68 (23.5%)[6]	RR 0.32 (0.13 to 0.83)[7]	160 fewer per 1000 (from 40 fewer to 205 fewer)	⊕⊕OO LOW	CRITICAL
								0%		-		
Clinical outcome (follow-up 13 - 102 days; assessed with: Duplicate antibiotic courses needed)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	2/66 (3%)	4/68 (5.9%)	RR 0.52 (0.10 to 2.72)[5]	28 fewer per 1000 (from 53 fewer to 101 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
Clinical outcome (follow-up 13 - 102 days; assessed with: Symptomatic UTI)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	2/66 (3%)	4/68 (5.9%)	RR 0.52 (0.10 to 2.72)[4]	28 fewer per 1000 (from 53 fewer to 101 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
Clinical outcome (follow-up 13 - 102 days; assessed with: Asymptomatic UTI)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	57/66 (86.4%)	60/68 (88.2%)	RR 0.98 (0.86 to 1.11)[4]	18 fewer per 1000 (from 124 fewer to 97 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
Unintended consequences (follow-up 13 - 102 days; assessed with: Side -effects)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	1/66 (1.5%)	2/68 (2.9%)	RR 0.52 (0.05 to 5.55)[4]	14 fewer per 1000 (from 28 fewer to 134 more)	⊕⊕OO LOW	CRITICAL
								0%		-		

[1] van der Wall (1992)
[2] Unknown/unclear risk of attrition and detection bias
[3] Low n (=202)
[4] No significant difference was found when antibiotic was compared to placebo intervention
[5] For placebo versus low dose RR 0.19 (95% CI 0.04 – 0.81)
[6] Placebo versus low dose
[7] For placebo versus higher dose RR 0.31 (95% CI 0.12 - 0.81)

Treatment studies

GRADE profile 5: Continuous versus intermittent antimicrobials for infective COPD

Author(s): van Zanten (2006)
Date: 2014-08-21
Question: **C**ontinuous treatment vs intermittent treatment for infective exacerbation of COPD
Settings: **Hospital**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continuous treatment	Intermittent treatment	Relative (95% CI)	Absolute		
Emergence of resistance (follow-up mean 2 days[1,2]; measured with: Pre-treatment and post-treatment MIC; Better indicated by lower values)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	47	46	No difference in bacterial susceptibility was found between the groups at baseline or follow-up.		⊕⊕OO LOW	CRITICAL
Clinical outcome (follow-up mean 2 days[1,2]; assessed with: Treatment success)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	37/40 (92.5%)	40/43 (93%)	RR 0.99 (0.88 to 1.12)	9 fewer per 1000 (from 112 fewer to 112 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
Clinical outcome (follow-up mean 2 days[1,2]; measured with: Treatment duration (days) ; Better indicated by lower values)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	40	43	The mean duration of treatment (days ± SD [range; median]) was9.3±2.6 [1-12; 10] for group I and 9.5±1.5 [4-11; 10] for group II.		⊕⊕OO LOW	CRITICAL

[1] Length of follow-up unclear
[2] Follow-up for microbiology only other outcome assessment follow-up unclear
[3] van Zanten 2006
[4] High risk of performance bias, unknown /unclear risk of selection, attrition and detection bias
[5] Low n (=93)

GRADE profile 6: Directly administered or directly observed treatment for HIV

Author(s): Brust (2011); Maru (2007)
Date: 2014-08-21
Question: **D**irectly administered / directly observed antiretroviral therapy vs self-administered / treatment as usual therapy for HIV
Settings: **Community**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Directly administered / directly observed antiretroviral therapy	Self-administered / treatment as usual therapy	Relative (95% CI)	Absolute		

Emergence of resistance (follow-up 8 - 24 weeks; assessed with: Number of individuals with major resistance mutations correlated with their therapy)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	0/3 (0%)	5/6 (83.3%)	RR 0.16 (0.01 to 2.19)	700 fewer per 1000 (from 825 fewer to 992 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
Emergence of resistance (follow-up mean 6 months; measured with: New mutations [per person year]; Better indicated by lower values)												
1[4]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[6]	none	88	53	Adjusted probability of developing 1 new drug mutation per year was 0.49 for DAART and 0.41 for SAT (RR 1.04, p=0.90)		⊕⊕OO LOW	CRITICAL
Patient adherence (follow-up 8 - 24 weeks; measured with: Adherence rate of individuals with new mutations in each arm; Better indicated by lower values)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	7	14	The median pill count adherence rate for the seven subjects who developed new mutations was not significantly different to the 14 subjects who did not develop resistance mutations.		⊕⊕OO LOW	IMPORTANT
Clinical outcome (follow-up mean 6 months; measured with: Virologic success; Better indicated by lower values)												
1[4]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[6]	none	51	53	70.5% for DAART versus 54.7% for SAT (p=0.02)		⊕⊕OO LOW	CRITICAL
Clinical outcome (follow-up mean 6 months; measured with: Mean reduction in HIV-1 RNA level; Better indicated by lower values)												
1[4]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[6]	none	51	53	-1.16 for DAART versus -0.29 for SAT (p=0.03)		⊕⊕OO LOW	CRITICAL
Clinical outcome (follow-up mean 6 months; measured with: CD4 lymphocyte count (cells/µL))												
1[4]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[6]	none	51	53	+58.8 for DAART and +24 for SAT (p=0.002)		⊕⊕OO LOW	CRITICAL

[1] Brust 2011
[2] Unknown / unclear risk of selection, attrition, performance and detection bias
[3] Low n (=77)
[4] Maru 2007
[5] High risk of attrition bias, unknown /unclear risk of selection, performance and detection bias
[6] Low n (=141) only 51 of those randomised to intervention completed the follow-up
[7] RNA level reduction > (or =) 1.0 log (10) or an HIV-1 RNA level <400 copies/ml at 6 months

GRADE profile 7: Inhaled antibiotics versus inhaled saline for respiratory infection in mechanically ventilated patients

Author(s): Palmer (2008); Palmer (2014)
Date: 2014-08-21
Question: Inhaled antibiotics vs placebo (inhaled saline) for respiratory infection in mechanically ventilated patients
Settings: Hospital (ICU)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Inhaled antibiotics	Placebo (inhaled saline)	Relative (95% CI)	Absolute		
Emergence of resistance (follow-up mean 14 days; assessed with: Number of individuals with resistant organisms at follow-up)												

2[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	2/43 (4.7%)	14/42 (33.3%)	RR 0.16 (0.04 to 0.6)[3]	280 fewer per 1000 (from 133 fewer to 320 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Clinical outcome (follow-up mean 14 days; assessed with: Mortality)												
2[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	10/43 (23.3%)	6/42 (14.3%)	RR 1.65 (0.64 to 4.26)[3]	93 more per 1000 (from 51 fewer to 466 more)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Clinical outcome (follow-up mean 14 days; measured with: WBC at end of therapy ($X10^3/mm^3$)); Better indicated by lower values)												
2[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	43	42	-	MD 0.88 lower (1.73 to 0.04 lower)[3]	⊕⊕⊕O MODERATE	CRITICAL
2[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	43	42		MD -2.84 lower (-7.81 lower to 2.12 higher with RE model)[3]	⊕⊕⊕O MODERATE	CRITICAL
Clinical outcome (follow-up mean 14 days; assessed with: Tracheostomy)												
1[4]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	9/19 (47.4%)	13/24 (54.2%)	RR 0.87 (0.48 to 1.59)	70 fewer per 1000 (from 282 fewer to 320 more)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Clinical outcome (follow-up mean 14 days; assessed with: Additional systemic antibiotics for new or persistent infection)												
1[4]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	8/19 (42.1%)	17/24 (70.8%)	RR 0.59 (0.33 to 1.07)	290 fewer per 1000 (from 475 fewer to 50 more)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Clinical outcome (follow-up mean 14 days; measured with: Clinical pulmonary infection score (CPIS); Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	none	24	18	MD 3.3 lower (4.89 to 1.71 lower)		⊕⊕⊕O MODERATE	CRITICAL
Clinical outcome (follow-up mean 14 days; measured with: Sputum volume per 4 hour; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	none	24	18	MD 5.20 lower (7.25 to 3.15 lower)		⊕⊕⊕O MODERATE	CRITICAL
Clinical outcome (follow-up mean 14 days; measured with: Percentage of patients with organisms eradicated)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	none	24	18	AA group 96% Placebo group 9%		⊕⊕⊕O MODERATE	CRITICAL

[1] Palmer 2008, Palmer 2014
[2] Low overall n (=85)
[3] I2 for pooled analysis = 0%
[4] Palmer 2008
[5] Low n (=43)
[6] Low n (=42)

GRADE profile 8: Short-course versus longer course antibiotics for ventilator associated respiratory infections

Author(s): Capellier (2005); Chastre (2003)
Date: 2014-08-20
Question: Short-course treatment vs longer-course treatment for ventilator associated respiratory infection?
Settings: Intensive care unit

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short-course treatment	Longer-course treatment	Relative (95% CI)	Absolute		
Emergence of resistance (follow-up 28 - 90 days; assessed with: Number of individuals with resistant recurrent/ resistant VAP)												
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	42/313 (13.4%)	33/204 (16.2%)	RR 1.08 (0.49 to 2.37)	3 fewer per 1000 (from 55 fewer to 74 more)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Clinical outcome (follow-up 21 - 90 days; assessed with: Cure at 21 days)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	99/116 (85.3%)	92/109 (84.4%)	RR 1.01 (0.91 to 1.13)	8 more per 1000 (from 76 fewer to 110 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
Clinical outcome (follow-up 21 - 90 days; assessed with: Mortality at 21 days)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	10/116 (8.6%)	9/109 (8.3%)	RR 1.04 (0.44 to 2.47)	3 more per 1000 (from 46 fewer to 121 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
Clinical outcome (follow-up 28 - 60 days; assessed with: All-cause mortality at 28 days)												
1[6]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[7]	none	37/197 (18.8%)	35/204 (17.2%)	RR 1.09 (0.72 to 1.66)	15 more per 1000 (from 48 fewer to 113 more)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Clinical outcome (follow-up 28 - 60 days; assessed with: Mortality at 60 days)												
1[6]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[7]	none	50/197 (25.4%)	57/204 (27.9%)	RR 0.91 (0.66 to 1.21)	25 fewer per 1000 (from 95 fewer to 59 more)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Clinical outcome (follow-up 21 - 90 days; assessed with: Mortality at 90 days)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	20/116 (17.2%)	19/109 (17.4%)	RR 0.99 (0.56 to 1.75)	2 fewer per 1000 (from 77 fewer to 131 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
Clinical outcome (follow-up 21 - 90 days; assessed with: Septic shock)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	9/116 (7.8%)	10/109 (9.2%)	RR 0.85 (0.36 to 2.0)	14 fewer per 1000 (from 59 fewer to 92 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
Clinical outcome (follow-up 21 - 90 days; assessed with: Relapse)												
1[3]	randomised	serious[4]	no serious	no serious	serious[5]	none	6/116	2/109	RR 2.82	33 more per 1000	⊕⊕OO	CRITICAL

	trials		inconsistency	indirectness			(5.2%)	(1.8%)	(0.58 to 13.67)	(from 8 fewer to 232 more)	LOW	
								0%		-		
Clinical outcome (follow-up 28 - 60 days; assessed with: Recurrence)												
1[6]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[7]	none	57/197 (28.9%)	53/204 (26%)	RR 1.11 (0.81 to 1.53)	29 more per 1000 (from 49 fewer to 138 more)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Clinical outcome (follow-up 28 - 60 days; measured with: Antibiotic free days; Better indicated by higher values)												
1[6]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[7]	none	57	53	-	MD 4.4 higher (3.14 to 5.66 higher)	⊕⊕⊕O MODERATE	CRITICAL
Clinical outcome (follow-up 28 - 60 days; measured with: Mechanical ventilation free days; Better indicated by higher values)												
1[6]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[7]	none	57	53	-	MD 0.40 lower (2.21 lower to 1.41 higher)	⊕⊕⊕O MODERATE	CRITICAL
Clinical outcome (follow-up 28 - 60 days; measured with: Organ failure free days; Better indicated by higher values)												
1[6]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[7]	none	57	53	-	MD 0.50 lower (2.22 lower to 1.22 higher)	⊕⊕⊕O MODERATE	CRITICAL
Unintended consequence (follow-up 21 - 90 days; assessed with: Adverse events)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	9/116 (7.8%)	4/109 (3.7%)	RR 0.75 (0.21 to 2.73)	9 fewer per 1000 (from 29 fewer to 63 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
Hospitalisation and healthcare use (follow-up 28 - 60 days; measured with: Length of ICU stay (days); Better indicated by lower values)												
1[6]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[7]	none	57	53	-	MD 2.5 higher (1.18 lower to 6.18 higher)	⊕⊕⊕O MODERATE	IMPORTANT

[1] Capellier 2012; Chastre 2003
[2] Capellier study unknown/unclear risk of selection, performance and detection bias. The Chastre study had an unknown/unclear risk of detection bias
[3] Capellier 2012
[4] Unknown/unclear risk of selection, performance and detection bias
[5] Low n (=225)
[6] Chastre (2003)
[7] Low n (=401)

GRADE profile 9: Short-course versus longer course treatment of UTI

Author(s): Copenhagen study group (1991); Stahl (1984)
Date: 2014-08-21
Question: Short-course treatment vs longer-course treatment for urinary tract infection
Settings: Community

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short-course treatment	Longer-course treatment	Relative (95% CI)	Absolute		
Emergence of resistance (follow-up 1 - 30 days[1]; assessed with: In vitro sensitivity of isolates)												
1[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	8/18 (44.4%)	14/18 (77.8%)	RR 0.57 (0.32 to 1.01)	334 fewer per 1000 (from 529 fewer to 8 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
Emergence of resistance (follow-up mean 3 months; assessed with: Number of individuals in whom resistance to treatment was induced)												
1[5]	randomised trials	very serious[6]	no serious inconsistency	no serious indirectness	serious[7]	none	3/3 (100%)	4/4 (100%)	RR 1.0 (0.62 to 1.6)	0 fewer per 1000 (from 380 fewer to 600 more)	⊕OOO VERY LOW	CRITICAL
								0%		-		
Clinical outcome (follow-up 1 - 30 days[1]; assessed with: No growth at 1 - 10 days after treatment)												
1[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	78/96 (81.3%)	60/78 (76.9%)[8]	RR 1.06 (0.90 to 1.23)	46 more per 1000 (from 77 fewer to 177 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
Clinical outcome (follow-up mean 3 months; assessed with: Cure rate)												
1[5]	randomised trials	very serious[6]	no serious inconsistency	no serious indirectness	serious[7]	none	7/10 (70%)	12/16 (75%)	RR 0.93 (0.57 to 1.53)	52 fewer per 1000 (from 322 fewer to 397 more)	⊕OOO VERY LOW	CRITICAL
								0%		-		
Clinical outcome (follow-up mean 3 months; assessed with: Relapse rate)												
1[5]	randomised trials	very serious[6]	no serious inconsistency	no serious indirectness	serious[7]	none	3/10 (30%)	4/16 (25%)	RR 0.40 (0.15 to 1.07)	150 fewer per 1000 (from 213 fewer to 18 more)	⊕OOO VERY LOW	CRITICAL
								0%		-		
Clinical outcome (follow-up mean 3 months; assessed with: Reinfection rate)												
1[5]	randomised trials	very serious[6]	no serious inconsistency	no serious indirectness	serious[7]	none	0/10 (0%)	2/16 (12.5%)	RR 0.31 (0.02 to 5.85)	86 fewer per 1000 (from 123 fewer to 606 more)	⊕OOO VERY LOW	CRITICAL
								0%		-		

[1] first follow-up at 1-10 days, final follow-up at 30 days
[2] Copenhagen study group (1991)
[3] Unknown/unclear risk of performance, attrition and detection bias
[4] Low n (=359)
[5] Stahl 1984
[6] High risk of performance and attrition bias, unknown /unclear risk of selection and detection bias
[7] Low n (=36) with only 26 completing the study
[8] Also 3 day pivemecillinam 67/90 (74%)

GRADE profile 10: High doses of quinolones versus lower doses of quinolones (systematic review)

Author(s): Falagas (2007)
Date: 2014-08-21
Question: High doses of quinolones vs lower doses of quinolones for reducing the emergence of resistance
Settings:

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High doses of quinolones	Lower doses of quinolones	Relative (95% CI)	Absolute		
Emergence of resistance (measured with: Proportion of patients with emergence of resistance; Better indicated by lower values)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[3]	Five of the included 12 studies had data on the emergence of resistance the results were, however not significant.				⊕⊕OO LOW	CRITICAL
Clinical outcome (measured with: Bacterial eradication (where reported separately); Better indicated by lower values)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[3]	Eight of the included 12 studies had data on bacterial eradication between the two interventions the results were conflicting with only five studies having higher eradication in the high dose arm (no significance test performed).				⊕⊕OO LOW	CRITICAL
Clinical outcome (measured with: Clinical failure (where reported separately); Better indicated by lower values)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[3]	Nine of the included 12 studies had data on clinical failure between the two interventions, four studies favoured the higher dose and five were equivocal (no significance test performed)				⊕⊕OO LOW	CRITICAL
Clinical outcome (measured with: Bacteriologic failure (where reported separately); Better indicated by lower values)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[3]	Four of the included 12 studies had data on bacteriologic failure; two studies favoured each intervention (low vs. high dose).				⊕⊕OO LOW	CRITICAL
Unintended consequences (measured with: Adverse events; Better indicated by lower values)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[3]	Five of the included 12 studies had data on adverse events between the two interventions, two studies favoured the higher dose group, two favoured the lower dose group and one study was equivocal (no significance test performed).				⊕⊕OO LOW	IMPORTANT

[1] Falagas 2007
[2] This systematic review did not have a sufficient search methodology; also study quality was not examined.
[3] Please see note above

GRADE profile 11: Procalcitonin levels versus usual care for commencing and stopping antimicrobial treatment

Author(s): Bouadma (2010)
Date: 2014-08-21
Question: Procalcitonin serum levels vs usual care for commencement and stopping of antibiotic therapy in ICU
Settings: Hospital (ICU)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Procalcitonin serum levels	Usual care	Relative (95% CI)	Absolute		
Emergence of resistance (follow-up 28 - 60 days; assessed with: Number of individuals with multi-drug resistant bacteria at follow-up)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	55/307 (17.9%)	52/314 (16.6%)	RR 1.08 (0.77 to 1.53)	13 more per 1000 (from 38 fewer to 88 more)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		

Clinical outcome (follow-up 28 - 60 days; assessed with: Mortality at 28 days)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	65/307 (21.2%)	64/314 (20.4%)	RR 1.04 (0.76 to 1.41)	8 more per 1000 (from 49 fewer to 84 more)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Clinical outcome (follow-up 28 - 60 days; assessed with: Mortality at 60 days)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	92/307 (30%)	82/314 (26.1%)	RR 1.15 (0.89 to 1.84)	39 more per 1000 (from 29 fewer to 219 more)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Clinical outcome (follow-up 28 - 60 days; measured with: Days without antibiotics; Better indicated by higher values)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	307	314	-	MD 2.7 higher (1.34 to 4.06 higher)	⊕⊕⊕O MODERATE	CRITICAL
Clinical outcome (follow-up 28 - 60 days; assessed with: Relapse (1 - 28 days))												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	20/307 (6.5%)	16/314 (5.1%)	RR 1.28 (0.68 to 2.42)	14 more per 1000 (from 16 fewer to 72 more)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Clinical outcome (follow-up 28 - 60 days; assessed with: Superinfection (1 - 28 days))												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	106/307 (34.5%)	97/314 (30.9%)	RR 1.12 (0.89 to 1.4)	37 more per 1000 (from 34 fewer to 124 more)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Clinical outcome (follow-up 28 - 60 days; measured with: Days without mechanical ventilation; Better indicated by lower values)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	307	314	-	MD 0.7 lower (2.43 lower to 1.03 higher)	⊕⊕⊕O MODERATE	CRITICAL
Hospital and healthcare usage (follow-up 28 - 60 days; measured with: Length of ICU stay (days); Better indicated by lower values)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	307	314	-	MD 1.5 higher (0.88 lower to 3.88 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Hospital and healthcare usage (follow-up 28 - 60 days; measured with: Length of hospital stay (days); Better indicated by lower values)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	307	314	-	MD 0.3 lower (3.26 lower to 2.66 higher)	⊕⊕⊕O MODERATE	IMPORTANT

[1] Bouadma (2010)
[2] Unclear risk of performance bias

GRADE profile 12: Single versus combination antibiotics for ventilator associated pneumonia

Author(s): Heyland
Date: 2014-08-21
Question: Single antibiotic vs combination antibiotics for ventilator associated pneumonia
Settings: Hospital (ICU)

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Single antibiotic**	**Combination antibiotics**	**Relative (95% CI)**	**Absolute**		
Emergence of resistance (follow-up mean 28 days; measured with: Percentage of those with acquired resistance to a single antibiotic class; Better indicated by lower values)												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	369	370	Monotherapy 9.3% Combination therapy 9.1% (p=0.99)		⊕⊕OO LOW	CRITICAL
Clinical outcome (follow-up mean 28 days; measured with: Adequate initial therapy; Better indicated by higher values)												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	369	370	Monotherapy 85.1% Combination therapy 93.1% (p=0.01)		⊕⊕OO LOW	CRITICAL
Clinical outcome (follow-up mean 28 days; measured with: Mortality; Better indicated by lower values)												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	369	370	The authors report no significant difference in mortality at 14 days (no data).		⊕⊕OO LOW	CRITICAL
Clinical outcome (follow-up mean 28 days; measured with: Time to end of mechanical ventilation (days, IQR); Better indicated by lower values)												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	369	370	Monotherapy 8.7 (3.8 – 24.8) Combination therapy 9.3 (3.8 – 21.6) (p=0.79)		⊕⊕OO LOW	CRITICAL
Hospital and healthcare usage (follow-up mean 28 days; measured with: Discharge from ICU (median days, IQR); Better indicated by lower values)												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	369	370	Monotherapy 12.1 (6.4 – 35.2) Combination therapy 12.8 (6.1 – 27) (p=0.84)		⊕⊕OO LOW	IMPORTANT
Hospital and healthcare usage (follow-up mean 28 days; measured with: Discharge from hospital (median days, IQR); Better indicated by lower values)												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	369	370	Monotherapy 45.8 (24.0 – 316.8) Combination therapy 39.1 (19.7 – undefined) (p=0.49)		⊕⊕OO LOW	IMPORTANT

[1] Heyland (2008)
[2] High risk of performance bias and unknown / unclear risk of detection bias

GRADE profile 13: Watchful waiting versus immediate antibiotic therapy for non-severe acute otitis media in children

Author(s): McCormick (2005)
Date: 2014-08-21
Question: Watchful waiting vs immediate antibiotic treatment for non-severe acute otitis media in children
Settings: Community

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Watchful waiting**	**Immediate antibiotic treatment**	**Relative (95% CI)**	**Absolute**		
Emergence of resistance (follow-up mean 12 days; assessed with: Penicillin (intermediate resistance and resistant) resistance of S. Pneumoniae)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	67/100 (67%)	89/100 (89%)	RR 0.75 (0.65 to 0.88)	222 fewer per 1000 (from 107 fewer to 312 fewer)	⊕⊕OO LOW	CRITICAL

								0%		-		
Clinical outcome (follow-up mean 12 days; assessed with: Resolution of AOM (ETG-5 score) at day 12 (less than 2 years old))												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	57/64 (89.1%)	40/54 (74.1%)	RR 1.2 (1.00 to 1.44)	148 more per 1000 (from 0 more to 326 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
Clinical outcome (follow-up mean 12 days; assessed with: Resolution of AOM (ETG-5 score) at day 12 (2 years or older))												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	41/43 (95.3%)	47/53 (88.7%)	RR 1.08 (0.96 to 1.21)	71 more per 1000 (from 35 fewer to 186 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
Clinical outcome (follow-up mean 12 days; assessed with: AOM Failure (at days 1 - 12) less than 2 years old)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	12/50 (24%)	4/65 (6.2%)	RR 3.90 (1.34 to 11.37)	178 more per 1000 (from 21 more to 638 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
Clinical outcome (follow-up mean 12 days; assessed with: AOM Recurrence (at days 13 - 33) less than 2 years old)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	10/50 (20%)	11/65 (16.9%)	RR 1.18 (0.55 to 2.56)	30 more per 1000 (from 76 fewer to 264 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
Clinical outcome (follow-up mean 12 days; assessed with: AOM Failure (at days 1 - 12) 2 years or older)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	9/50 (18%)	1/44 (2.3%)	RR 7.92 (1.04 to 60.06)	157 more per 1000 (from 1 more to 1000 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
Clinical outcome (follow-up mean 12 days; assessed with: AOM Recurrence (at days 13 - 33) 2 years or older)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	3/50 (6%)	9/44 (20.5%)	RR 0.29 (0.08 to 1.02)	145 fewer per 1000 (from 188 fewer to 4 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
Clinical outcome (follow-up mean 12 days; assessed with: AOM Cure less than 2 years old)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	28/50 (56%)	50/65 (76.9%)	RR 0.73 (0.55 to 0.96)	208 fewer per 1000 (from 31 fewer to 346 fewer)	⊕⊕OO LOW	CRITICAL
								0%		-		
Clinical outcome (follow-up mean 12 days; assessed with: AOM Cure 2 years or older)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	38/50 (76%)	34/44 (77.3%)	RR 0.88 (0.72 to 1.07)	93 fewer per 1000 (from 216 fewer to 54 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
Clinical outcome (follow-up mean 12 days; measured with: Pain medication; Better indicated by lower values)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	102	105	-	MD 4.3 higher (2.66 to 5.94 higher)	⊕⊕OO LOW	CRITICAL
Unintended consequence (follow-up mean 12 days; assessed with: Adverse event)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	5/108 (4.6%)	13/111 (11.7%)	RR 0.40 (0.15 to 1.07)	70 fewer per 1000 (from 100 fewer to 8 more)	⊕⊕OO	CRITICAL

								0%		-	LOW	
Hospital or healthcare usage (follow-up mean 12 days; assessed with: Extra office visit)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	22/108 (20.4%)	14/111 (12.6%)	RR 1.62 (0.87 to 2.99)	78 more per 1000 (from 16 fewer to 251 more)	⊕⊕OO LOW	IMPORTANT
								0%		-		
Hospital or healthcare usage (follow-up mean 12 days; assessed with: Emergency department visit)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	4/108 (3.7%)	1/111 (0.9%)	RR 4.11 (0.47 to 36.2)	28 more per 1000 (from 5 fewer to 317 more)	⊕⊕OO LOW	IMPORTANT
								0%		-		
Hospital or healthcare usage (follow-up mean 12 days; assessed with: Extra phone calls)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	26/108 (24.1%)	26/111 (23.4%)	RR 1.03 (0.64 to 1.65)	7 more per 1000 (from 84 fewer to 152 more)	⊕⊕OO LOW	IMPORTANT
								0%		-		

[1] McCormick (2005)
[2] High risk of performance bias, unknown /unclear risk of selection, attrition and detection bias
[3] Low n (=95)

GRADE profile 14: Statistical process charts and structured diagnostic tools versus usual care for ward acquired *S. Aureus*

Author(s): Curran (2008)
Date: 2014-08-21
Question: Statistical process charts and structured diagnostic tools vs usual care for ward acquired S. Aureus
Settings: Hospital

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Statistical process charts and structured diagnostic tools**	**Usual care**	**Relative (95% CI)**	**Absolute**		
Emergence of resistance (follow-up mean 24 months[1]; measured with: Reduction in incidence of ward-acquired MRSA pre-post intervention in each arm; Better indicated by lower values)												
1[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	0[5]	-	SPC arm pre to post intervention mean reduction of 32.3% (95% CI: 19.3 – 45.3) new MRSA cases (p<0.001). SPC + Tools arm pre to post intervention mean reduction of 19.6% (95% CI: 4.1 – 35.1) new MRSA cases (p=0.015). Control arm pre to post intervention mean reduction of 23.1% (95% CI: 11.8 – 34.4) new MRSA cases (p<0.001).		⊕⊕OO LOW	CRITICAL

[1] Also a 25 month observation period prior to intervention
[2] Curran (2008)
[3] Unknown/ unclear risk of selection, performance and detection bias
[4] The total n of included patients is unclear from the study
[5] Not stated

GRADE profile 15: Post-prescription review vs usual care for infections

Author(s): Lesprit 2013
Date: 2014-10-03
Question: Post-prescription review vs usual care for infections
Settings: Secondary care (Hospital)

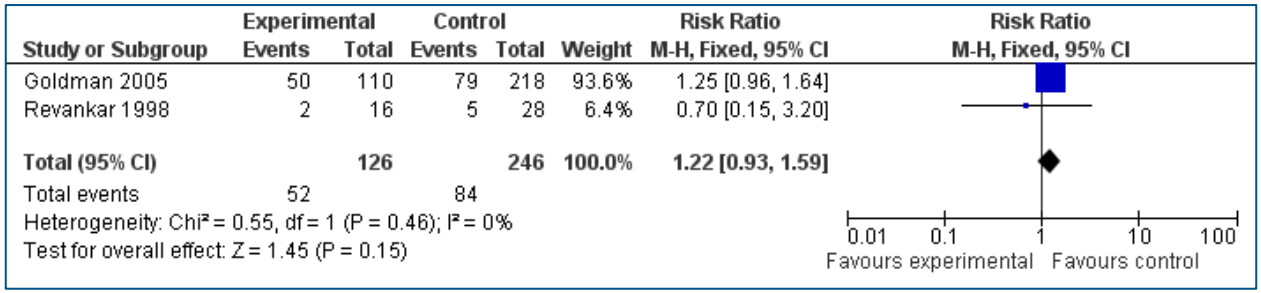
Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Post-prescription review	Usual care	Relative (95% CI)	Absolute		
Hospital mortality (60 days) (follow-up 0 -60 days)												
1	randomised trials	serious1	no serious inconsistency	no serious indirectness	no serious imprecision	none	37/376 (9.8%)	38/377 (10.1%)	RR 0.98 (0.64 to 1.50)	2 fewer per 1000 (from 36 fewer to 50 more)	□□□□ MODERATE	CRITICAL
								0%		-		
New course of antibiotic therapy												
1	randomised trials	serious1	no serious inconsistency	no serious indirectness	no serious imprecision	none	17/376 (4.5%)	25/377 (6.6%)	RR 0.68 (0.37 to 1.24)	21 fewer per 1000 (from 42 fewer to 16 more)	□□□□ MODERATE	CRITICAL
								0%		-		
Antibiotic for relapsing infection												
1	randomised trials	serious1	no serious inconsistency	no serious indirectness	no serious imprecision	none	13/376 (3.5%)	30/377 (8%)	RR 0.43 (0.23 to 0.82)	45 fewer per 1000 (from 14 fewer to 61 fewer)	□□□□ MODERATE	CRITICAL
								0%		-		
Total antibiotic course length (measured with: Median days (IQR); Better indicated by lower values)												
1	randomised trials	serious1	no serious inconsistency	no serious indirectness	no serious imprecision	none	6 (4 – 9)	7 (5 – 9)	p<0.0001		□□□□ MODERATE	CRITICAL
Broad spectrum antibiotic course length (measured with: Median days (IQR); Better indicated by lower values)												
1	randomised trials	serious1	no serious inconsistency	no serious indirectness	no serious imprecision	none	2 (0 – 5)	4 (0 – 7)	p=0.0003		□□□□ MODERATE	CRITICAL
Narrow to intermediate spectrum antibiotic course length (Copy) (measured with: Median days (IQR); Better indicated by lower values)												
1	randomised trials	serious1	no serious inconsistency	no serious indirectness	no serious imprecision	none	5 (0 – 7)	4 (0 – 8)	p=0.13		□□□□ MODERATE	CRITICAL
ICU admission (follow-up 0 -60 days; assessed with: Within 7 days of randomisation)												

Author(s): Lesprit 2013 Date: 2014-10-03 Question: Post-prescription review vs usual care for infections Settings: Secondary care (Hospital)												
1	randomised trials	serious1	no serious inconsistency	no serious indirectness	no serious imprecision	none	7/376 (1.9%)	6/377 (1.6%)	RR 1.17 (0.40 to 3.45)	3 more per 1000 (from 10 fewer to 39 more)	□□□□ MODERATE	IMPORTANT
								0%		-		
Length of stay (overall) (measured with: Median days (IQR); Better indicated by lower values)												
1	randomised trials	serious1	no serious inconsistency	no serious indirectness	no serious imprecision	none	15 (9 -25)	15 (9 – 27)	p=0.95		□□□□ MODERATE	IMPORTANT
Length of stay (community acquired infection) (measured with: Median days (IQR); Better indicated by lower values)												
1	randomised trials	serious1	no serious inconsistency	no serious indirectness	no serious imprecision	none	5 (3 – 10)	6 (3 – 14)	p=0.06		□□□□ MODERATE	CRITICAL
Emergence of resistance (assessed with: Resistant organisms at follow-up)												
1	randomised trials	serious1	no serious inconsistency	no serious indirectness	no serious imprecision	none	23/376 (6.1%)	27/377 (7.2%)	RR 0.85 (0.50 to 1.46)	11 fewer per 1000 (from 36 fewer to 33 more)	□□□□ MODERATE	CRITICAL
								0%		-		

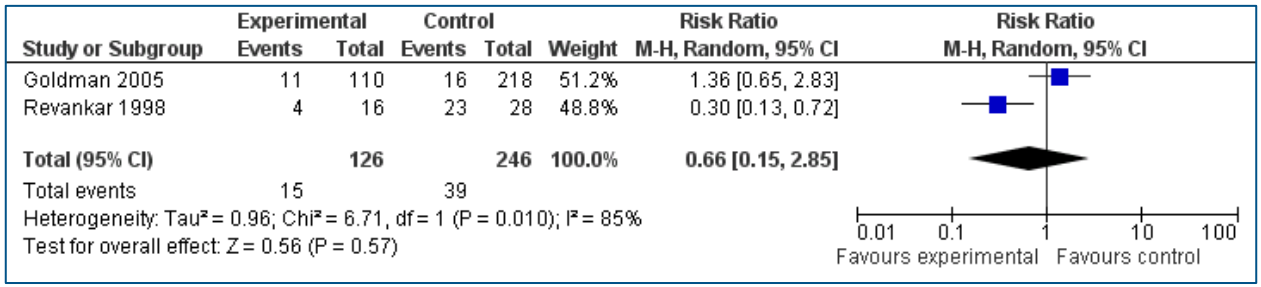
[1] There was an unclear risk of performance and detection bias

Pooled (meta) analyses

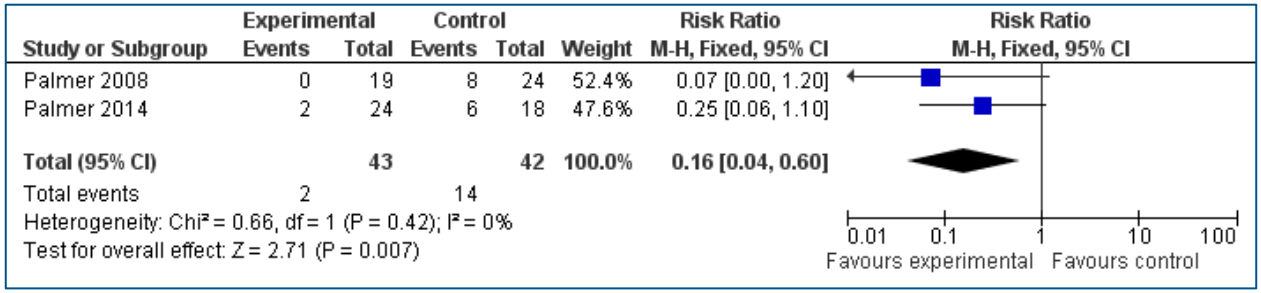
Goldman (2005) and Revankar (2008) for emergence of resistance



Goldman (2005) and Revankar (1998) for number of candida infections

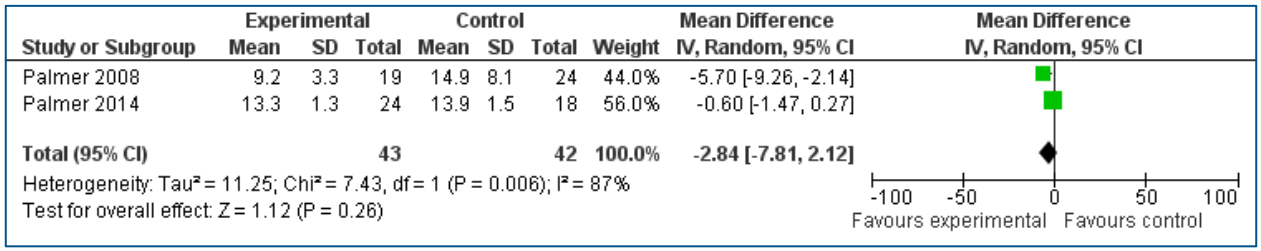


Palmer (2008) and Palmer (2014) for emergence of resistance

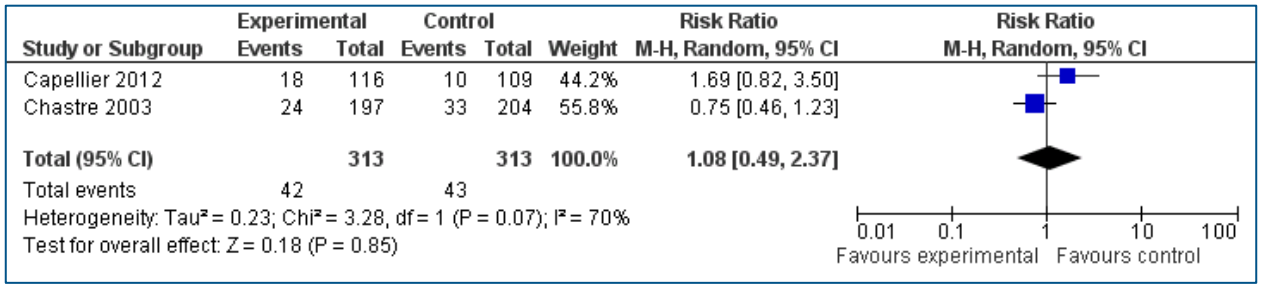


Palmer (2008) and Palmer (2014) for mortality

Palmer (2008) and Palmer (2014) for white cells at follow-up



Capellier (2012) and Chastre (2003) for emergence of resistance



Heterogeneity

The term is used in meta-analyses (pooled analyses) and systematic reviews to describe when the results of a test or treatment (or estimates of its effect) differ significantly in different studies. Such differences may occur as a result of differences in: the populations studied, the outcome measures used or because of different definitions of the variables involved. It is the opposite of homogeneity.

Heterogeneity can be measured using the I^2 statistic, a guide to its approximate interpretation is provided by the Cochrane Handbook.

0% to 40%: might not be important;

30% to 60%: may represent moderate heterogeneity*;

50% to 90%: may represent substantial heterogeneity*;

75% to 100%: considerable heterogeneity*.

*The importance of the observed value of I2 depends on (i) magnitude and direction of effects and (ii) strength of evidence for heterogeneity (e.g. P value from the chi-squared test, or a confidence interval for I^2).

In this analyses we have not included more than two data sets in any meta-analysis in most cases the sources of heterogeneity, where significant heterogeneity exists, is clear (small study effects etc.). Random effects models have been used to incorporate the heterogeneity into the modelling where appropriate. In only one case (Palmer (2008) and Palmer (2014) for white cells) did the use of random effects modelling change the direction of the pooled outcome. This is detailed in the evidence statements.

D.2.2 Decision making

Within the GRADE profiles below the individual studies in the Cochrane reviews that included systematic reviews and meta-analysis have been assessed separately. For the Cochrane review based on individual patient data meta-analysis this has been assessed overall (Schuetz, 2013)

GRADE profile 16: Antimicrobial use

Reference	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Outcomes	Other	Quality
Arroll (2002)	RCT	Very serious[1]	N/A	Serious[2]	Serious [3]	Antibiotic use, delayed antibiotics N=32/67 (47.8%), immediate antibiotics N=55/67 (82.1%), OR 0.20 (95%CI, 0.09 to 0.44)		⊕OOO VERY LOW
Butler (2012)	RCT	Very serious[4]	N/A	Serious[5]	No serious	%reduction intervention relative to control (difference in means, 95%CI) 4.2 (0.6 to 7.7), p=0.02		⊕⊕OO LOW
Dowell (2001)	RCT	Very serious [6]	N/A	No serious	Serious [3]	Antibiotic use, delayed antibiotics N=43/95 (45.3%), immediate antibiotics N=92/93 (98.9%), OR 0.00 (95%CI, 0.02 to 0.08)		⊕OOO VERY LOW
Gerber (2013)	Cluster RCT	Very serious [4]	N/A	Serious [7]	No serious	Antibiotic prescribing decrease; intervention 26.8% to 14.3%, control 28.4% to 22.6%, difference of differences 6.7% (p=0.01)		⊕OOO VERY LOW
Gjelstad (2013)	Cluster RCT	Very serious [8]	N/A	Serious [10]	No serious	Change in prescribing rates, mean (95%CI); intervention -1.29 (-2.43 to -0.16), control 1.49 (0.58 to 2.40)		⊕OOO VERY LOW

Reference	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Outcomes	Other	Quality
						After intervention OR for prescribing an antibiotic 0.72 (95%CI, 0.61 to 0.84)		
Linder (2009)	Cluster RCT	Very serious [8]	N/A	Serious [9]	No serious	Antibiotic prescribing; intervention N=4601 (39%) of visits, control N=4316 (43%), OR 0.8 (95%CI, 0.6 to 1.4), p=0.30		⊕OOO VERY LOW
Little (1997)	RCT	Very serious[4]	N/A	Serious [10]	No serious	Antibiotic use, delayed antibiotics N=55/176 (31.3%), immediate antibiotics N=210/211 (99.5%), OR 0.00 (95%CI, 0.00 to 0.02)		⊕OOO VERY LOW
Little (2001)	RCT	Very serious [8]	N/A	Serious [10]	No serious	Antibiotic use, delayed antibiotics N=36/150 (42%), immediate antibiotics N=132/151 (87.4%), OR 0.05 (95%CI, 0.02 to 0.08)		⊕OOO VERY LOW
Little (2005)	RCT	Very serious[4, 11]	N/A	Serious [10]	No serious	Antibiotic use, delayed antibiotics N=55/176 (31.3%), immediate antibiotics N=210/211 (99.5%), OR 0.00 (95%CI, 0.00 to 0.02)		⊕OOO VERY LOW
Seager (2006)	Cluster RCT	Very serious [4]	N/A	No serious	Serious [3,12]	Antibiotic prescribing; control group 32% (ref, OR 1), guideline group 29%, OR 0.83 (95%CI, 0.55 to 1.21), intervention group 23%, OR 0.63 (95%CI, 0.41 to 0.95)		⊕OOO VERY LOW
Shojania (1998)	RCT	Very serious [8]	N/A	Serious [13]	Serious [14]	Patients per physician prescribed vancomycin, mean (SD); intervention 7.4±11.4, control 10.3±15.1, p=0.02		⊕OOO VERY LOW
Spiro (2006)	RCT	Very serious [4]	N/A	Serious[13]	No serious	Antibiotic use, delayed antibiotics N=50/132 (37.9%), immediate antibiotics N=116/133 (87.2%), OR 0.09 (95%CI, 0.05 to 0.17)		⊕OOO VERY LOW
Welschen (2004)	RCT	Very serious [8]	N/A	Serious [10]	Serious [14]	Change in prescription rates, %change (SD); intervention -4 (15.6), control 8 (19.2), mean difference (95%CI) -12 (-18.9 to -4.0)		⊕OOO VERY LOW

[1] single-blind/no blinding, unclear how data collected/measured
[2] small number of GPs selected from a groups already using delayed prescribing
[3] did not achieve aimed for sample size
[4] allocation concealment unclear, no blinding
[5] previous year's antibiotic dispensing rate from the randomised practices was 15%lower than the Welsh average
[6] no details on recruitment
[7] small number of primary care practices, or unclear how selected
[8] lack of randomisation details or inadequate randomisation, no blinding
[9] intervention linked to US longitudinal record system
[10] unclear prescriber recruitment or self-selected prescriber participation (such as members of peer review groups/continuing education groups/research network members)
[11] differences in patient recruitment between prescribers
[12] high drop-out rate following randomisation, per protocol analysis
[13] single hospital site
[14] no sample size consideration

GRADE profile 17: Appropriate prescription/selection of antimicrobial

Reference	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Outcomes	Other	Quality
Camins (2009)	RCT	Very serious [1]	N/A	Serious [2]	Serious [3]	Appropriate initial antimicrobial use; RR (95%CI) 1.35		⊕OOO

Reference	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Outcomes	Other	Quality
						(1.22 to 1.49), p<0.001 Appropriate and antimicrobial use; RR (95%CI) 1.34 (1.25 to 1.43), p<0.001		VERY LOW
Draitsaris (2001)	RCT	Serious [4]	N/A	Serious [5]	Serious [3]	Prescriptions meeting guidelines; intervention (122/162, 75%), control (102/147, 69%), p=0.24		⊕OOO VERY LOW
Seager (2006)	Cluster RCT	Very serious [6]	N/A	No serious	Serious [3,7]	Inappropriate antibiotic prescribing; control group 18% (ref, OR 1), guideline group 15%, OR 0.82 (95%CI, 0.53 to 1.29), intervention group 7%, OR 0.33 (95%CI, 0.21 to 0.54)		⊕OOO VERY LOW
Solomon (2001)	RCT	Serious [4]	N/A	Serious [2]	Serious [8]	Number of days of unnecessary target antibiotic use per 2week interval, mean (SD); intervention 8.5±7.8, control 7.6±4.7, p=0.80		⊕OOO VERY LOW

[1] no details on randomisation
[2] single hospital site
[3] did not achieve aimed for sample size
[4] no allocation concealment, insufficient blinding
[5] two hospital sites
[6] lack of randomisation details, no blinding
[7] high drop-out rate following randomisation, per protocol analysis
[8] no sample seize consideration

GRADE profile 18: Duration of therapy

Reference	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Outcomes	Other	Quality
Christakis (2001)	RCT	Very serious [1]	N/A	Serious [2]	No serious	<10days of therapy, change from baseline; intervention (44.43%, SE 4.24%), control (10.48%, 5.25%), for the difference p=0.000		⊕OOO VERY LOW
Fine (2003)	Cluster RCT	Very serious [3]	N/A	Serious [4]	No serious	Duration of therapy in days; HR 1.23 (1.00 to 1.52), p=0.069		⊕OOO VERY LOW
Lesprit (2012)	RCT	Very serious [8]	N/A	Serious [6]	No serious	Duration of therapy; intervention, median (IQR) 6 (4 to 9), control 7 (5 to 9), p<0.0001		⊕OOO VERY LOW
Shojania (1998)	RCT	Very serious [5]	N/A	Serious [6]	Serious [7]	Duration of therapy, mean (SD); intervention 2.0±1.1, control 1.8±1.1, p=0.05		⊕OOO VERY LOW

[1] allocation concealment unclear, no blinding, authors noted the potential for differences between the groups, baseline data collected in summer, intervention in autumn/winter
[2] single outpatient clinic
[3] lack of randomisation details, allocation concealment unclear, no blinding
[4] patient s with pneumonia
[5] lack of randomisation details, no allocation concealment, no blinding
[6] single hospital site
[7] no sample size consideration
[8] no blinding, unclear how data collected/measured

GRADE profile 19: Mortality

Reference	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Outcomes	Other	Quality
Camins (2009)	RCT	Very serious [1]	N/A	Serious [2]	Serious [3]	In-hospital mortality; intervention N=11/390 (3%), control N=18/194 (5%), p=0.18		⊕OOO VERY LOW
Lesprit (2012)	RCT	Very serious [9]	N/A	Serious [2]	No serious	60day in-hospital mortality; intervention, N (%) 37 (9.8%), control 38 (10.1%), p=0.91		⊕OOO VERY LOW
McGregor (2006)	RCT	Very serious [1]	N/A	Serious [4]	Serious [5]	In-hospital mortality; intervention N=73 (3.26%), control N=67 (2.95%), p=0.55		⊕OOO VERY LOW
Solomon (2001)	RCT	Serious [6]	N/A	Serious [2]	Serious [7]	Death during admission, %; intervention 2.3%, control 2.2%, p=0.90		⊕OOO VERY LOW

[1] no details on randomisation, allocation concealment unclear, no blinding
[2] single hospital site
[3] did not achieve aimed for sample size
[4] intervention linked to US electronic system, single hospital site
[5] interim analysis, no sample size consideration
[6] no allocation concealment, insufficient blinding
[7] no sample seize consideration

GRADE profile 20: Length of hospitalisation

Reference	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Outcomes	Other	Quality
Camins (2009)	RCT	Very serious [1]	N/A	Serious [2]	Serious [3]	Length of stay; intervention, median (range), 7days (1 to 50), control 8days (2 to 86), p=0.03		⊕OOO VERY LOW
Lesprit (2012)	RCT	Very serious [9]	N/A	Serious [2]	No serious	Length of stay; intervention, median (IQR) 15days (9 to 25), control 15 (9 to 27), p=0.01		⊕OOO VERY LOW
McGregor (2006)	RCT	Very serious [1]	N/A	Serious [4]	Serious [5]	Length of stay; intervention, median (IQR) 3.84days (2.12 to 7.57), control 3.99days (2.19 to 7.57), p=0.38		⊕OOO VERY LOW
Fine (2003)	Cluster RCT	Very serious [1]	N/A	Serious [6]	No serious	Length of stay in days; HR 1.16 (0.97 to 1.38), p=0.11		⊕OOO VERY LOW
Solomon (2001)	RCT	Serious [7]	N/A	Serious [2]	Serious [8]	Length of admission, days, mean (SD); intervention 4.8±6.0, control 4.8±5.5, p=0.94		⊕OOO VERY LOW

*due to study design begins the GRADE assessment at low
[1] no details on randomisation, allocation concealment unclear, no blinding
[2] single hospital site
[3] did not achieve aimed for sample size
[4] intervention linked to US electronic system, single hospital site
[5] interim analysis, no sample size consideration
[6] patients with pneumonia
[7] no allocation concealment, insufficient blinding
[8] differences between pre and post-intervention groups

GRADE profile 21: adverse events

Reference	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Outcomes	Other	Quality
Vomiting								
Little (1997)	RCT	Very serious[1]	N/A	Serious [2]	No serious	Antibiotic use, delayed antibiotics N=45/179 (8.4%), immediate antibiotics N=18/215 (8.4%), OR 1.00 (95%CI, 0.49 to 2.05)		⊕OOO VERY LOW
Spiro (2006)	RCT	Very serious [1]	N/A	Serious[3]	No serious	Antibiotic use, delayed antibiotics N=15/132 (11.4%), immediate antibiotics N=15/133 (11.3%), OR 1.01 (95%CI, 0.47 to 2.16)		⊕OOO VERY LOW
Diarrhoea								
Arroll (2002)	RCT	Very serious[1]	N/A	Serious[2]	Serious [3]	Antibiotic use, delayed antibiotics N=11/67 (16.4%), immediate antibiotics N=12/62 (19.4%), OR 0.82 (95%CI, 0.33 to 2.02)		⊕OOO VERY LOW
Little (1997)	RCT	Very serious[1]	N/A	Serious [2]	No serious	Antibiotic use, delayed antibiotics N=23/179 (12.9%), immediate antibiotics N=23/215 (10.7%), OR 1.23 (95%CI, 0.67 to 2.28)		⊕OOO VERY LOW
Little (2001)	RCT	Very serious [4]	N/A	Serious [2]	No serious	Antibiotic use, delayed antibiotics N=14/150 (9.3%), immediate antibiotics N=25/135 (18.5%), OR 0.45 (95%CI, 0.22 to 0.91)		⊕OOO VERY LOW
Spiro (2006)	RCT	Very serious [1]	N/A	Serious[3]	No serious	Antibiotic use, delayed antibiotics N=10/132 (7.6%), immediate antibiotics N=31/133 (23.3%), OR 0.27 (95%CI, 0.13 to 0.58)		⊕OOO VERY LOW
Rash								
Little (1997)	RCT	Very serious[1]	N/A	Serious [2]	No serious	Antibiotic use, delayed antibiotics N=11/180 (6.1%), immediate antibiotics N=14/215 (99.5%), OR 0.93 (95%CI, 0.41 to 2.11)		⊕OOO VERY LOW
Little (2001)	RCT	Very serious [4]	N/A	Serious [2]	No serious	Antibiotic use, delayed antibiotics N=8/150 (5.3%), immediate antibiotics N=6/135 (4.4%), OR1.21 (95%CI, 0.41 to 3.58)		⊕OOO VERY LOW
Stomach ache								
Little (1997)	RCT	Very serious[1]	N/A	Serious [2]	No serious	Antibiotic use, delayed antibiotics N=48/180 (26.7%), immediate antibiotics N=66/215 (99.5%), OR 0.82 (95%CI, 0.53 to 1.27)		⊕OOO VERY LOW

[1] allocation concealment unclear, no blinding
[2] unclear prescriber recruitment or self-selected prescriber participation (such as members of peer review groups/continuing education groups/research network members)
[3] single hospital site
[4] lack of randomisation details or inadequate randomisation, no blinding

GRADE profile 22: point-of-care; antibiotic use

Reference	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Outcomes	Other	Quality
Andreeva	Cluster RCT	Very serious[1]	N/A	Serious[2]	Serious[3]	Antibiotic prescribing, CRP N=18/49, standard care		⊕OOO

Reference	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Outcomes	Other	Quality
(2013)						N=22/38, RR (95%CI) 0.63 (0.40 to 1.00)		VERY LOW
Baer (2013)	RCT	Serious[4]	N/A	Serious[5]	Serious[6]	Antibiotic prescribing (community-acquired pneumonia), PCT N=77/108, control N=83/105, OR (95%CI) 0.66 (0.35 to 1.23)		⊕OOO VERY LOW
Cals (2009)	Cluster RCT	Very serious[4]	N/A	Serious[2]	Serious [17]	Antibiotic prescribing, CRP , N=39/110 (43%), usual care N=67/120 (80%)		⊕OOO VERY LOW
Cals (2010)	RCT	Very serious[4]	N/A	Serious[2]	No serious	Antibiotic prescribing, CRP N=56/129, standard care N=73/129, RR(95%CI) 0.77 (0.60 to 0.98)		⊕OOO VERY LOW
Diederichsen (2000)	RCT	Very serious[1]	N/A	No serious	Serious[7]	Antibiotic prescribing, CRP N=179/414, standard care N=184/398, RR (95%CI) 0.94 (0.80 to 1.09)		⊕OOO VERY LOW
Esposito (2011)	RCT	Very serious[8]	N/A	Serious[5]	Serious[8]	Never given antibiotics, PCT N=24/155, between group difference for rate and duration of antibiotics, p<0.05		⊕OOO VERY LOW
Gonzales (2011)	RCT	Very serious[9]	N/A	Serious[10]	Serious[6]	Antibiotic prescribing, CRP 37% (95%CI) 26 to 48%, control 31% (95%CI) 19 to 43%, p=0.46		⊕OOO VERY LOW
Manzour (2010)	RCT	Very serious[11]	N/A	Serious[10]	No serious	Antibiotic prescribing, PCT N=48/192, control N=54/192), % difference (95%CI) -3 (-12 to 6)		⊕OOO VERY LOW
Schuetz (2013)	Individual patient meta-analysis	No serious	Serious[12]	No serious	Serious[13]	Initiation of antibiotic prescribing, PCT N=1341/2085, control N=1778/2126, adjusted OR (95%CI), 0.24 (0.20 to 0.29), p<0.001		⊕⊕OO LOW

[1] randomisation unclear, allocation concealment unclear, no blinding, physician recruitment to trial
[2] unclear how selected GPs selected
[3] following adjustment in Cochrane analysis does not meet aimed for sample size
[4] no blinding, physician recruitment to trial
[5] adult values used for children or unclear if children's values used
[6] did not achieve aimed for sample size
[7] no sample size consideration
[8] incomplete outcome reporting
[9] allocation concealment unclear, no blinding
[10] single hospital site
[11] randomisation unclear, allocation concealment unclear, no blinding, physician recruitment to trial
[12] variation in the risk of bias consideration in the included studies, no blinding
[13] variation in adherence to procalcitonin algorithm
[17] factorial design trial, testing for significance not done for antibiotic prescribing

GRADE profile 23: point-of-care; mortality

Reference	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Outcomes	Other	Quality
Schuetz (2013)	Individual patient meta-analysis	No serious	Serious[1]	No serious	Serious[2]	Mortality, PCT N=118/2085, control N=134/2126, adjusted OR (95%CI), 0.29 (0.71 to 1.23), p=0.754		⊕⊕OO LOW

[1] variation in the risk of bias consideration in the included studies, no blinding

Reference	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Outcomes	Other	Quality
[2] variation in adherence to procalcitonin algorithm								

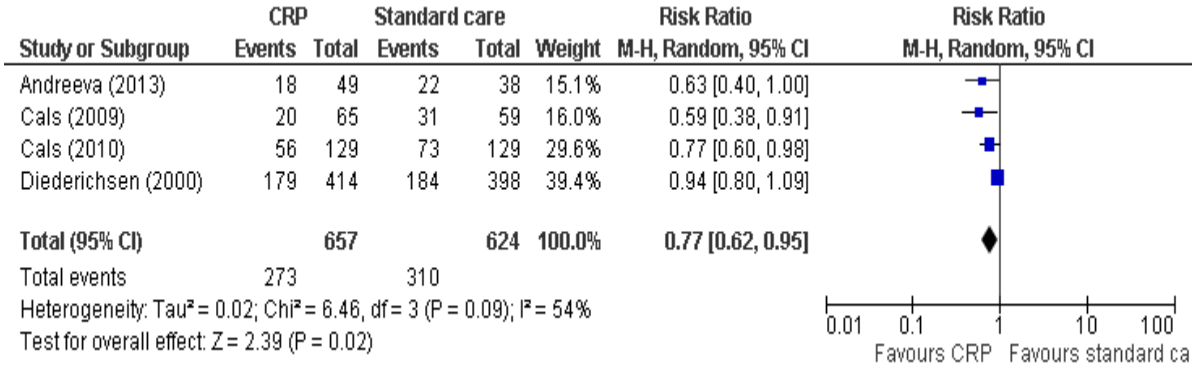
GRADE profile 24: point-of-care; length of stay

Reference	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Outcomes	Other	Quality
Gonzales (2011)	RCT	Very serious[1]	N/A	Serious[2]	Serious[3]	Length of stay, median minutes (IQR), CRP 283 (95%CI) 200 to 362, control 285 (95%CI) 208 to 369, p=0.73		⊕OOO VERY LOW

[1] allocation concealment unclear, no blinding
[2] single hospital site
[3] did not achieve aimed for sample size

Forest plot 1:

Figure 1: CRP, antibiotic prescribing (Aabenhus, 2014)



D.2.3 Barriers to decision making

Quality assessment checklist used as outlined in Appendix H.

D.2.4 Timely adoption and diffusion of a new antimicrobial

GRADE profile 25: reported susceptibility vs usual reporting

Author(s): McNulty (2011)
Date: 2014-10-07
Question: Amendment of reported susceptibility vs usual reporting be used for adoption and diffusion of new antibiotics?
Settings: Primary care

Quality assessment							No of patients	Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Absolute (95% CI)		
Cefalexin prescribing rate (follow-up up to 14 months; measured with: Survey results)										
1	observational studies	serious1, 2	no serious inconsistency	serious1	no serious imprecision	none	N/A	OR 9.88 higher (3.0 to 32.51)	LOW	CRITICAL
Co-amoxiclav prescribing rate (follow-up up to 14 months; measured with: Survey results)										
1	observational studies	serious1, 2	no serious inconsistency	serious1	no serious imprecision	none	N/A	OR 0.30 lower (0.16 to 0.57)	LOW	CRITICAL
Cefalexin prescribing rate (follow-up up to 14 months; measured with: MIQUEST query)										
1	observational studies	serious1, 2	no serious inconsistency	serious1	no serious imprecision	none	N/A	OR 1.5 higher (1.18 to 1.95)	LOW	CRITICAL
Co-amoxiclav prescribing rate (follow-up up to 14 months; measured with: MIQUEST query)										
1	observational studies	serious1, 2	no serious inconsistency	serious1	no serious imprecision	none	N/A	OR 0.75 lower (0.58 to 0.97)	LOW	CRITICAL
Cefalexin (second antibiotic) prescribing rate (follow-up up to 14 months; measured with: MIQUEST query)										
1	observational studies	serious1, 2	no serious inconsistency	serious1	no serious imprecision	none	N/A	OR 2.18 higher (1.44 to 3.30)	LOW	CRITICAL
Co-amoxiclav (second antibiotic) prescribing rate (follow-up up to 14 months; measured with: MIQUEST query)										
1	observational studies	serious1, 2	no serious inconsistency	serious1	no serious imprecision	none	N/A	OR 2.44 higher (2.01 to 2.97)	LOW	CRITICAL
Ciprofloxacin prescribing rate (follow-up up to 14 months; measured with: MIQUEST query)										
1	observational studies	serious1, 2	no serious inconsistency	serious1	no serious imprecision	none	N/A	OR 0.66 lower (0.485 to 0.897)	LOW	CRITICAL

Author(s): McNulty (2011) **Date: 2014-10-07** **Question: Amendment of reported susceptibility vs usual reporting be used for adoption and diffusion of new antibiotics?** **Settings: Primary care**										
Cefradine prescribing rate (follow-up up to 14 months; measured with: MIQUEST query; After, but not during, the intervention period)										
1	observational studies	serious1, 2	no serious inconsistency	serious1	no serious imprecision	none	N/A	OR 0.73 lower (0.60 to 0.89)	LOW	CRITICAL
Nitrofurantoin prescribing rate (follow-up up to 14 months; measured with: MIQUEST query)										
1	observational studies	serious1, 2	no serious inconsistency	serious1	no serious imprecision	none	N/A	OR 1.20 higher (1.02 to 1.41)	LOW	CRITICAL
Cefalexin prescribing rate (follow-up up to 14 months; measured with: PACT data)										
1	observational studies	serious1, 2	no serious inconsistency	serious1	no serious imprecision	none	N/A	OR 1.20 higher (1.12 to 1.30)	LOW	CRITICAL
Co-amoxiclav prescribing rate (follow-up up to 14 months; measured with: PACT data)										
1	observational studies	serious1, 2	no serious inconsistency	serious1	no serious imprecision	none	N/A	OR 0.92 lower (0.89 to 0.96)	LOW	CRITICAL
All oral Cephalosporins prescribing rate (follow-up up to 14 months; measured with: PACT data)										
1	observational studies	serious1, 2	no serious inconsistency	serious1	no serious imprecision	none	N/A	OR 1.04 higher (1.00 to 1.09)	LOW	CRITICAL
Nitrofurantoin prescribing rate (follow-up up to 14 months; measured with: PACT data)										
1	observational studies	serious1, 2	no serious inconsistency	serious1	no serious imprecision	none	N/A	OR 1.12 higher (1.06 to 1.19)	LOW	CRITICAL

Appendix E: Economic evidence tables

E.1 Reducing antimicrobial resistance.

No economic evidence was identified

E.2 Decision making

Evidence Table 70: Jensen KM. Cost effectiveness of abbreviating the duration of intravenous antibacterial therapy with oral fluoroquinolones

Jensen KM; Paladino, JA. Cost effectiveness of abbreviating the duration of intravenous antibacterial therapy with oral fluoroquinolones. *PharmacoEconomics* 11(1):64-74. 1997.

Study details	Population and interventions	Costs	Health outcomes	Cost effectiveness
Economic analysis: Cost effectiveness analysis (CEA) **Study design:** Randomised controlled trial data from two trials informed a decision tree model. **Approach to analysis:** Perspective: Integrated Health Network perspective (IHN) i.e. a wider scope of both inpatient and outpatient care costs. Time horizon: Not stated Discounting: No discounting was applied, since benefits occurred at the same time as costs.	**Population** Hospitalised adult patients (≥18 years of age) with serious bacterial infections, caused by organisms that were susceptible to the parenteral antibacterials and the oral fluoroquinolones used were enrolled if therapy was anticipated to last a minimum of 7 to 8 days. **Intervention** Parenteral antibacterials for only 2 to 4 days, followed by either oral ciprofloxacin (750mg every 12 hours) or oral enoxacin (400mg every 12 hours), for a total therapy duration of at least 7 to 8 days **Comparator** Standard duration therapy with parenteral antibacterials, usually	**Total cost** At level 4 the mean cost ± SEM was: Intervention:$4818 ± $269 Control: $5028 ± $294 (p=0.14[1]) **Currency & cost year:** US Dollars ($), 1995 **Cost components incorporated:** Level 1: drug acquisition cost only Level 2: level 1 plus costs of laboratory drug monitoring, treatment of adverse events, secondary antibacterials and preparation and administration Level 3: level 2 plus costs of physician care. diagnostic and therapeutic procedures and	The probability of clinical success was 0.76 for the switch therapy group and 0.72 for the standard IV therapy group, a non-significant difference (p=0.7). The probability of treatment failure was 0.19 for the switch therapy group and 0.21 for the standard IV therapy group, respectively (p=0.7). The probability of failure due to lack of efficacy was 0.08 in the switch therapy group and 0.20 in the standard IV therapy group (p=0.03), and due to adverse drug reaction 0.11 and 0.01, respectively (p=0.02). Adverse events which were probably related to a study drug	**ICER:** No incremental analysis was performed. The cost-effectiveness ratios were $6339 for each successful outcome in the switch therapy group versus $6983 in the standard group. **Analysis of uncertainty:** One way sensitivity analysis was conducted on the probability of treatment success, the cost per day of hospitalisation and drug cost were varied. At level 4 substantial drug acquisition cost changes were required before standard IV therapy became more cost effective. The model was not sensitive to hospitalisation costs.

Jensen KM; Paladino, JA. Cost effectiveness of abbreviating the duration of intravenous antibacterial therapy with oral fluoroquinolones. *PharmacoEconomics* 11(1):64-74. 1997.				
	7 to 8 days, with subsequent change to oral antibacterials allowed.	outpatient visits Level 4: level 3 plus the base cost per hospital day ($US270)	occurred in 50% of switch therapy patients and in 33% of standard IV therapy patients (p=0.02). Additionally 3 patients died but this did not alter the results of modelling, and are not further discussed.	The model was sensitive to changes in the probability of treatment success (if standard IV therapy was effectiveness was increased by 8% to 80% and switch therapy was decreased by 6% to 70%).
1 Wilcoxon Rank Sum Test SEM=Standard Error of the Mean				

Evidence Table 71: McGregor, JC. *et al*. (2006) Impact of a computerized clinical decision support system on reducing inappropriate antimicrobial use: a randomized controlled trial

McGregor JC, Weekes E, Forrest GN, Standiford HC, Perencevich EN, Furuno JP et al. Impact of a computerized clinical decision support system on reducing inappropriate antimicrobial use: a randomized controlled trial. *J Am Med Inform Assoc* 2006; 13(4):378-384.				
Study details	**Population and interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Authors state that this is a cost effectiveness analysis (CEA). No summary measure of health benefit was included by the authors (costs and benefits were not combined). Therefore, the study was effectively a cost-consequences analysis. **Study design:** Data from a US randomized controlled trial in adult inpatients **Approach to analysis:** Perspective: Appears to adopt a payer perspective only Time horizon: Not stated	**Population** Adult inpatients admitted to wards managed by the antimicrobial management team (all wards except shock trauma, cancer, and pediatric wards) between May 10 and August 3, 2004 were randomized to one arm of the trial. **Intervention** Standard care provided by an antimicrobial management team but supplemented with the web-based clinical decision support system designed to assist in the management of antimicrobial utilization. **Comparator**	**Total cost** During the 3-month study period, the University of Maryland Medical Center spent $285,812 on antimicrobials in the intervention arm and $370,006 in the control arm. **Currency & cost year:** US Dollars ($), [cost year not stated] **Cost components incorporated:** Hospital antimicrobial expenditure only.	*Patient mortality:* No significant difference in the in-hospital mortality between patients assigned to the intervention and the control arms (p=0.55) *Length of hospitalization:* No significant difference was observed in the length of hospitalization between the two study arms (p=0.38). *Frequency of testing for Clostridium difficile:* Fewer patients in the intervention than the control arm experienced diarrhoea as a side effect of antimicrobial use as indicated by testing for C.	**ICER:** No incremental analysis was performed. The intervention arm was associated with savings of $84,194 (22.8%) ($37.64 per patient in the intervention arm). **Analysis of uncertainty:** No sensitivity analysis was performed.

McGregor JC, Weekes E, Forrest GN, Standiford HC, Perencevich EN, Furuno JP et al. Impact of a computerized clinical decision support system on reducing inappropriate antimicrobial use: a randomized controlled trial. *J Am Med Inform Assoc* 2006; 13(4):378-384.				
Discounting: Not stated	Standard care provided by the team.		difficile, though the difference was not statistically significant (5.7% vs. 6.6%) patients, respectively; p=0.21. There were also no significant differences in the number of positive C. difficile tests (p=0.49) between the intervention and control groups.	

Evidence Table 72: Scheetz, MH *et al*., (2009) Cost-effectiveness analysis of an antimicrobial stewardship team on bloodstream infections: a probabilistic analysis

Scheetz, MH; Bolon, MK; Postelnick, M *et al* (2009) Cost-effectiveness analysis of an antimicrobial stewardship team on bloodstream infections: a probabilistic analysis. *Journal of Antimicrobial Chemotherapy* (2009) 63, 816–825				
Study details	**Population and interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost utility analysis **Study design:** Decision analytic model with data identified by a systematic review of the literature (experimental and observational studies and one clinical guideline report) **Approach to analysis:** Perspective: Institutional perspective Time horizon: Not reported Discounting: No discounting applied	**Population:** Patients with bloodstream infections that were either Gram-negative or Staphylococcus aureus during their hospital admission were included in the model. The analysis covered the duration of hospital stay. **Intervention:** The presence of an Antimicrobial Stewardship Team (AST) who switch patients from receiving no treatment for significant Blood Stream Infections (BSIs) into the category of active treatment for their infection. The use of decision support was included in the model. **Comparator:**	**Total cost (Base case):** Intervention: $40144 Standard treatment: $39776 **Currency & cost year:** US Dollars ($), no cost year given (or any inflationary factors to costs). **Cost components incorporated:** Hospital costs (including intensive care costs), superinfection, AST cost, cost of a computerised clinical decision support tool (including support and maintenance). Cost of BSI based upon the incidence of BSI at a large academic medical centre.	**Total QALYs (Base case):** Intervention: 8.01 QALYs Comparator: 7.92 QALYs Please note that the utility weights associated with having bloodstream infections were based on authors' assumptions.	**ICER:** The base case ICER for AST compared with standard care was $4089 per QALY gained. **Probability cost-effective:** Results from the probabilistic sensitivity analysis demonstrated there was more than 90% likelihood that an AST would be cost-effective at a level of $10000 per QALY. **Analysis of uncertainty:** One-way sensitivity analysis of probability of receiving an active antibiotic on general floors[1] resulted in ICERs that ranged from $2014 to $22696 per QALY. For ICU patients the ICER ranged from $3358 to

Scheetz, MH; Bolon, MK; Postelnick, M *et al* (2009) Cost-effectiveness analysis of an antimicrobial stewardship team on bloodstream infections: a probabilistic analysis. *Journal of Antimicrobial Chemotherapy* (2009) 63, 816–825				
	Standard care (no AST).			$3683 per QALY. In a probabilistic sensitivity analyses, the 95% confidence interval for the incremental cost-effectiveness ratio ranged from dominant (cheaper and more effective) to $24,379 per QALY.
1 The model was stratified according to the likelihood of being on a general ward (floor) or an intensive care unit (ICU)				

Evidence Table 73: Hunter, R (2015) Cost-Effectiveness of Point-of-Care C-Reactive Protein Tests for Respiratory Tract Infection in Primary Care in England

Hunter, R (2015) Cost-Effectiveness of Point-of-Care C-Reactive Protein Tests for Respiratory Tract Infection in Primary Care in England. *Advances in Therapy* (2015) 32:69–85				
Study details	**Population and interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost utility analysis **Study design:** Decision analytic model with data identified from previous studies used for the model probabilities **Approach to analysis:** Perspective: NHS (payer) perspective Time horizon: 3 year time horizon for the Markov model	**Population:** A hypothetical cohort of 100 patients with assumed characteristics of adult patients that attend primary care with respiratory tract infection (RTI) symptoms [50 years old, 62% female] based on data from the Cals JW *et al* (2013) study. **Intervention:** The model compares three strategies of point-of-care C-reactive protein (POC CRP) testing for patients presenting with RTI. These were: • GP plus POC CRP test with antimicrobials prescribed	**Total cost (discounted) over 3 years per 100 patients:** Current practice: £18,081 GP plus POC CRP: £18,039 PN plus POC CRP: £17,401 GP plus POC CRP and communication: £18,431 **Currency & cost year:** UK pounds (£) the cost year(s) are given as 2012/2013 prices. **Cost components incorporated:** Cost per POC CRP test only[1] (test material – reagent, depreciation of machine, cost of	**QALYs (discounted) over 3 years per 100 patients:** Current practice: 255.630 GP plus POC CRP: 255.764 PN plus POC CRP: 255.761 GP plus POC CRP and communication: 255.588 **Antibiotics prescribed (courses) over 3 years per 100 patients:** Current practice: 184 GP plus POC CRP: 136 PN plus POC CRP: 167 GP plus POC CRP and communication: 137	**ICER:** No ICER was presented for these analyses **Probability cost-effective:** In a probabilistic sensitivity analysis, at a willingness to pay (WTP) of £20,000 per QALY, GP plus CRP has a higher NMB than current practice for 77% of iterations and practice nurse plus CRP has a higher NMB than current practice for 82% of iterations. **Analysis of uncertainty:** In probabilistic sensitivity analysis (3 year time horizon,

Hunter, R (2015) Cost-Effectiveness of Point-of-Care C-Reactive Protein Tests for Respiratory Tract Infection in Primary Care in England. *Advances in Therapy* (2015) 32:69–85				
Discounting: 3.5% discount rate applied for both future costs and benefits	accordingly • Practice nurse (PN) plus POC CRP test with the nurse undertaking the POC CRP test and then passing the results to the GP to prescribe accordingly • GP plus POC CRP test and communication training (as for first bullet except that the GP has received training on communication with patients regarding RTI and antimicrobials. **Comparator:** GP care based upon the GPs views and patient expectation.	GP training, GP cost for duration of test, PN cost for duration of test, cost per antibiotic prescription, cost of communication training; Unit costs for GP consultation, GP out-of-hours, hospital outpatients, hospital admission, chest x-ray, blood and other (sputum, spirometry).	**Infections over 3 years per 100 patients:** Current practice: 217.89 GP plus POC CRP: 202.97 PN plus POC CRP: 202.97 GP plus POC CRP and communication: 199.98	100 patients and 1000 iterations) the GP plus CRP test strategy is dominant (costs less and results in more QALYs) compared to current practice in 50% of simulations; in 65% of simulations the practice nurse plus CRP test strategy is dominant and in 19% the GP plus CRP and communication training strategy is dominant.
[1] The costs in the model do not appear to include the purchase or maintenance of the Afinion™ Analyzer, it is stated that only the incremental costs of the CRP test and treatment of RTI are included (i.e. it is assumed that the analyzer is already in place in the practice and being used for estimation of POC HbA1c, for example)				

E.3 Barriers to decision making

No economic evidence was identified.

E.4 Timely adoption and diffusion of a new antimicrobial

No economic evidence was identified.

Appendix F: Linking evidence to recommendations

This appendix shows identify the evidence that has been used to devise the guideline recommendations. Supporting evidence is either from the evidence statements and/or guideline development group (GDG) discussions. All GDG discussions are captured in the evidence to recommendations section of the full guideline (sections 5.5, 6.5, 7.5 and 8.5)

The guideline includes 4 evidence reviews written in corresponding sections of the full guideline:

- Section 5: Reducing antimicrobial resistance
- Section 6: Decision-making
- Section 7: Barriers to decision-making
- Section 8: Timely adoption and diffusion of a 'new' antimicrobial

Each recommendation has a short code indicating where the evidence has come from. The number(s) in the code refer to the section of the full guideline where the statement is from. For example **Recommendation 21** has the code 5.4.1 which refers to the evidence statement(s) in section 5.4.1 in the guideline. Each recommendation may have more than 1 code.

Where a recommendation is not directly taken from the evidence statements, but is inferred from the evidence during GDG discussions, this is indicated by IDE (inference derived from the evidence).

Recommendation 1: 7.6 (IDE)

Recommendation 2: 7.6 (IDE)

Recommendation ~~2~~3: 7.6 (IDE)

Recommendation ~~3~~4: 7.6 (IDE)

Recommendation ~~4~~5: 6.5 (IDE); 8.5 (IDE)

Recommendation ~~5~~6: 5.5 (IDE)

Recommendation 7: 7.6 (IDE)

Recommendation 8: 6.5 (IDE); 7.6 (IDE); 8.5 (IDE)

Recommendation ~~6~~9: 6.5 (IDE); 7.6 (IDE)

Recommendation ~~7~~10: 5.5 (IDE); 6.5 (IDE); 7.6 (IDE)

Recommendation ~~8~~11: 7.6 (IDE)

Recommendation ~~9~~12: 7.6 (IDE); 8.5 (IDE)

Recommendation ~~10~~13: 5.5 (IDE)

Recommendation ~~11~~14: 5.5 (IDE); 8.5 (IDE)

~~**Recommendation 12:** 6.5 (IDE); 7.6 (IDE); 8.5 (IDE)~~

~~**Recommendation 13:** 7.6 (IDE)~~

~~**Recommendation 14:** 6.5 (IDE); 7.6 (IDE); 8.5 (IDE)~~

Recommendation 15: 7.6 (IDE)

Recommendation 16: 7.6 (IDE)

Recommendation 17: 7.6 (IDE)

Recommendation 18: 5.5 (IDE); 7.6 (IDE); 8.5 (IDE)

Recommendation 19: 7.6 (IDE)

Recommendation 20: 5.5 (IDE)

Recommendation 21: 8.5 (IDE)

Recommendation 22: 8.4.1

Recommendation 23: 7.6 (IDE)

Recommendation 24: 7.6 (IDE)

Recommendation 25: 5.4.1; 5.5 (IDE)

Recommendation 26: 5.5 (IDE); 6.5 (IDE); 7.6 (IDE)

Recommendation 27: 5.5 (IDE); 8.5 (IDE)

Recommendation 28: 5.5 (IDE); 8.5 (IDE)

Recommendation 29: 5.5 (IDE); 8.5 (IDE)

Recommendation ~~28~~30: 6.4.1

Recommendation ~~29~~31: 5.5 (IDE)

Recommendation 3~~0~~2: 5.5 (IDE)

Recommendation 3~~1~~3: 5.5 (IDE); 6.4.1; 6.5 (IDE)

Recommendation 3~~2~~4: 5.4.1; 5.5 (IDE); 6.4.1; 6.5 (IDE)

Recommendation 3~~3~~5: 5.5 (IDE)

Recommendation 3~~4~~6: 7.6 (IDE)

Recommendation 3~~5~~7: 5.5 (IDE)

Recommendation 3~~6~~8: 5.4.1; 5.5 (IDE)

Recommendation 3~~7~~9: 5.4.1

Recommendation ~~40~~38: 8.5 (IDE)

Recommendation ~~41~~39: 8.4.2

Recommendation 4~~0~~0: 8.4.2

Recommendation 4~~1~~1: 8.4.2

Recommendation 4~~2~~2: 8.5 (IDE)

Recommendation 4~~3~~3: 8.5 (IDE)

Recommendation 4~~4~~4: 8.3.2 (Table 18); 8.5 (IDE)

Recommendation 4~~5~~5: 8.4.2

Recommendation 4~~86~~: 8.5 (IDE)

Recommendation 4~~97~~: 8.4.2

Recommendation 50~~48~~: 8.4.2

Recommendation 51~~49~~: 8.5 (IDE)

Appendix G: Organisations providing written or oral evidence

Organisations providing written evidence submissions

Organisation:
Abertawe Bro Morgannwg University Health Board
Airedale NHS Foundation Trust
Alder Hey Children's NHS Foundation Trust
Alere Ltd
Aneurin Bevan University Health Board
Barnet & Chase Farm (Royal free Trust)
Barts Health NHS trust- Whipps Cross Hospital
British Thoracic Society
British Thoracic Society
Calderdale and Huddersfield NHS Trust
City Hospitals Sunderland NHSFT
Colchester Hospitals NHS Foundation Trust
Croydon Health Services NHS Trust
Derbyshire Community Health Services NHS Trust
Ealing Hospital, London North West Healthcare NHS Trust
East and North Herts NHS Trust
Epsom and St. Heliers University Hospitals NHS Trust
Frimley Health- Wexham Park
Golden Jubilee National Hospital
Great Ormond Street
Health and Social Care Board NI
Hinchingbrooke NHS Trust
Homerton University Hospital
Hull and East Yorkshire Hospitals
Ipswich Hospital NHS Trust
Kettering General Hospital
North East London Commissioning support unit - Anglia
NHS Borders
NHS Greater Glasgow and Clyde
NHS Highland
NHS Orkney
NHS Shetland
NHS South East Staffordshire & Seisdon Peninsula CCG
NHS Stafford & Surrounds CCG
NHS Tayside
NHS West Kent CCG
North Bristol NHS Trust
North of England Commissioning Support Unit
Northampton General Hospital
Nottingham University Hospitals

Organisation:
Oxford University Hospitals NHS Trust
Peterborough and Stamford Hospitals NHS Foundation Trust
Public Health England
Princess Alexandra NHS Hospital Trust
Royal Bolton Hospital
Royal Bournemouth Hospital
Royal Cornwall Hospitals NHS Trust
Royal Derby Hospital
Royal Devon and Exeter NHS Foundation Trust
Royal Devon and Exeter NHS Foundation Trust
Royal Free London NHS Foundation Trust
Royal Free London NHS Foundation Trust
Royal National Orthopaedic Hospital
Salford Royal NHS Foundation Trust
Scottish Antimicrobial Prescribing Group
Sheffield CCG
South Tees Hospitals NHS Foundation Trust
Southport and Ormskirk NHS Trust
Stockport NHSFT
Sussex Community NHS Trust
Taunton and Somerset NHS Foundation Trust
The Royal Bournemouth Hospital
University Hospital of South Manchester
University College London Hospitals NHS Foundation Trust
University Hospital Southampton
University Hospitals Bristol NHS Foundation Trust
University Hospitals of Leicester NHS Trust
Walsall Healthcare Trust
West Hertfordshire Hospitals NHS Trust
Whittington Health Integrated Care Organisation (including Whittington Hospital, Islington and Haringey Community Services)
Western Health and Social Care Trust
Wye Valley NHS Trust
York Teaching Hospitals
Yorkshire and Humber CSU

Appendix H: Quality assessment checklist

Originally published in the British Journal of Medicine see:
http://www.bmj.com/content/suppl/2004/05/27/328.7451.1312.DC1#e

Critical appraisal checklist for a questionnaire study

Research question and study design	
Was a questionnaire the most appropriate method?	
Validity and reliability	
Have claims for validity been made, and are they justified? (Is there evidence that the instrument measures what it sets out to measure?)	
Have claims for reliability been made, and are they justified? (Is there evidence that the questionnaire provides stable responses over time and between researchers?)	
Format	
Are example questions provided?	
Did the questions make sense, and could the participants in the sample understand them? Were any questions ambiguous or overly complicated?	
Piloting	
Are details given about the piloting undertaken	
Was the questionnaire adequately piloted in terms of the method and means of administration, on people who were representative of the study population?	
Sampling	
Was the sampling frame for the definitive study sufficiently large and representative?	
Distribution, administration and response	
Was the method of distribution and administration reported	
Were the response rates reported, including details of participants who were unsuitable for the research or refused to take part?	
Have any potential response biases been discussed?	