Prevention of ventilator associated pneumonia.

Produced by
The University of Sheffield, School of Health and Related Research (ScHARR)

Authors
Roy Jones, Research Associate
Jon Karnon, Senior Research Fellow
Carolyn Czoski-Murray, Research Fellow
Robert Williams, Placement Student

Correspondence to
Carolyn Czoski-Murray, Research Fellow ScHARR,
University of Sheffield, 30 Regent Court, Sheffield S1 4DA
Tel: 0114 222 0678
Fax: 0114 272 4095
E-mail: c.murray@sheffield.ac.uk

Date completed

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Dr. Duncan Young, John Radcliffe Hospital, Oxford.
Jon Silcock, Lecturer in Pharmacy, School of Healthcare, university of Leeds.
John Dade, Critical Care Pharmacist, Leeds Teaching Hospitals NHS Trust.
Derek Bainbridge, Nurse Consultant, Rotherham General Hospital.
List of abbreviations

BNF  British National Formulary
BSAC  British Society for Antimicrobial Chemotherapy
CI  Confidence Interval
DVT  Deep Vein Thrombosis
HAP  Hospital Acquired Pneumonia
ICU  Intensive Care Unit
IHI  Institute for Healthcare Improvement
MHS  Major Heart Surgery
NNIS  National Nosocomial Infection Surveillance
NNT  Numbers Needed to Treat
NICE  National Institute for Health and Clinical Excellence
RCT  Randomised Controlled Trial
RRR  Relative Risk Reduction
SDD  Selective Decontamination of the Digestive Tract
VAP  Ventilator Associated Pneumonia
Abstract

Objectives: To assess the clinical and cost effectiveness of prophylactic antibiotics, body position, kinetic bed therapy and care bundles for the prevention of ventilator associated pneumonia.

Data sources: Searches of main electronic databases were conducted in April and June 2007.

Review methods: Systematic reviews and randomised controlled trials were included if they had the interventions of interest as one of the treatment arms and the population were intensive care unit patients requiring mechanical ventilation for 48 hours or more.

Results: Prophylactic antibiotics, There are concerns that use of topical antibiotics in selective decontamination of the digestive tract may lead to microbial resistance. Furthermore, incidence of clostridium difficile colitis and central line infections are reported to increase in those who received prolonged prophylactic antibiotics. Ampicillin-sulbactam, orabase with gentamicin, colistin, and vancomycin, and gentamicin, polymyxin E and amphotericin B all showed a statistical significant reduction in the incidence of VAP. Body position None of the RCTs on body positioning appeared to be robust well conducted studies, There are concerns regarding that when patients are positioned between 30 and 45 patients have slid down in bed and, if skin integrity is compromised, the shearing of skin occurs. Of the three RCTs, only one reported a statistically significant reduction in the incidence of VAP, using a semi recumbent body position of 45 degrees. Kinetic bed therapy Two systematic reviews of kinetic bed therapy for the prevention of VAP in ICU patients were identified, only one was judged to be a robust systematic review. It was noted that poor methodological quality clinical trials were included in the meta-analysis. Both reviews carried out a meta-analysis and both studies found that kinetic bed therapy is associated with a significant reduction in the odds of developing nosocomial pneumonia in mechanically ventilated patients. Care bundles Only two studies that recorded VAP rates before and after the introduction of a ventilator bundle were identified Both of these studies used the IHI care bundle as a basis, but added other components to it both reported a reduction in VAP rates after the introduction of a ventilator bundle. The results of the cost-effectiveness analysis of interventions aimed at preventing VAP in ICU patients undergoing MV shows that there are three main interventions that have the highest probabilities of being the most cost-effective options. These are an SDD alone antibiotic regimen, a SDD + non-SDD antibiotic regimen, and the more extensive care bundle.

Conclusions: Prophylactic antibiotics, There is no evidence to support the routine use of ceftazidime for prophylaxis, but ampicillin-sulbactam, orabase with gentamicin, colistin, and vancomycin, and gentamicin, polymyxin E and amphotericin B did all show a statistical significant reduction in the incidence of VAP, but further research on the complications caused by antibiotic use is needed before firm recommendations can be made. Body position, semi recumbent patient position is a low-cost and practical intervention but, a backrest elevation of 45 degrees is not always achieved.
Kinetic bed therapy Two meta-analyses on kinetic bed therapy both report a statistically significant reduction in the incidence of VAP, however, doubts have been raised regarding the quality of the trials used. Further high-quality research is required before a definite recommendation can be made. Care bundles. Non randomised studies indicate that the use of care bundles, whether the IHI model or a modified version, can reduce VAP rates. Adherence to all elements of a particular care bundle could be problematic, furthermore, no evidence was presented in the two studies that would assist in the identification of which care bundle component is the most beneficial. UK-specific data would improve the quality of the presented cost effectiveness analyses; however, there does seem to be sufficient evidence to conclude that some form of intervention to prevent VAP would be a cost-effective use of NHS resources
Executive summary

Aim of the review

This review is undertaken as an examination of the risk to intensive care patients of contracting ventilator associated pneumonia, and possible complications and adverse effects of the interventions for the prevention of ventilator associated pneumonia.

Background

Ventilator associated pneumonia (VAP) is defined as nosocomial pneumonia in a patient on mechanical ventilator support (by endotracheal tube or tracheostomy) for ≥48 hours. VAP is a medical condition that results from infection which colonise the alveoli responsible for absorbing oxygen. It is distinguished from other kinds of infectious pneumonia because of the different types of micro-organisms responsible, antibiotics used to treat, methods of diagnosis, ultimate prognosis, and effective preventive measures.

VAP is the most common nosocomial infection in intensive care units (ICU), and represents 31% of all ICU acquired infections. VAP occurs in 9% – 27% of all intubated patients although published incidence of VAP in Intensive Care Units (ICUs) is estimated as being between 15% and 50%.

As VAP is linked with higher morbidity, mortality and costs, preventing ventilated patients from developing VAP is an important patient safety objective. VAP is thought to be a common complication of the acute respiratory distress syndrome, and the significant burden of VAP justifies the implementation of specific preventive strategies.

The interventions identified for consideration by this review are prophylactic antibiotics, body position, kinetic bed therapy (also known as, kinetic therapy, continuous lateral rotational therapy, oscillation therapy, and continuous postural oscillation) and care bundles (combinations of various interventions) that are used to reduce the risk of contracting VAP. This review has concentrated on examining the previously stated interventions and does not present an inclusive list of all possible preventative strategies for VAP. An example of a care bundle is the IHI (Institute for Healthcare Improvement) ventilator bundle which includes four key components, elevation of the head of the bed, Sedation Hold, Peptic ulcer disease (PUD) prophylaxis and Deep Vein thrombosis (DVT) prophylaxis (unless contraindicated).

Methods

Systematic reviews were conducted to identify and assess all literature relating to the prevention of VAP in adults in ICUs. For the purpose of this review, VAP can be defined as the onset of pneumonia in an ICU patient receiving mechanical ventilation occurring 48 hours or more, after the patient was placed on mechanical ventilation.

Searchers were carried out in April and June 2007 for systematic reviews and randomised controlled trials (RCTs) relating to the prevention of VAP. Due to the
short time scale of this systematic review, studies were restricted to those in the English language. Systematic reviews and RCTs that had the interventions of interest as one of the treatment arms were included in this review.

A comprehensive literature search was performed in April 2007. Searches were not intended to identify literature on the complications of interventions for the prevention of VAP but designed to retrieve:

- Papers describing the epidemiology of VAP
- Papers on the clinical effectiveness of different strategies to prevent VAP
- Papers on the cost effectiveness and comparative costs of the different methods/treatments

In June 2007 further focused searches were performed to retrieve papers on the clinical and cost effectiveness of the following prevention strategies:

- Body position
- Prophylactic antibiotics
- Kinetic bed therapy
- Care bundles

**Results**

**Prophylactic antibiotics**

The search retrieved one systematic review and six RCTs of prophylactic antibiotics for the prevention of VAP in ICU patients. All the RCTS of antibiotic interventions seem to be reasonably well designed and conducted, although half of the included RCTs had small numbers of patients in the intervention and control groups. Each RCT had different exclusion criteria, and expectation of time on mechanically ventilation was also varied.

All but two RCTs showed a statistically significant result that a prophylactic antibiotic reduces the incidence of VAP. Of the four RCTs showing that antibiotics reduced the incidence of VAP, different types of antibiotic agents or different dosages were used, the antibiotic agents used were;

- ampicillin-sulbactam,
- orabase with gentamicin, colistin, and vancomycin,
- ceftazidime,
- and a concentration of gentamicin, polymyxin E and amphotericin B.

There are concerns that the use of topical antibiotics in selective decontamination of the digestive tract may lead to microbial resistance. The incidence of clostridium difficile colitis and central line infections has been reported to increase in those who received prolonged prophylactic antibiotic compared to those who did not.

Ceftazidime has been evaluated in two RCTs, whilst the smaller RCT showed a significant reduction in the incidence of VAP, the larger RCT did not. There is no evidence to support the routine use of ceftazidime for prophylaxis. Ampicillin-sulbactam, orabase with gentamicin, colistin, and vancomycin, and gentamicin, polymyxin E and amphotericin B all showed a statistical significant reduction in the incidence of VAP.
**Body position**
The search retrieved one review and three RCTs of body positioning for the prevention of VAP in ICU patients. None of the RCTs on body positioning appeared to be robust well conducted studies, one RCT reported difficulties in achieving the proposed angle of semi recumbent position.

There are concerns that when patients are positioned between 30 and 45 degrees patients have slid down in bed and, if skin integrity is compromised, the shearing of skin occurs, further concerns are the possibility of patient discomfort.

Of the three RCTs, only one reported a statistically significant reduction in the incidence of VAP, using a semi recumbent body position of 45 degrees. Although both the studies examining a semi recumbent position aimed for patients to be in a semi recumbent position of 45 degrees, one study failed to maintain such an objective, whilst the other did not report if the objective was achieved.

**Kinetic bed therapy**
The search retrieved two systematic reviews of kinetic bed therapy for the prevention of VAP in ICU patients. Only one of the two reviews, was judged to be a robust systematic review, as it conduction a comprehensive literature search using wide-ranging search terms compared to the other review on kinetic bed therapy. However, it was noted that poor methodological quality clinical trials were included in their meta-analysis.

Several studies of rotational therapy (which includes kinetic therapy and continuous lateral rotation therapy) have reported that patients withdrew from the treatment group due to not being able to tolerate continuous rotation.

Both reviews carried out a meta-analysis and the conclusions from both studies were that kinetic bed therapy is associated with a significant reduction in the odds of developing nosocomial pneumonia in mechanically ventilated patients.

**Care bundles**
No RCTs of a care bundle intervention were identified, the only identified studies of care bundles were two studies that recorded VAP rates before and after the introduction of a ‘ventilator bundle’. Both studies used the IHI care bundle as a basis, but added other components to it.

There is a scarcity of published research on the use of care bundles for the prevention of VAP. This review did not uncover any studies that addressed the risk to the patients of using a care bundle. The choice of components of a care bundle would be based on a literature review and the unit’s clinicians’ experience-based recommendations on which component to include and which are medically contraindicated.

Non randomised studies indicate that the use of care bundles, whether the IHI model or a modified version, can reduce VAP rates. Adherence to all elements of a particular care bundle could be problematic.
Discussion
All published research evidence reported in this review has originated from the US or Europe, where current practice may differ from the UK. Selective decontamination of the digestive tract for the prevention of VAP is not a standard practice in the UK.

The diagnosis of VAP is a controversial area, and use of standard clinical criteria is inadequate. A definitive diagnosis of pneumonia remains difficult in the ventilated patient, for despite its common occurrence, there is still no agreed upon ‘gold standard’ for the diagnosis of VAP and controversy persists over its true incidence. There is a compelling need for accurate diagnosis of VAP to avoid potentially significant detrimental effects from overuse of antibiotics when the diagnosis is solely based on clinical criteria.

Prophylactic antibiotics
Regarding the impact that prolonged prophylactic antibiotic use has on the development of nosocomial pneumonia and antibiotic use complications, it was found that the incidence of antibiotic complications were two times greater for patients who received prolonged prophylactic antibiotics than for patients who did not.

A before-after study tested the hypothesis that a new program of antibiotic strategy control can minimise the incidence of VAP. In the before period ceftazidime associated with ciprofloxacin was widely prescribed for the empiric and therapeutic treatment of VAP, the incidence of VAP in patients who received mechanical ventilation for more than 48 hours was 22.1%. It was suggested that new strategy of antibiotics use could be an efficient means to reduce the incidence of VAP caused by antibiotic-resistant bacteria, but that further studies are needed to validate these data.

Body position
It has been recommended by the United States Centers for Disease Control and Prevention that patients receiving mechanical ventilation have the head of the bed elevated 30-45 degrees to help prevent nosocomial pneumonia.

A number of studies have examined the length of time patients were in a semi-recumbent position. One study reported that 66.5% of patients were in a semi-recumbent body position, whilst another study found that patients were at backrest elevations less than 30 degrees 72% of the time and less than 10 degrees 39% of the time, concluding that patients spent the majority of the time at backrest elevations less than 30 degrees. This was confirmed in another study that observed that the most common body position was 15 to 30 degrees from the horizontal.

A study that examined nurses’ accuracy in estimating backrest elevation, concluded that that nurses are able to estimate backrest elevation accurately.

Kinetic bed therapy
In a clinical practice guideline for the prevention of VAP, it was recommended that clinicians consider the use of kinetic beds. This was based on evidence from eight trials. Seven of the eight as ‘level 2’ and the other trial at level 3 (poor methodology quality), also the systematic review expressed reservations about drawing conclusions due to the poor methodological quality of the included trials.
Care bundles
The IHI present a ‘how to guide’ which included information on how to calculate, record and measure VAP rate (per 1,000 ventilator days). It was not clear from either of the two studies using a care bundle if they used the same method as that suggested by the IHI.

A study reported in 2005 that ICUs with the highest rates of compliance with the ventilator bundle had the highest rates of VAP reduction, with In units with > 95% compliance, VAP rates decreased from 6.6 to 2.7 per 1,000 ventilator days a 59% reduction. Another study reported that a decrease in VAP rate occurred when compliance with the care bundle was audited and feedback given to the staff on both a daily and weekly basis, but it was noted that compliance was not always 100%, and varied from week to week. It was also noted that not every patient would be able to meet the criteria for all the care bundle components.

Conclusions

Prophylactic antibiotics
Ceftazidime has been evaluated in two RCTs, whilst the smaller RCT showed a significant reduction in the incidence of VAP, the larger RCT did not. There is no evidence to support the routine use of ceftazidime for prophylaxis. Ampicillin-sulbactam, orabase with gentamicin, colistin, and vancomycin, and gentamicin, polymyxin E and amphotericin B all showed a statistical significant reduction in the incidence of VAP, but further research on the complications caused by antibiotic use is needed before firm recommendations can be made.

Body position
A semi recumbent patient position is a low-cost and practical intervention and while the large trial did not find a statistically significant reduction in the incidence of VAP, a smaller, earlier trial did. This may have been due to the larger trial not achieving a targeted backrest elevation of 45 degrees. As discussed in the larger trial and in a number of articles, a backrest elevation of 45 degrees is not always achieved.

Kinetic bed therapy
The two meta-analyses on kinetic bed therapy both report a statistically significant reduction in the incidence of VAP, however, doubts have been raised regarding the quality of the trials used. Further high-quality research is required before a definite recommendation can be made.

Care bundles
Non randomised studies indicate that the use of care bundles, whether the IHI model or a modified version, can reduce VAP rates. Adherence to all elements of a particular care bundle could be problematic. Furthermore, no evidence was presented in the two studies that would assist in the identification of which care bundle component is the most beneficial. For care bundles to work effectively, the various professionals in an ICU will need education on a care bundle and be prepared to adapt their working practice to implement all components of a care bundle.
Economic conclusions
Whilst better and more UK-specific data would improve the quality of the presented analyses, there does seem to be sufficient evidence to conclude that some form of intervention to prevent VAP would be a cost-effective use of NHS resources.

Recommendations for further research
Prophylactic antibiotics
Further research is required on the use of prophylactic antibiotics to reduce the incidence of VAP and the long-term effects of prolonged antibiotic use.

Body position
Large, robust and methodically sound RCTs are needed to evaluate the effect of semi-recumbent position at 45 degrees on the incidence of VAP, and maintaining an elevation of 45 degrees.

Kinetic bed therapy
Robust and methodically sound RCTs are needed to evaluate the effect of Kinetic bed therapy on the reduction of VAP.

Care bundles
RCTs are needed to evaluate the effect of care on VAP rates, and if possible, which particular component or components has the most beneficial effect.
1. **Background**

In relation to patient safety, ventilator associated pneumonia (VAP) is a risk to the patient’s health and recovery. This review is undertaken as an examination of the risk to intensive care patients of contracting VAP, and possible complications and adverse effects of the interventions for the prevention of VAP. Of the intervention studies included in the review, none provide UK based data. Obtaining information on VAP from a UK perspective was not possible as relevant data was not available. The review will be undertaken in line with the National Institute for Health and Clinical Excellence’s (NICE) normal evaluative methods, which incorporates specialist clinical and patient advice as well as published evidence.

1.1 **Description of underlying health problem**

VAP is defined as nosocomial pneumonia in a patient on mechanical ventilator support (by endotracheal tube or tracheostomy) for ≥48 hours. VAP is the most common nosocomial infection in intensive care units (ICU), and represents 31% of all ICU acquired infections. As VAP is linked with higher morbidity, mortality and costs, preventing ventilated patients from developing VAP is an important patient safety objective.

1.2 **Epidemiology**

VAP occurs in 9% – 27% of all intubated patients although published incidence of VAP in Intensive Care Units (ICUs) is estimated as being between 15% and 50% depending on the population of interest. Rello et al reported the findings from a large US database in the incidence of VAP. The US database contained information on approximately 750,000 hospital admission annually. For the period January 1998 to June 1999, Rello et al identified 9,080 patients who required admission to an ICU and received mechanical ventilation for >24 hours. The authors did not present the number of patients who were admitted to the ICU who did not require mechanical ventilation. No studies were identified that gave UK based estimates. A study by Hugonnet et al estimates that more than 40% of ICU patients receive mechanical ventilation.

Tejerinas et al conducted a retrospective analysis of a database from a prospective, multicentre, international cohort of 5,183 adult patients who received mechanical ventilation for more than 12 hours at 361 intensive care units (ICUs) from 20 countries for the month of March 1998. VAP was present in 15% (439) of patients. The confidence interval (CI) for this figure was 14%-16%.

In 1996, Elatrous et al reported the results of a one-year prospective survey that aimed to determine the incidence of VAP in an eight-bed ICU located in Tunisia. During the study period (January 1991 to December 1991), 318 patients were admitted to the ICU. Of these, 73 patients, were required to be mechanically ventilated for more than 48 hours. Twenty-eight (38%) developed VAP, yielding a pneumonia rate of 46 episodes per 1,000 patient-ventilator-days.

Obtaining accurate estimates of the incidence of VAP is difficult as criteria used to diagnose VAP vary from study to study. Most of the included studies did report either the median or mean time spent on mechanical ventilation.
1.3 Aetiology
VAP is a medical condition that results from infection which colonise the alveoli responsible for absorbing oxygen. VAP is distinguished from other kinds of infectious pneumonia because of the different types of micro-organisms responsible, antibiotics used to treat, methods of diagnosis, ultimate prognosis, and effective preventive measures. According to the British Society for Antimicrobial Chemotherapy (BSAC) a wide range of bacteria is associated with Hospital Acquired Pneumonia (HAP) and VAP, polymicrobial cultures are common in VAP, while anaerobes and fungi are uncommon. In a consultation document, BSAC commented that in recent years the prevalence of meticillin-resistant staphylococcus aureus (MRSA) and other multi-resistant organisms have been increasing, especially in late-onset VAP.

1.4 Diagnosis
VAP is most accurately diagnosed by quantitative culture and microscopy examination of lower respiratory tract secretions. However, for the diagnosis of VAP, as well as the patient being mechanically ventilated for more than 48 hours, usually three or more of the following are required: fever, leukocytosis, changes in sputum, radiographic evidence of progressive or new infiltrates and the worsening of oxygen requirements.

BSAC report that pneumonia is difficult to diagnose in mechanically ventilated patients, as many of the diagnostic criteria for pneumonia in non-ventilated patients are not specific to infection in mechanically ventilated patients and may be associated with non-infective disorders such as acute lung injury. BSAC stated that a number of attempts have been made to develop diagnostic techniques to improve the specificity of the diagnosis, including invasive bronchoscopic techniques, but that this has not yet been reliably achieved. This means that diagnosis of ventilator-associated pneumonia is still based on a combination of radiological and clinical criteria.

Cook in a narrative review, expressed concerns that while the diagnostic challenge of VAP will continue to stimulate debate, another diagnostic uncertainty is the influence of different VAP diagnostic criteria on clinical decision making, and interpreting the literature. Cook suggested that clinicians are likely to administer more (and perhaps broader spectrum) antibiotics to patients with VAP suspected only on clinical grounds.

1.5 Prognosis
The mortality of patients who developed VAP has been reported as between 38% and 50%. Bercault and Boulain reported the results of a prospective, matched cohort study designed to evaluate the mortality rate attributable to nosocomial VAP in an ICU. The study ran from January 1996 to April 1999, in an 18-bed adult medical-surgical ICU in France. 135 patients developed nosocomial pneumonia and these were matched with 135 control patients who did not develop nosocomial pneumonia.

The authors of the study reported that the crude ICU mortality rate was higher in patients with nosocomial pneumonia than in control patients (41% compared to 14%, p< 0.0001). The authors concluded that nosocomial pneumonia is independently associated with death in ICU when compared to the other risk factors evaluated.
As this review includes adults admitted to surgical or medical ICU, it is of interest to know if, the mortality rates from VAP differ between these two groups of patients. Leroy et al\textsuperscript{19} reported in 2001, the results of an observational cohort study that was interested in the prognosis of medical versus surgical ICU patients developing VAP. One hundred and twenty-five patients exhibiting VAP were included, 87 were in the medical group and 38 in the surgical group.

The study\textsuperscript{19} identified a number of risk factors of VAP mortality these were patient related (immunosuppression, chronic respiratory insufficiency, chronic neurologic diseases, aspiration, and inadequate nutritional status), technique related (surgical tracheostomy, invasive monitoring of blood pressures, and hemodialysis or Hemofiltration) or pharmacologic interventions related (anti-acid or histamine type-2 receptor antagonists or omeprazole, sedative drugs, corticosteroids, and inotropic drugs).

The authors concluded that, after adjusting for the evaluated main risk factors of VAP mortality, status on ICU admission, medical versus surgical status, had no significant impact on mortality associated with VAP. However, given the small sample size of the surgical group and that it was an observational study, not a RCT, it can not be accepted as definitive proof.

1.6 **Significance in terms of ill-health (burden of disease)**

VAP is a primary problem in intensive care units, and causes complications in 8-28\%\textsuperscript{20} of patients receiving mechanical ventilation. Chaste and Fagon reported that while VAP is a severe disease, it has been not clearly demonstrated that pneumonia is responsible for the higher mortality rate of this group of patients. The authors believe that two independent factors make it difficult to assign responsibility unambiguously. The first is, the difficulty in establishing a firm diagnosis, i.e., to clearly identify patients with VAP; therefore, widely diverging VAP mortality rates reported might reflect not only differences in the populations studied but also differences in the diagnostic criteria used.

Patients with VAP have significantly longer duration of mechanical ventilation and ICU stay.\textsuperscript{10,8} Bercaut and Boulain\textsuperscript{18} reported from their prospective, matched cohort study, that length of ICU stay was higher in patients with nosocomial pneumonia than in control patients (31 ± 19 days compared to 26 ± 17 days, p < 0.0001), the authors concluded that VAP increases the length of ICU stay.

1.7 **Summary of interventions**

The interventions identified for consideration by this review are prophylactic antibiotics, body position, kinetic bed therapy and care bundles (combinations of various interventions) that are used to reduce the risk of contracting VAP. This review has concentrated on examining the previously stated interventions and does not present an inclusive list of all possible preventative strategies for VAP. An example of a care bundle is the IHI (Institute for Healthcare Improvement) ventilator bundle\textsuperscript{21} which includes four key components, elevation of the head of the bed, Sedation Hold, Peptic ulcer disease (PUD) prophylaxis and Deep Vein thrombosis (DVT) prophylaxis (unless contraindicated).
Selective decontamination of the digestive tract for the prevention of VAP is not a standard practice in the UK, the options used in the UK are physical measures (e.g. keeping the patient’s head up), chlorhexidine mouthwash or spray or combination of antibiotics (oral application and intravenous) for decontamination, personal communication, Jon Silcock, School of Healthcare, University of Leeds.
2. Methods
Systematic reviews were conducted to identify and assess all literature relating to the prevention of VAP in adults in ICUs. For the purpose of this review, VAP can be defined as the onset of pneumonia in an ICU patient receiving mechanical ventilation occurring 48 hours or more, after the patient was placed on mechanical ventilation.

2.1 Search strategies
Searches were carried out in April and June 2007 for systematic reviews and randomised controlled trials (RCTs) relating to the prevention of VAP. Due to the short time scale of this systematic review, studies were restricted to those in the English language. Only systematic reviews and RCTs that had the interventions of interest as one of the treatment arms were included in this review. The search strategies used are displayed in appendix 1.

A comprehensive literature search was performed in April 2007. Searches were designed to retrieve:
- Papers describing the epidemiology of VAP
- Papers on the clinical effectiveness of different strategies to prevent VAP
- Papers on the cost effectiveness and comparative costs of the different methods/treatments.

The search did not intend to identify literature on the complications of interventions for the prevention of VAP.

In June 2007 further focused searches were performed to retrieve papers on the clinical and cost effectiveness of the following prevention strategies:
- Body position
- Prophylactic antibiotics
- Kinetic bed therapy
- Care bundles

The following electronic bibliographic databases were searched:
1. Cumulative index to nursing and allied health literature (CINAHL)
2. Cochrane Database of Systematic Reviews (CDSR)
3. Cochrane Central Register of Controlled Trials (CENTRAL)
4. Embase
5. Medline
6. Medline In-Process & Other Non-Indexed Citations
7. NHS Database of Abstracts of Reviews of Effects (DARE)
8. NHS Health Technology Assessment (HTA) Database

For the focused searches the following electronic bibliographic databases were also searched:
9. BIOSIS previews (Biological Abstracts)
10. OHE Health Economic Evaluations Database (HEED)
11. Science Citation Index (SCI)
12. Social Sciences Citation Index (SSCI)
Attempts were also made to identify ‘grey’ literature by searching current research registers (e.g. National Research Register, Current Controlled Trials Register). The reference lists of included studies and relevant review articles were also checked. No date or language restrictions were applied to these searches.

At the request of the committee an addition search was carried out in July on the pharmacist’s abstract website, the search did not produce any additional information.

2.2 Validity assessment
Published papers were assessed according to the accepted hierarchy of evidence, whereby meta-analyses of high quality RCTs are considered to be the most authoritative forms of evidence, and expert opinion is considered to be the least authoritative. A table summarising data on quality assessment can be found in Appendix 2.

2.3 Data abstraction
All abstracts were read and those studies which met the inclusion criteria were identified. Data from identified studies, reviews and other evidence were extracted by the reviewer using a standardised data extraction form.
3. Results

3.1 Prophylactic antibiotics
The search retrieved one systematic review and six RCTs of prophylactic antibiotics for the prevention of VAP in ICU patients.

Chan et al\textsuperscript{22} conducted a systematic review and meta-analysis of antibiotic and antiseptic oral decontamination for the prevention of VAP. The antibiotics can be either topical (ointment or cream) or systemic (e.g. an aerosol). An antibiotic is a chemical compound that inhibits or eliminates the growth of microorganisms, such as bacteria, fungi, or protozoans. The term antibiotic is commonly used to refer to substances with anti-bacterial, anti-fungal, or anti-parasitical activity.

For oral application of antibiotics, four RCTs were identified by Chan et al\textsuperscript{22} and all were included in a meta-analysis. The antibiotics in the four trials were all topical antibiotics;
- orabase with gentamicin, colistin, and vancomycin, 4 times daily;
- Iseganan 3 ml (9 mg) six times daily;
- gentamicin gel four times daily and polymyxin B and gentamicin gel three times daily.

Details on the dosage given was only available for one trial\textsuperscript{23}. The meta analysis of these four trials (a total of 1098 patients) of antibiotic oral decontamination did not show a statistically significant reduction in VAP rates (relative risk 0.69, 95% confidence interval 0.41 to 1.18; p=0.18; I\textsuperscript{2}=59.4%).

The conclusions reached by Chan et al\textsuperscript{22} was that, for oral application of antibiotics did not significantly reduce the incidence of VAP but more evidence is needed before firm conclusions can be made on the effect of antibiotic oral decontamination.

Chan et al\textsuperscript{22} analysed antibiotic and antiseptic prophylaxis as two distinct approaches to oral decontamination, a short analysis of Chan et al\textsuperscript{22} results of antiseptic agents is given in appendix 3.

Of the four trials identified by Chan et al,\textsuperscript{22} one was a foreign language publication\textsuperscript{24} and therefore outside the remit of this review, two\textsuperscript{23,25} were included in this review and the fourth was a conference abstract\textsuperscript{26}. The abstract contained little information on the incidence of VAP, Chan et al\textsuperscript{22} contacted the author for further information. The advantage of a meta-analysis is that it is a statistical procedure that integrates the results of several independent studies, that the analyst believes are combinable. Chan et al\textsuperscript{22} combined all antibiotics together, for this review, it is of interest to know which type of antibiotic gives better outcomes.

Table 1 displays the summary information of the identified RCTS of antibiotic prevention of VAP.
### Table 1: Summary information of included antibiotic studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Study type</th>
<th>Publication</th>
<th>Intervention (n)</th>
<th>Comparator (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Claridge et al(^5)</td>
<td>2007</td>
<td>RCT</td>
<td>Journal article</td>
<td>Aerosolised ceftazidime (53)</td>
<td>Placebo (52)</td>
</tr>
<tr>
<td>Wood et al(^7)</td>
<td>2002</td>
<td>RCT</td>
<td>Journal article</td>
<td>Aerosolised ceftazidime (20)</td>
<td>Placebo (20)</td>
</tr>
<tr>
<td>Kollef et al(^3)</td>
<td>2006</td>
<td>RCT</td>
<td>Journal article</td>
<td>Iseganan (352)</td>
<td>Placebo (367)</td>
</tr>
<tr>
<td>Acquarolo et al(^4)</td>
<td>2005</td>
<td>RCT</td>
<td>Journal article</td>
<td>Ampicillin-sulbactam plus standard treatment</td>
<td>Standard treatment</td>
</tr>
<tr>
<td>Bergman et al(^5)</td>
<td>2001</td>
<td>RCT</td>
<td>Journal article</td>
<td>Orabase with 2% gentamicin, 2% colistin, and 2% vancomycin. (87)</td>
<td>Placebo in both control arms (78 and 61)</td>
</tr>
<tr>
<td>Garcia et al(^8^9)</td>
<td>1998</td>
<td>RCT</td>
<td>Journal article</td>
<td>Gentamicin, polymyxin E and amphotericin B (131)</td>
<td>Placebo (140)</td>
</tr>
</tbody>
</table>

#### 3.1.1 Ceftazidime
Claridge et al\(^5\) reported on a RCT that compared aerosolised ceftazidime with placebo. The reported study looked to be a well carried out and methodology sound RCT, with a larger sample size than a previous RCT on ceftazidime.\(^2^7\) This was a single institution double-blind RCT that compared a seven day course of aerosolised ceftazidime with a placebo. Ceftazidime 250 mg was given as an aerosol every 12 hours for 7 days or until the patients were either extubated or off the ventilator, whichever came first. The main outcome evaluated was the incidence of VAP at two weeks and 30 days. A total of 105 patients were randomised to the two groups, with no statistical differences between baseline characteristics noted.

Wood et al\(^2^7\) reported in 2002 on a RCT that compared aerosolised ceftazidime with placebo. This was a small single institution double-blind RCT that compared patients who received aerosolised ceftazidime 250 mg every 12 hours or placebo (normal saline) for up to seven days. The main outcome was the development of VAP at day 7 and day 14. A total of 59 patients were enrolled, 19 were excluded from the analysis, leaving 40 patients, 20 in each group.

#### 3.1.2 Iseganan
A multinational double-blind RCT by Kollef et al\(^2^3\) evaluated the efficacy of iseganan for the prevention of VAP. Forty-eight centres from six countries (France, Spain, Switzerland, the Netherlands, United Kingdom, and United States) took part in this RCT. Patients on mechanical ventilation were randomised to oral topical iseganan or placebo. Patients either received 3 ml iseganan oral solution (9 mg) or placebo six times per day for up to 14 days. Drug administration was discontinued before day 14 if the patient developed microbiologically confirmed VAP or was extubated. Between September 9, 2003, and June 22, 2004, 725 patients were enrolled, of these, 371 received iseganan and 354 received a placebo. Sixteen patients (nine in the iseganan arm, seven in the placebo arm) were randomised, but did not receive any of the study drugs, this left 709 patients (362 in the iseganan arm, 347 in the placebo arm) who were included in an intention-to-treat analysis. The two arms were comparable at baseline characteristics except that, on average, the patients in the iseganan arm were 3 years older than the patients in the placebo arm.
3.1.3 Ampicillin-sulbactam
In 2005, Acquarolo et al.\textsuperscript{28} described the findings of a single centre, prospective, randomised, open study, that evaluated whether a three day course of ampicillin-sulbactam prophylaxis (3 g every six hours for three days) plus standard treatment could reduce the occurrence of early-onset VAP in comatose mechanically-ventilated patients compared to standard treatment alone. Standard treatment was defined as semi-recumbent position whenever possible, stress ulcer prophylaxis with intravenous ranitidine (50 mg every six hours) and enteral feeding, unless gastric emptying was altered, in which case parenteral nutrition was used. The authors defined VAP as pneumonia occurring more than 48 hours after endotracheal intubation and initiation of mechanical ventilation, and early-onset VAP was defined as pneumonia occurring during the first four days of mechanical ventilation. The main outcome measure was the occurrence of early-onset VAP. This study was stopped after 42 patients had been enrolled; due to protocol violations (reasons not stated) four patients were excluded, leaving 38 patients in the final analysis.

3.1.4 Orabase with gentamicin, colistin, and vancomycin
Bergman et al.\textsuperscript{25} in 2001, gave the results of a prospective randomised, double-blind, placebo controlled study. Patients in the intervention group received topical antimicrobial prophylaxis (TAP), consisting of an orabase with 2% gentamicin, 2% colistin, and 2% vancomycin, four times a day until extubation. Patients were also randomised into two control groups; one control group (A) studied in the presence of patients receiving topical prophylaxis and the other control group (B) in an intensive care unit where no topical prophylaxis was used.

3.1.5 Gentamicin, polymyxin E and amphotericin B
A double-blind, randomised, placebo-controlled trial of Selective Decontamination of the Digestive Tract (SDD) on 271 consecutive patients in five Spanish ICUs was carried out by Garcia et al.\textsuperscript{29} and reported in 1998. The purpose of SDD is to eradicate potentially disease-producing micro-organisms from the oropharynx and gastrointestinal tract of ICU patients, thus reducing the incidence of nosocomial sepsis, particularly pneumonia. The five ICUs treated medical and surgical patients. Patients were included in the study if they were expected to require mechanical ventilation for a minimum of 48 hours. The SDD treatment group received an orally applied paste containing a 2% concentration of gentamicin, polymyxin E and amphotericin B, the control group received a placebo.

3.1.6 Quantity and quality of research available
Table 2, displays the inclusion/exclusion criteria of each include RCT, along with the primary and secondary outcomes of the study.
Each RCT had different exclusion criteria, and expectation of time on mechanically ventilation was also varied. The extent to which the results of included trials can provide a reasonable basis for generalisation to a UK ICU setting is unclear.
Table 3 shows some of the characteristics of the patients who participated in the RCTs. The mean age for patients included in the RCTS was in the late 50’s, except for the RCTs of ceftazidime by Claridge et al\(^5\) and Wood et al\(^{27}\) whose populations were younger. All RCTs reported that intervention and control groups were comparable.

Table 3: Antibiotic study Population characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient characteristics</th>
<th>N</th>
<th>Mean age (years)</th>
<th>% male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Claridge et al(^5)</td>
<td>Ceftazidime</td>
<td>53</td>
<td>Ceftazidime</td>
<td>37.3</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>52</td>
<td>Placebo</td>
<td>35.6</td>
</tr>
<tr>
<td>Wood et al(^{27})</td>
<td>Ceftazidime</td>
<td>20</td>
<td>Ceftazidime</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>20</td>
<td>Placebo</td>
<td>41</td>
</tr>
<tr>
<td>Acquarolo et al(^{28})</td>
<td>Ampicillin-sulbactam</td>
<td>19</td>
<td>Ampicillin-sulbactam</td>
<td>54.8</td>
</tr>
<tr>
<td></td>
<td>Standard treatment</td>
<td>19</td>
<td>Standard treatment</td>
<td>54.6</td>
</tr>
<tr>
<td>Kollef et al(^3)</td>
<td>Iseganan</td>
<td>362</td>
<td>Iseganan</td>
<td>60.5</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>347</td>
<td>Placebo</td>
<td>57.7</td>
</tr>
<tr>
<td>Bergmans et al(^{25})</td>
<td>TAP</td>
<td>87</td>
<td>TAP</td>
<td>56.6</td>
</tr>
<tr>
<td></td>
<td>Control A</td>
<td>78</td>
<td>Control A</td>
<td>58.1</td>
</tr>
<tr>
<td></td>
<td>Control B</td>
<td>61</td>
<td>Control B</td>
<td>58.7</td>
</tr>
<tr>
<td>Garcia et al(^{29})</td>
<td>SDD</td>
<td>131</td>
<td>SDD</td>
<td>55.0</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>140</td>
<td>Placebo</td>
<td>55.1</td>
</tr>
</tbody>
</table>

All the RCTS of antibiotic interventions seem to be reasonably well designed and conducted, they all appear to have included balanced populations, see appendix 4 and table 4. Only two RCTs, both evaluating ceftazidime\(^5,27\) reported that there was no statistically significant differences between the intervention and control groups.
### Table 4: Quality assessment of antibiotic studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Randomisation</th>
<th>Withdrawals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Claridge et al⁷</td>
<td>Eligible patients were randomly assigned to receive either ceftazidime or placebo by a computer generated assignment and recorded by a member of the pharmacy department.</td>
<td>None stated.</td>
</tr>
<tr>
<td>Wood et al²⁷</td>
<td>Randomisation was determined by a computer, assignment to receive ceftazidime or placebo were kept in sealed envelopes and opened on patient enrolment.</td>
<td>Seventeen patients were excluded from the analysis because they were extubated (10 patients), developed VAP (six patients) or died (one patient) before receiving three days study treatment. One patient was further excluded because treatment started more than 48 hours after admission, and another patient was excluded because of an invalid informed consent agreement.</td>
</tr>
<tr>
<td>Acquarolo et al²⁸</td>
<td>Eligible patients randomly assigned to receive ampicillin-sulbactam plus standard treatment or standard treatment alone by a randomised schedule created by computer generated numbers.</td>
<td>Four patients withdrawn due to protocol violations (violations not stated).</td>
</tr>
<tr>
<td>Kollef et al²³</td>
<td>Randomisation was performed by a computer generated scheme that stratified by study center and by an admitting diagnosis of trauma or non-trauma. Investigators enrolled eligible patients through an interactive voice response system, which assigned a drug kit number to the investigator. Randomisation was concealed and kept by a designated independent statistician at a contract research organization.</td>
<td>In the iseganan arm, 35 patients were withdrawn and one was missing, which left 326 patients who completed the iseganan arm.</td>
</tr>
<tr>
<td>Bergmans et al²⁵</td>
<td>The randomisation process was not fully described</td>
<td>None stated</td>
</tr>
<tr>
<td>Garcia et al²⁹</td>
<td>Patients were randomised through a computer-generated random number table and were stratified by center.</td>
<td>None stated</td>
</tr>
</tbody>
</table>

#### 3.1.7 Outcomes: Incidence of VAP in antibiotic studies

Claridge et al⁵ in 2007 reported the findings of a double blind RCT comparing aerosolised ceftazidime versus placebo on the incidence of VAP. The authors carried out an intention-to-treat analysis and reported that the incidence of VAP at two weeks was 46% (24/52) in the placebo group and 40% (21/53) in the ceftazidime group. At thirty days, there was little difference in the incidence of VAP, with 50% (26/52) of the placebo group and 49% (26/53) ceftazidime group developing VAP.
In the earlier study of ceftazidime versus placebo on the incidence of VAP, Wood et al\textsuperscript{27} reported that at day 14, the incidence of VAP in the ceftazidime group was 15\%, compared to 55\% in the placebo group. This was statistically significant, \( p = 0.021 \).

In their study of ampicillin-sulbactam prophylaxis plus standard treatment versus standard treatment alone, Acquarolo et al\textsuperscript{28} reported that 39.5\% of all patients developed early-onset VAP, 57.9\% in the standard treatment group and 21.0\% in the ampicillin-sulbactam group (\( p = 0.022 \)). The authors concluded that antibiotic prophylaxis with ampicillin-sulbactam significantly reduced the occurrence of early-onset VAP in critically ill comatose mechanically ventilated patients.

For the study of iseganan, Kollef et al\textsuperscript{23} reported that, on day 14 of the trial, the rate of VAP was 16\% (45/282) in patients in the iseganan arm and 20\% (57/284) in the placebo arm (\( p = 0.145 \)). The conclusions reached by the authors were than iseganan is not effective in improving VAP rates in patients on prolonged mechanical ventilation.

Bergman et al\textsuperscript{25} in their study reported that incidence of VAP in the treatment group (\textit{orabase with 2\% gentamicin, 2\% colistin, and 2\% vancomycin}) was 10\%, compared to 31\% in control group A and 23\% in control group B. The authors conclusions were that, when compared with preventive strategies for VAP which aim to modulate either gastric or intestinal colonisation, prevention of oropharyngeal colonisation is more effective.

For the study on SDD, Garcia et al\textsuperscript{29} reported that VAP occurred in 11.4\% of the SDD treatment group and 29.3\% of the control group, this was statistically significant (\( p < 0.001 \)). The conclusion reached by the authors was that SDD reduces the rate of VAP.

Table 5 displays the incidence of VAP for treatment and control groups from the included studies on antibiotics for the prevention of VAP. Not all the RCTs provided the reduction in risk of VAP, (RR), where it was not reported the RR was calculated, only two RCTs presented the Number Needed to Treat, RR and NNT are presented in table 5.

Table 5: \textbf{Prophylactic antibiotics: VAP incidence}

<table>
<thead>
<tr>
<th>Study</th>
<th>Incidence of VAP %</th>
<th>RR</th>
<th>NNT</th>
<th>Authors reported P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Claridge et al\textsuperscript{5}</td>
<td>Ceftazidime</td>
<td>40% (21/53)</td>
<td>0.14</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>46% (24/52)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wood et al\textsuperscript{27}</td>
<td>Ceftazidime</td>
<td>15% (3/20)</td>
<td>0.73</td>
<td>p=0.021</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>55% (11/20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acquarolo et al\textsuperscript{28}</td>
<td>Ampicillin-sulbactam plus standard treatment</td>
<td>21% (4/19)</td>
<td>0.64</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Standard treatment</td>
<td>58% (11/19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kollef et al\textsuperscript{23}</td>
<td>Iseganan</td>
<td>16% (45/282)</td>
<td>0.21</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>20% (57/284)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bergmans et al\textsuperscript{25}</td>
<td>TAP</td>
<td>10% (9/87)</td>
<td></td>
<td>p=0.001</td>
</tr>
<tr>
<td></td>
<td>Placebo group A</td>
<td>31% (24/78)</td>
<td>0.07</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Placebo group B</td>
<td>53% (14/61)</td>
<td>0.55</td>
<td>8</td>
</tr>
<tr>
<td>Garcia et al\textsuperscript{29}</td>
<td>SDD</td>
<td>11% (15/131)</td>
<td>0.61</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>29% (41/140)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NS = Not significant
All but two RCTs\textsuperscript{5,23} showed a statistically significant result that prophylactic antibiotics reduces the incidence of VAP. Of the four RCTs showing that antibiotics reduced the incidence of VAP, all used different types of antibiotic agents, Acquarolo et al\textsuperscript{28} where ampicillin-sulbactam was used, Bergmans et al\textsuperscript{25} where orabase with gentamicin, colistin, and vancomycin was used, and Garcia et al\textsuperscript{29} where a concentration of gentamicin, polymyxin E and amphotericin B was used.

Claridge et al\textsuperscript{5} used ceftazidime at the same dose as Wood et al\textsuperscript{27} but despite the Claridge\textsuperscript{5} study having a larger sample size, it failed to show that ceftazidime reduced the incidence of VAP. In the Wood study,\textsuperscript{27} 19 of the original 59 patients were excluded, mainly due to early extubation.

It should be noted that the study by Bergmans et al\textsuperscript{25} was included in Chan’s\textsuperscript{22} meta-analysis, which, while on its own was statistically significant, combined in a meta-analysis of similar studies, the overall results were not statistically significant, this may be due to possible differences in regimens and dosage of the different antibiotics.

3.2 Body position
The search retrieved one review and three RCTs of body positioning for the prevention of VAP in ICU patients.

Torres et al\textsuperscript{30} studied patients requiring ventilation that were either in the supine (flat on back) or semi recumbent body position. The authors concluded that time spent in a supine position and the heights of backrest position are critical factors in the occurrence of aspiration, which increases the risk of pneumonia in mechanically ventilated patients. Elevation of the head of the bed (between 30 and 45 degrees) is based on the notion that gravity will reduce the possibility of regurgitation in an overly distended stomach. However, the use of higher backrest positions for critically ill patients is not reported to be common practice in the United States,\textsuperscript{31} no published information is available to say whether it is common practice in the UK.

Hess\textsuperscript{32} in 2005, presented a review of the evidence related to the use of rotational beds, prone position (face downwards) and semi recumbent position (reclining) as procedures to prevent VAP. This review was not a systematic review and therefore does not meet the inclusion criteria for this systematic review. However, due to the paucity of evidence on body positions for the prevention of VAP, it is mentioned here in an endeavour to present a comprehensive review of use of body position in the prevention of VAP. Hess\textsuperscript{32} identified three studies that studied ventilated patients in a semi-recumbent position Torres et al,\textsuperscript{30} Orozco-Levi et al,\textsuperscript{33} and Drakulovic et al.\textsuperscript{34} Hess reported that only the study by Drakulovic et al\textsuperscript{34} assessed the effect of semi recumbent position on VAP. The conclusions reached by Hess that the available evidence suggests that semi recumbent position should be used routinely to reduce the risk of VAP.

3.2.1 Semi recumbent position
In 1999 Drakulovic et al\textsuperscript{34} reported the findings of a randomised trial examining the effect of body position on the incidence of VAP. The object of the study was to assess whether the incidence of nosocomial pneumonia could be reduced by semi recumbent body position, feeding of patients was either parenteral or enteral depending on the decision of the clinician in charge. Ninety patients were randomly
assigned with semi recumbent or supine body position. Four patients were excluded from the analysis as one died during resuscitation two hours after initiation of the protocol, and three because of protocol violation (re-intubated patients all in semi recumbent position). A total of 86 patients (65 male and 21 female, mean age 65 years completed the RCT.

Van Nieuwenhoven et al\textsuperscript{35} reported in 2006 the results of a randomised study examining the feasibility and effects of the semi recumbent position to prevent VAP. Between January 1999 and December 2000, adult patients at four ICUs in three Netherland hospitals were eligible for the study, subject to the inclusion and exclusion criteria. Of the 255 eligible patients, 34 refused consent, leaving 221 for the study, 112 in the semi recumbent group and 109 in the supine group. Of these 221 patients, 181 were ventilated for more than 48 hours (89 in semi recumbent group/92 in supine group).

3.2.2 Prone position
Beuret et al\textsuperscript{36} in 2002, reported on the findings of a prospective, randomised controlled study, set in a 16 bed ICU, evaluating prone position as prevention of lung injury. Whilst the primary objective was to reduce the incidence of lung worsening, the prevention of VAP was a secondary objective of the study. During April 1997 and April 2000, 279 patients were assessed for entry into the study. Two hundred and twenty four met the exclusion criteria and consent was not given for another two patients. In all, 53 patients were randomised to the two groups, two patients in the supine group died and were therefore excluded from the final analysis.

3.2.3 Quantity and quality of research available
Table 6 displays the summary information of the RCTs that evaluated body position for the prevention of VAP. Table 7 shows the inclusion/exclusion criteria of each include RCT, along with the primary and secondary outcomes of the study.

<table>
<thead>
<tr>
<th>Table 6: Summary information of included body position studies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study</strong></td>
</tr>
<tr>
<td>Drakulovic et al\textsuperscript{34}</td>
</tr>
<tr>
<td>Van Nieuwenhoven et al\textsuperscript{35}</td>
</tr>
<tr>
<td>Beuret et al\textsuperscript{36}</td>
</tr>
</tbody>
</table>

Each RCT had different inclusion and exclusion criteria, therefore, the extent to which the results of included trials on body position can provide a reasonable basis for generalisation to a UK ICU setting is unclear.
Two of the RCTs of body position on the incidence of VAP had small numbers of participants in the intervention and control groups, however Van Nieuwenhoven et al\textsuperscript{35} study was larger, see table 8.

The Drakulovic et al\textsuperscript{34} RCT of body position seem to be reasonably well designed and conducted, while the RCT by Beuret\textsuperscript{36} gives little detail on the design of study. All three studies appear to have included balanced populations, although the Beuret et al\textsuperscript{36} RCT had a younger population. No RCT reported any statistically significant difference between populations, see appendix 4 and table 9.
### Table 9: Quality assessment of body position studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Randomisation</th>
<th>Withdrawals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drakulovic et al(^{34})</td>
<td>The patients were randomly assigned to semi recumbent or supine body positions by a computer generated list.</td>
<td>90 patients were originally randomly assigned, four patients were excluded from the analysis: one died during resuscitation two hours after initiation of the protocol and three were excluded because of protocol violation, all were patients in semi recumbent position.</td>
</tr>
<tr>
<td>Van Nieuwenhoven et al(^{35})</td>
<td>Patients were randomly assigned to semi recumbent or supine body positions on a one-to-one allocation basis, by means of a closed non-transparent numbered envelope. An independent person mixed the envelopes before numbering generated the allocations.</td>
<td>34 patients (or their relatives) refused to participate, 40 were ventilated for less than 48 hours.</td>
</tr>
<tr>
<td>Beuret et al(^{36})</td>
<td>Patients were randomly assigned to prone or supine body position, but the randomisation process was not described.</td>
<td>53 patients met the exclusion criteria and their relatives agreed to consent to the patient’s participation in the study. Two patients in the supine group were excluded from the analysis because of death during the first 24 hours after randomisation.</td>
</tr>
</tbody>
</table>

3.2.4 Outcomes: Incidence of VAP in body position studies

In the study by Drakulovic et al\(^{34}\), the 86 intubated and mechanically ventilated patients were randomly assigned to semi recumbent (n=39) or supine (n=47) body position. Semi recumbent position was at a 45 degree angle, supine position was 0 degrees. They found that frequency of clinically suspected nosocomial pneumonia was lower in the semi recumbent group than in the supine group (three of 39 [8%] vs 16 of 47 [34%]; 95% CI for difference 10·0–42·0, p=0·003). This was also true for microbiologically confirmed pneumonia (semi recumbent two of 39 [5%] vs supine 11 of 47 [23%]; 95% CI for difference 4·2–31·8, p=0·018). The conclusions reached were that the semi recumbent body position reduces the frequency and risk of nosocomial pneumonia.

Van Nieuwenhoven et al\(^{35}\) reported that a semi recumbent position at a 45 degree angle was aimed for to be compared with a supine position (classed as standard care) of ten degrees. The targeted semi recumbent position was not achieved for 85% of the study time. In this study a backrest elevation of nearly 28 degrees was achieved for the semi recumbent group. VAP was diagnosed in 11% of the semi recumbent group and 7% in the supine group. The authors concluded that the achieved difference (28 degrees compared to 10 degrees) did not prevent the development of VAP.

Beuret at al\(^{36}\) randomised 25 patients to prone position and 26 patients to supine position, prone position was strictly horizontal, supine position was head and trunk positioned at a 20 degree angle. The authors reported that the incidence of VAP was
20% in the prone position group compared to 38.4% in the supine position group, this was not statistically significant (p=0.14).

None of the RCTs on body position appeared to be robust well conducted studies, see appendix 4. The Drakulovic\textsuperscript{34} and Van Nieuwenhoven\textsuperscript{35} present conflicting results. The largest RCT by Van Nieuwenhoven\textsuperscript{35} reported difficulties in achieving the proposed angle of semi recumbent position, while the other two RCTs\textsuperscript{34,36} did not report on if the proposed angle of semi recumbent or supine position was achieved. Larger, more robust, and well conducted RCTs are needed to provide conclusive results.

Table 10 shows the incidence of VAP for treatment and control groups from the included studies on body position for the prevention of VAP. Only one of the RCTs provided the reduction in risk of VAP, (RR), where it was not reported the RR was calculated, no RCTs presented the Number Needed to Treat, results are presented in table 10.

Table 10: Body positioning: VAP incidence

<table>
<thead>
<tr>
<th>Study</th>
<th>Body position (degrees)</th>
<th>Incidence of VAP %</th>
<th>RR</th>
<th>Authors reported P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drakulovic et al\textsuperscript{34}</td>
<td>45</td>
<td>Semi recumbent</td>
<td>8% (3/39)</td>
<td>0.76</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>Supine</td>
<td>34% (16/47)</td>
<td></td>
</tr>
<tr>
<td>Van Nieuwenhoven et al\textsuperscript{35}</td>
<td>45</td>
<td>Semi recumbent</td>
<td>11% (12/112)</td>
<td>-0.46</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>Supine</td>
<td>7% (8/109)</td>
<td></td>
</tr>
<tr>
<td>Beuret et al\textsuperscript{36}</td>
<td>0</td>
<td>Prone</td>
<td>20% (5/25)</td>
<td>0.48</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>Supine</td>
<td>38% (10/26)</td>
<td></td>
</tr>
</tbody>
</table>

NG = Not given

Of the three RCTs, only one, the study by Drakulovic et al\textsuperscript{34} reported a statistically significant reduction in the incidence of VAP, using a semi recumbent body position of 45 degrees. Although both the Drakulovic et al\textsuperscript{34} and Van Nieuwenhoven\textsuperscript{35} studies aimed for patients to be in a semi recumbent position of 45 degrees, the Van Nieuwenhoven\textsuperscript{35} study failed to maintain such an objective.

3.3 Kinetic bed therapy

Kinetic bed therapy, also known as, kinetic therapy, continuous lateral rotational therapy, oscillation therapy, and continuous postural oscillation, involves nursing the patient on a bed that systematically mechanically rotate patients with 40 degree turns to one side (80 degree total arc) in an attempt to prevent the respiratory complications of immobility.

The clinical effectiveness searches identified one systematic review of kinetic bed therapy published in 2006 and another published in 2007. No new RCTs of kinetic bed therapy were identified by the clinical effectiveness searches. Therefore this review will only include in this section the published systematic reviews on kinetic bed therapy. Of the two reviews, the Delaney et al\textsuperscript{37} was more robust than the one by Goldhill et al\textsuperscript{38} as they reported conducting a literature search of more databases than Goldhill et al\textsuperscript{38}. The search terms reported by Delaney et al\textsuperscript{37} appeared to be more encompassing than those used by Goldhill et al\textsuperscript{38}. Delaney et al\textsuperscript{37} searched for any studies up to those published in early June 2005, while Goldhill et al\textsuperscript{38} searched for
studies published between 1966 and 2004. As would be expected, by using different search terms and covering different time periods, Delaney et al\textsuperscript{37} review included studies not in Goldhill et al\textsuperscript{38} review and vice versa. There was some overlap, in the meta analysis of incidence of VAP, nine of the ten studies included in the Delaney et al\textsuperscript{37} were in the meta analysis undertaken by Goldhill et al.\textsuperscript{38}

A systematic review on kinetic bed therapy to prevent nosocomial pneumonia in mechanically ventilated patients by Delaney et al\textsuperscript{37} was reported in 2006. Fifteen prospective clinical trials were identified which included a total of 1,169 participants, however, the authors reported that the methodological quality of most of the included studies were poor. Of these fifteen studies, ten reported the incidence of pneumonia on ventilated patients and were included in a meta-analysis. The authors of the systematic review reported that there was a significant reduction in the incidence of ventilator associated nosocomial pneumonia (pooled odds ratio (OR) 0.38, 95% confidence interval (CI) 0.28 to 0.53, \textit{p}< 0.001), but no reduction in mortality (pooled OR 0.96, 95%CI 0.66 to 1.14), duration of mechanical ventilation (pooled standardized mean difference (SMD) -0.14 days, 95%CI, -0.29 to 0.02), duration of intensive care unit stay (pooled SMD -0.064 days, 95% CI, -0.21 to 0.086) or duration of hospital stay (pooled SMD 0.05 days, 95% CI -0.18 to 0.27).

Delaney et al\textsuperscript{37} concluded that that kinetic bed therapy is associated with a significant reduction in the odds of developing nosocomial pneumonia in mechanically ventilated patients. However, it is not associated with a significant reduction in the mortality, duration of mechanical ventilation, or ICU or hospital length of stay. The authors stated that given the lack of consistent benefit and the poor methodological quality of the clinical trials included in their analysis, definitive recommendations regarding the use of this therapy could not be made.

In the Goldhill et al\textsuperscript{38} review, the authors also reported a reduction in the incidence of pneumonia with a pooled odds ratio of 0.38 (95% CI 0.27-0.53, \textit{p}<0.001), extremely similar to that reported by Delaney et al.\textsuperscript{30} The quality of the included studies was assessed by use of guidelines and the meta analysis was performed on those studies that fulfilled basic quality standards for which sufficient outcome data were available.

Hess\textsuperscript{32} in his review of patient positioning and VAP reported on a meta-analysis of rotational therapy, only three of nine studies used involved Kinetic bed therapy. The studies were by Gentilello et al,\textsuperscript{39} Summer et al,\textsuperscript{40} and Fink et al,\textsuperscript{41} the remainder used continuous lateral rotation therapy. The conclusion by Hess\textsuperscript{32} was that rotational therapy should be considered in selected patients.

### 3.4 Care bundles

According to the article by the Institute for Healthcare Improvement (IHI),\textsuperscript{21} a care bundle is, in general, a grouping of best practices with respect to a disease process that individually improve care, but when applied together result in substantially greater improvement. The primary components of the IHI care bundle are: (1) elevate the head of the patient’s bed (semi recumbent positioning), (2) interrupt sedation daily (sedation hold), and apply prophylaxis for (3) peptic ulcer and (4) deep venous thrombosis. Whilst each individual component of a care bundle will have an effect, it
is not possible to attribute what effect each component has. For the results to be
generalisable, all components need to be implemented and considered as a whole.

3.4.1 Quantity and quality of research available
No RCTs of a care bundle intervention were identified, the only identified studies of
care bundles were two studies that recorded VAP rates before and after the
introduction of a ‘ventilator bundle’. Both the Cocanour et al.\textsuperscript{42} and Berriel-Cass et
al\textsuperscript{43} studies (both published in 2006) used the IHI care bundle\textsuperscript{21} as a basis, but added
to it, see table 16. One of the care bundle component, semi recumbent body position,
is been covered in this review, the remaining three have not as they were outside the
scope of the review. The IHI\textsuperscript{21} report that a randomised trials have been carried out on
sedation hold, and prophylaxis for peptic ulcer /deep venous thrombosis.

The Cocanour et al\textsuperscript{42} study collected information on VAP (rate per 1,000 ventilator
days) from January 2002 to June 2002, and from the introduction of the ventilator
bundle, June 2002 to June 2003. The Berriel-Cass et al\textsuperscript{43} also collected the same type
of information, from July 2003 to February 2004 when they introduced the ventilator
bundle, and then from February 2004 to January 2006.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Study type</th>
<th>Publication</th>
<th>Ventilator bundle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocanour et al.\textsuperscript{42}</td>
<td>2006</td>
<td>Before/After study</td>
<td>Journal article</td>
<td>IHI care bundle with endotracheal suctioning, hand washing, hand washing, oral care, getting patient out of bed, glove and nonpermeable apron use, use of sleeved Yankauers, changing nasogastric irrigation fluids daily, chlorhexidine baths twice weekly and strict glucose control.</td>
</tr>
<tr>
<td>Berriel-Cass et al\textsuperscript{43}</td>
<td>2006</td>
<td>Before/After study</td>
<td>Journal article</td>
<td>IHI care bundle with an oral care bundle.</td>
</tr>
</tbody>
</table>

The study by Cocanour et al\textsuperscript{42} reported that the incidence of VAP ranged from 22.3 to
32.7 per 1,000 ventilator days (January 2002 to June 2002) before the introduction of
a ventilator bundle, and then ranged from 22.3 to 23.4 per 1,000 ventilator days in the
following four months (June 2002 to September 2002). In October 2002, the VAP rate
was reported to be close to the National Nosocomial Infection Surveillance (NNIS)
90\textsuperscript{th} percentile for VAP in a trauma ICU (28.6 per 1,000 ventilator days). From
October 2002 an intervention that audited the compliance with the ventilator bundle
was introduced. From November 2002 to June 2003, the VAP rate was between 0 and
12.8 per 1,000 ventilator days.

Berriel-Cass et al\textsuperscript{43} reported that the ICU VAP rate per 1,000 ventilator days
decreased from an average of 8.2 per 1,000 (13 months January 2003 – January 2004) to 3.3 per 1,000 (24 months February 2004 – January 2006). The authors believed that
head of bed elevation and oral care had a major impact on reducing the incidence of
VAP.
3.5 Safety/adverse effects

As with any intervention, there is always the possibility of an adverse event occurring, therefore this section examines what risk there is to the patient from an intervention to prevent VAP. Chaste and Fagon\(^{20}\) wrote that VAP is thought to be a common complication of the acute respiratory distress syndrome, Heyland et al\(^{44}\) in their prospective matched cohort study found that VAP is associated with an excess ICU length of stay and a trend towards increased risk of death. Keenan et al\(^ {45}\) concluded that VAP remains the nosocomial ICU infection of greatest concern. Whilst Hugonnet et al\(^ {9}\) concluded that the significant burden of VAP justifies the implementation of specific preventive strategies and the need for further research with the ultimate objective of improving patient safety.

Critically ill patients, such as those requiring mechanical ventilation, are at increased risk of bleeding from stress-induced gastroduodenal ulceration. ICUs use pharmacological prophylaxis on most patients to prevent gastrointestinal bleeding. A prophylaxis for peptic ulcer (such as in the ventilator care bundle by the IHI) could encourage growth of bacteria in the stomach. If ventilated patients get small amounts of gastric contents into the lungs, this may cause VAP. Cook et al\(^ {46}\) in a review, concluded that there is strong evidence of reduced clinically important gastrointestinal bleeding with histamine2-receptor antagonists. The authors also concluded that sucralfate may be as effective in reducing bleeding as gastric pH-altering drugs and is associated with lower rates of pneumonia and mortality.

3.5.1 Prophylactic antibiotics

Mehta and Niederman\(^ {47}\) in their 2003 paper looking at controversies and dilemmas of nosocomial pneumonia in ICUs expressed concerns regarding the use of oral decontamination with antibiotics. The authors believed that routine use of that particular technique do not appear to be justified (and presumably should not be used) and that, the long-term effects on antibiotic resistance of widespread topical use of potent antimicrobial agents need further study.

One antibiotic complication is Clostridia difficile, (anaerobic spore-forming bacteria. Hoth et al\(^ {48}\) conducted a retrospective study examining prophylactic antibiotics administered for more than 48 hours, in mechanically ventilated ICU patients. The authors reported that Clostridium difficile colitis and central line infections were significantly increased in those who received prolonged prophylactic antibiotic compared to those who did not. Hoth et al\(^ {48}\) concluded that justification for the use and duration of prolonged prophylactic antibiotics require careful re-evaluation as this practice is associated with significant clinical complications, leading to increase use of patient resources, lengthened hospital stay and higher costs.

Kollef and Silver\(^ {49}\) in a non-systematic review of VAP, suggested that the evidence of direct topical administration of antibiotics to prevent the incidence of VAP does not improve patient outcome and is associated with the development of nosocomial pneumonia due to antibiotic-resistant bacteria. The authors recommended that unnecessary use of all antibiotics, particularly broad-spectrum agents, be avoided unless clear indications for their use are present. Cook\(^ {50}\) also expressed concerns regarding the use of topical antibiotics in SDD, stating that long-term persistent antibiotic prophylaxis may lead to microbial resistance.
3.5.2 Body position

Dračulović et al. in their study of supine body position as a risk factor for nosocomial pneumonia, undertook a logistic-regression of previously described risk factors for pneumonia in ICU mechanically ventilated patients. The authors stated that enteral feeding and body position showed a significant interaction in the analysis of clinically suspected pneumonia, and believed that they had clearly shown in their study that care of mechanically ventilated patients (with a nasogastric tube in place) in a supine body position increases the risk of nosocomial pneumonia.

In the IHI ‘how to guide’ for ventilator bundles, the IHI acknowledges that for their recommendation that patients positioned between 30 to 45 degrees, some concerns regarding that position have included patients sliding down in bed and, if skin integrity is compromised, the shearing of skin. Other concerns are the possibility of patient discomfort. The IHI reported that although it is difficult to assess for these concerns in a controlled manner, anecdotal experience is that neither has been a complaint of care providers or patients when able to speak off the ventilator.

3.5.3 Kinetic bed therapy

Summer et al. reported that in their study of kinetic bed therapy, one patient was removed from the kinetic bed therapy group due to difficulty maintaining intravenous and monitoring lines during rotation. Indeed, Summer et al. said that continuous turning on a kinetic treatment table could only be tolerated by patients who are obtunded (mentally dulled), particularly if they are intubated.

Hess reported in his review of patient positioning and VAP, that several studies of rotational therapy (which includes kinetic therapy and continuous lateral rotation therapy) reported that patients withdrew from the treatment group due to not being able to tolerate continuous rotation.

In their review of rotational bed therapy, Goldhill et al. reported that some patients who are awake find it difficult to tolerate continuous rotation, particularly at the higher degrees of rotation, and that in general, acute lateral rotation therapy may be best suited to unconscious or sedated patients. Ahrens et al. in a study of the effect of kinetic therapy on pulmonary complications, recommended using kinetic therapy for critically ill patients who can tolerate the therapy, although they acknowledged that some patients may require increased sedation.

3.5.4 Care bundles

Very little published research is available on the use of care bundles for the prevention of VAP. This review did not uncover any that addressed the risk to the patients of using a care bundle. The choice of components of a care bundle would be based on a literature review and the unit’s clinicians’ experience-based recommendations on which component to include and which are medically contraindicated.

3.6 Discussion

Each of the proposed four interventions will be discussed in turn. The problems of diagnosis of VAP will also be discussed, as an accurate and agreed definition of VAP is essential to evaluate any intervention to reduce the incidence of VAP.
All published research evidence reported in this review has originated from the US or Europe, where current practice may differ from the UK. Selective decontamination of the digestive tract for the prevention of VAP is not a standard practice in the UK, personal communication, Jon Silcock, School of Healthcare, University of Leeds.

At one trust, oral decontamination is not used, however, ventilator care bundles and oral hygiene methods are (personal communication, Derek Bainbridge, Nurse Consultant, Rotherham General Hospital). Information on current UK practice for the prevention of VAP is practice based and to date no research based evidence is available.

### 3.6.1 Diagnosis

Baughman\(^5\) stated that the diagnosis of VAP remains a controversial area, and that the use of standard clinical criteria has been found to be inadequate. This view is shared by others, such as Brown et al\(^5\) who reported that despite advances in diagnostic modalities, a definitive diagnosis of pneumonia remains difficult in the ventilated patient. Minei et al\(^5\) in 2006, stated that despite its common occurrence, there is still no agreed upon ‘gold standard’ for the diagnosis of VAP and controversy persists over its true incidence. Lomaestro\(^5\) also commented on the issue that no ‘gold standard’ for diagnosing VAP existed, in the year 2004.

Brown et al\(^5\) said that there is a compelling need for accurate diagnosis of VAP to avoid potentially significant detrimental effects from overuse of antibiotics when the diagnosis is solely based on clinical criteria.

### 3.6.2 Prophylactic antibiotics

Koontz, Chang and Meredith\(^5\) reported that administration of empiric antibiotic treatment does not impact on the incidence of subsequent VAP. Early attempts using parenteral or aerosolised prophylactic antibiotics were met by emergence of resistant bacteria and an increase in VAP related mortality.\(^5\) Indeed, Kollef\(^\) in 1999 reported that the use of aerosolised antibiotics for the prevention of VAP had been abandoned because of its lack of efficacy and the subsequent emergence of antibiotic resistant infections.

Regarding the impact that prolonged prophylactic antibiotic use has on the development of nosocomial pneumonia and antibiotic use complications, Hoth et al\(^4\) conducted a retrospective study of ICU patients. The authors found that the incidence of antibiotic complications were two times greater for patients who received prolonged prophylactic antibiotics than for patients who did not.

A before-after study reported by Gruson et al\(^5\) in 2004, tested the hypothesis that a new program of antibiotic strategy control can minimise the incidence of VAP. In the before period (January 1995 to December 1996) ceftazidime associated with ciprofloxacin was widely prescribed for the empiric and therapeutic treatment of VAP, the incidence of VAP in patients who received mechanical ventilation for more than 48 hours was 22.1%. The authors concluded that the results suggested that new strategy of antibiotics use could be an efficient means to reduce the incidence of VAP caused by antibiotic-resistant bacteria, but that further studies are needed to validate these data.
Dodek et al\textsuperscript{60} searched for relevant RCTs and systematic reviews that involved VAP patients for a clinical practice guideline for the prevention of VAP. Evidence was obtained from 10 meta-analyses on various strategies for the prevention of VAP. These strategies included physical strategies (for example frequency of ventilator circuit changes, type of airway humidification etc), positioning strategies, and pharmacologic strategies. On use of prophylactic antibiotics (including selective decontamination of the digestive tract), the authors concluded that selective digestive decontamination using topical antibiotics (intratracheal or oral) or intravenous and topical antibiotics is associated with a decreased incidence of VAP. The authors recommend that topical antibiotics alone should not be used but would not make any recommendation regarding intravenous antibiotics alone because of insufficient evidence.

3.6.3 Body position
It has been recommended by the United States Centers for Disease Control and Prevention that patients receiving mechanical ventilation have the head of the bed elevated 30-45 degrees to help prevent nosocomial pneumonia. Dillon, Munro and Grap\textsuperscript{31} conducted a study which examined nurses’ accuracy in estimating backrest elevation. A total of 67 nurses took part in the study. The authors found a high correlation between the nurses’ estimates and measured angles. The conclusions reached were that nurses are able to estimate backrest elevation accurately.

To evaluate the extent to which nurses working in intensive care units implement best practices when managing adult patients receiving mechanical ventilation Carson et al\textsuperscript{61} conducted a survey of nurses attending education seminars in the United States. The authors reported that 1,200 completed a 29-item questionnaire about the type and frequency of care provided. For the practice of elevation of the head of the bed to 30 to 45 degrees from horizontal, 34% of nurses reported maintaining that elevation for 75% of the day, and 52% reported maintaining that elevation for 100% of the day.

In their one-day prevalence study of Major Heart Surgery (MHS) patients in ICUs, Bouza et al\textsuperscript{62} also reported on compliance with recommended strategies for the prevention of VAP. In this study, 66.5% (109) of patients were in a semi-recumbent body position.

In 2005, Grap et al\textsuperscript{63} reported on a non-experimental, longitudinal, descriptive study carried out to describe the relationship between backrest elevation and development on VAP. The study was carried out in a 12 bed ICU with about 1,000 admissions a year, of which about 50% require mechanical ventilation. Backrest elevation was measured continuously with a transducer system. Data were obtained from laboratory results and medical records from the start of mechanical ventilation up to 7 days.

Grap et al\textsuperscript{63} reported that there were 66 patients in the sample (mean age 55 years, 58% men), these were intubated primarily because of respiratory failure. Patients remained in the study for a mean of 4.2 days and were monitored for up to 7 days, for a total of 276 patient days. A total of 37 subjects were in the study on day 4, and 21 remained in the study on day 7 when the Clinical Pulmonary Infection Score was determined. During the 276 patient days, mean time of continuous monitoring of backrest elevation per study day was 16.2 hours (range 1.7-23.9). Mean overall
backrest elevation during the entire study period was 21.7º (range 0-88 degrees). During all study days, patients were at backrest elevations less than 30 degrees 72% of the time and less than 10 degrees 39% of the time. Changes in backrest elevations during the study were not significant.

The conclusions reached by Grap et al\textsuperscript{63} were that the patients spent the majority of the time at backrest elevations less than 30º. Only the combination of early, low backrest elevation and severity of illness affected the incidence of ventilator associated pneumonia.

A qualitative study using semi-structured interviews and focus groups was undertaken by Cook et al\textsuperscript{64} to understand the perspective of ICU clinicians regarding the determinants and consequences of semi recumbency. Ninety-three ICU clinicians, including bedside nurses, respiratory therapists, physiotherapists, nutritionists etc. took part in the study. The authors found that the participants readily acknowledged that most patients were not nursed in a semi recumbent position. The conclusions reached by the authors were that under-use of semi recumbent position was influenced by insufficient awareness of its benefit, real and perceived deterrents, poor agreement about implementation responsibility and lack of enabling and reinforcing strategies.

A prospective multicentre observational study was carried out by Reeve and Cook,\textsuperscript{65} to determine the extent to which mechanically ventilated patients are nursed in the semi recumbent position. The study was conducted in four university-affiliated ICUs in Canada, caring for mixed medical/surgical patients. The authors observed that the most common body position was 15-30 degrees from the horizontal. The authors concluded that, although RCTs suggest that the supine position is associated with higher rates of VAP compared with the semi-recumbent position, few mechanically ventilated patients were nursed in a semi-recumbent position.

Helman et al\textsuperscript{66} using a prospective, pre-, and post- intervention observational study, found that standardising the process of care via the addition of an order specifying head of bed position, significantly increased the number of patients who were placed in the semi recumbent position.

Nursing ICU patients in a semi recumbent position may reduce or solve some problems, but may cause or worsen others, according to Woodrow.\textsuperscript{67} While current literature suggests the semi recumbent position presents more benefits than harm, Woodrow\textsuperscript{67} suggests that the semi recumbent position be alternated with other positions in order to minimise complications, such as sacral pressure sores.

A multivariate analysis of VAP by Kollef\textsuperscript{3} reported on the identification of factors associated with the development of VAP in different ICU populations, medical, surgical or cardiothoracic. Kollef\textsuperscript{3} examined head positioning and outcome. Fifty three patients were in the supine position, and 224 in the semi recumbent position during the first 24 hours of mechanical ventilation. 34.0% of those in the supine position developed VAP, compared to 11.2% of those in the semi recumbent position (p<0.001).

Dodek et al\textsuperscript{60} in a clinical practice guideline for the prevention of VAP, recommend the use of semi-recumbent positioning, with a goal of 45 degrees, in patients without
contraindications. This was based on the evidence of one RCT by Drakulovic et al\textsuperscript{34} which Dodek et al\textsuperscript{60} classed as ‘level 2’ evidence (one of the following characteristic was unfulfilled: concealed randomization, blinded outcome adjudication, an intention-to-treat analysis, or an explicit definition of VAP). As mentioned in section 3.2.4, this was a small RCT that was not particularly robust.

3.6.4 Kinetic bed therapy

In their clinical practice guideline for the prevention of VAP, Dodek et al\textsuperscript{60} recommended that clinicians consider the use of kinetic beds, based on evidence from eight trials. The authors also concluded that the use of kinetic beds is associated with decreased incidence of VAP. However, Dodek et al\textsuperscript{60} conducted their review in 2004 and all the eight trials they considered were included in the 15 trials covered by Delaney et al\textsuperscript{37} 2006 review. Indeed, Dodek et al\textsuperscript{60} classified seven of the eight as ‘level 2’ and the other trial at level 3 (allocation was not strictly random). Where Delaney et al\textsuperscript{37} expressed reservations about drawing conclusions due to the poor methodological quality of the included trials, Dodek et al\textsuperscript{60} uses the term recommended as having no reservations about endorsing the intervention. Given that Delaney et al\textsuperscript{37} conducted a fairly robust review, it would seem that Dodek et al\textsuperscript{60} is basing recommendations on poor quality trials.

3.6.5 Care bundles

In 2006, IHI\textsuperscript{21} presented the case for the ‘ventilator bundle’, referred to as a care bundle in this review, as a set of evidence based interventions for patients on mechanical ventilation. The IHI present a ‘how to guide’\textsuperscript{21} which included information on how to calculate, record and measure VAP rate (per 1,000 ventilator days). It was not clear from either of the two studies\textsuperscript{43,42} using a care bundle if they used the same method as that suggested by the IHI.\textsuperscript{21}

Resar et al\textsuperscript{68} reported that between July 2002 and January 2004, 61 ICUs were encouraged to implement a number of collaborative faculty-recommended improvements, including implementation of the IHI ventilator bundle. ICU team members posted data monthly on a Web-based extranet and submitted narrative descriptions describing the changes tested and the strategies implemented. Of these 61 ICUs, 35 measured both VAP data and adherence to the bundle. Resar et al\textsuperscript{68} found that ICUs with the highest rates of compliance with the ventilator bundle had the highest rates of VAP reduction. In the 21 units with > 95% compliance, the VAP rates decreased from 6.6 to 2.7 per 1,000 ventilator days to 2.7 (p < 0.001) a 59% reduction.

It was reported by Resar et al\textsuperscript{68} that when joining the collaborative community, the 61 ICUs were using some of the bundle elements about 90% of the time, but few were using all of the elements more than 10% of the time on every ventilated patient every day. Only 21 of 61 teams in the collaborative achieved full bundle adherence of ≥ 95%, suggesting that further study will be needed to confirm the relationship between use of the ventilator bundle and the direct decrease of VAP rates.

Cocanour et al\textsuperscript{42} reported that a decrease in VAP rate occurred when compliance with the care bundle was audited and feedback given to the staff on both a daily and weekly basis, but noted that compliance was not always 100%, and varied from week
to week. It was noted that not every patient would be able to meet the criteria for all the care bundle components.

Tolentino-DelosReyes et al\textsuperscript{69} conducted a clinical education project to assess nurses’ knowledge regarding the use of the Centers for Disease Control and Prevention ‘care bundle’. The Centers for Disease Control and Prevention care bundle was elevation of the head, continuous removal of subglottic secretions, change of ventilator circuits no more often than every 48 hours and washing of hands before and after contact with each patient. The authors of this study\textsuperscript{69} reported that the education sessions designed to inform nurses about this particular care bundle and its use to prevent VAP, had a significant effect on participants’ knowledge and subsequent clinical practice.
4. Economic evaluation

4.1 Economic Background

The systematic review of the literature identified varying evidence on four broad categories of interventions aimed at the prevention of VAP in mechanically ventilated patients in ICU: prophylactic antibiotics, body positioning, kinetic bed therapy, and holistic care bundles. The only identified full economic evaluation of a prevention strategy estimated the incremental cost per additional survivor of antibiotics to selectively decontaminate the digestive tract. This study provided some useful data to inform our analysis, but the reported cost-effectiveness results were of limited value as the study was undertaken from a Spanish perspective, and they only reported a surrogate outcome, i.e. survivors to discharge from hospital.

The objective of the current study was to estimate the incremental cost per quality adjusted life year (QALY) gained of a range of alternative interventions aimed at reducing the incidence of VAP in patients undergoing mechanical ventilation (MV) within an ICU. The analysis is presented from the perspective of the UK National Health Service (NHS) and includes only costs incurred by the health service. Relevant costs and outcomes are discounted at an annual rate of 3.5%.

4.2 Methods

A relatively simple decision model was used as a framework for the evaluation of alternative interventions aimed at preventing VAP. The subsequent sections describe the model structure, followed by a detailed description of the data, analyses, and assumptions used to populate the model in order to estimates the incremental cost per QALY gained of the alternative evaluated interventions.

4.3 Model structure

The primary cost-effectiveness analysis of interventions aimed at preventing VAP was based on a simple decision modelling framework that comprises two main elements. The basic model structure is presented in Figure 1.
The model requires estimates of the probabilities of VAP in ICU patients on MV for each of the five specified prevention intervention options (including no intervention). Following the occurrence of VAP, the model incorporates the additional costs incurred by patients with VAP over and above the costs incurred by similar patients (i.e. ICU patients on MV) that do not develop VAP. The final stage of the model describes the probability of patients with VAP surviving to discharge. For patients who survive to discharge, it is necessary to estimate the number of QALYs gained over their remaining lifetime, and any costs that are related to the initial occurrence of VAP (e.g. recurrences).

The corresponding pathways for patients who do not develop VAP do not incorporate any health service costs because the VAP pathways includes only additional costs incurred as a result of VAP. The model does describe probabilities of in-hospital death, and estimates a QALY profile for those that survive to discharge.

A key issue concerning the population of the model is whether prevented cases of VAP are less severe, i.e. if the implementation of an intervention reduces the incidence of VAP compared to the no intervention option, are the remaining cases of VAP in the intervention group generally more severe than the VAP cases in the no intervention group.

The following sections describe the data and assumptions used to populate the four categories of input parameters required by the defined model.
4.4 Probabilities of VAP by prevention intervention option

Data from the systematic review of the effectiveness of alternative interventions aimed at preventing VAP were used to inform parameters describing the incidence of VAP in patients in ICU receiving ventilation. The review mainly identified trials that reported incidence rates in patients subject to an intervention, and subject to a control (e.g. placebo in the prophylactic antibiotic studies).

The process for applying estimates of effectiveness involved firstly identifying a baseline incidence rate (with confidence intervals) for patients not subject to any defined intervention. Secondly, measures of the relative risk (RR) of developing VAP (with confidence intervals) were estimated for each of the defined interventions, including separate estimates of effect for sub-groups of interventions within each defined class of intervention (e.g. alternative anti-biotics regimens) and within sub-groups of ventilated ICU patients. Potential sub-groups of ventilated ICU patients were sought from the eligibility criteria of included studies and from any sub-group analyses reported by the included studies.

With respect to combining results from separate studies, as well as informing comparisons of cost-effectiveness between interventions, studies were assessed for potential factors of heterogeneity. These included characteristics such as duration of follow-up, drop out/compliance (with whatever intervention is being tested), as well as patient eligibility criteria and type of intervention within a class of intervention e.g. type of anti-biotic.

4.5 No intervention

The baseline incidence rate of VAP is required to inform the baseline comparator of no specific intervention aimed at preventing VAP. It is difficult to define the baseline scenario, as different ICUs will have different methods of working. With no evidence to guide UK-specific estimates of VAP incidence in patients undergoing MV in an ICU, data from a large scale systematic review were used. Safdar et al identified 89 studies reporting the risk of VAP in patient receiving MV. In 38 prospective cohort studies including 48,112 patients, the pooled incidence was 9.7% (95% CI 7.0 – 12.5%), but in the control arm of 51 randomised controlled trials including 4,802 patients the pooled incidence was 22.8% (18.8 – 26.9%). The authors cite differences in recruitment to cohort studies and to RCTs as the reason for the difference in incidence – the cohort studies usually included consecutive recruitment whilst the RCTs tended to recruit higher risk patients. Due to this recruitment issue and the fact that the cohort studies included a far larger sample, the 9.7% estimate is taken as the mean estimate of VAP incidence. The upper confidence interval is raised to 15% to reflect the implied increase by the RCT data.

4.6 Antibiotic prophylaxis

The summary effectiveness measures from the five RCTs of alternative prophylactic antibiotic regimens are presented in Table 12. An additional study by Acquarolo et al was excluded from the analysis as it only presented effectiveness for the
prevention of early onset pneumonia (EOP). Whilst it presents details of the number of cases of late onset pneumonia (LOP), it is clear that some of the EOP cases also developed LOP as the aggregate EOP and LOP numbers sum to over the sample size in the control group.

Only one regiment was evaluated twice – Ceftazidime, with the Wood et al reporting a highly significant reduction in VAP, whilst Claridge et al did not find a significant difference. The latter study included well over twice as many patients (in the final analysis (105 vs 40). From both a practical and methodological viewpoint, more weight may be attached to the study that did not identify a significant result. The Wood study had stricter inclusion criteria: patients were expected to require at least seven days of mechanical ventilation. All randomised patients were included in the intention to treat analysis presented by Claridge et al, whilst in the Wood study 19 (of 59 randomised) patients were excluded from the analysis because they were extubated (10 patients), developed VAP (six patients), died before receiving three days study treatment (one patient), started treatment more than 48 hours after admission (one patient), or had an invalid informed consent agreement (one patient). The paper does not describe which treatment groups the 19 patients were in, but it does not seem sensible to exclude patients because they develop VAP or die before treatment is completed – that is a shortcoming of the intervention and should be represented.

Kollef et al present only outcomes at 14 days (i.e. individual patients were followed up for a maximum of 14 days). Although the other studies do not explicitly state the length of their follow-up period, it is assumed that they followed patients to the time at which MV was stopped (or they developed VAP or died). Judging by the presented Kaplan Meier curves the other studies seem to present outcomes to the end of the longer follow-up period.

Bergmans et al present a unique study design. They specify two control groups, one of which comprised the patients randomised to placebo from a possible allocation to either the active medication or a placebo (i.e. half patients in the ICU were receiving the active medication). The other control group were in an ICU that had been randomised to receive only the placebo (i.e. all patients in the ICU received the placebo). This design allowed for the potential effects of reduced incidence due to reduced infection within an ICU due to half of the patients receiving a preventative intervention. The results indicate no significant difference in the comparisons between the alternative control groups.

A potential issue in the analysis of the antibiotic regimens is that their effectiveness may reduce over time. The assumption of a constant level of effectiveness is intuitive for the other evaluated interventions, but there is an issue of the duration of effectiveness of the antibiotic regimens that could affect cost-effectiveness. If positive effectiveness is assumed to be maintained indefinitely, then their cost-effectiveness would increase with longer durations of MV as the intervention costs are front loaded. Some evidence comes from the effectiveness studies. Claridge et al report that there was no significant difference in the rates of VAP at two weeks and at 30 days. However, the rate increases from 40% to 49%, and 46% to 50% in the intervention
and control groups, respectively. This indicates a potential fall off in effectiveness beyond 2 weeks.

Wood et al present a Kaplan Meier curve of VAP incidence, which shows a marked increase in incidence in the intervention group after 14 days (specifically from around 17/18 days), whilst incidence in the control arm appears to remain more constant. The excluded study by Acquarolo shows that EOP occurred in 21% and 58% of intervention and control patients, whilst LOP occurred in 53% and 47% of intervention and control patients, respectively. The study by Bergmans et al also presents Kaplan Meier curves of time without VAP. Visually, these indicate a slight increase in incidence beyond 10 days study period. These results also indicate a lessening effectiveness over time of prophylactic antibiotic regimens.

All but one of the studies seem to include all cases of VAP that occur over the duration of the patients’ ICU stay, only Kollef et al cut-off their analysis at 14 days. Thus, the presented RRRs account for the impact of reduced effectiveness over time, if we assume that the MV durations in the included studies are similar to MV duration in the UK.

Assessing the relevant combination of studies to inform separate interventions to be included in the cost-effectiveness analyses, it was noted that the objective of the interventions evaluated by Bergmans et al, and Garcia et al involved the selective decontamination of the digestive tract (SDD). Both interventions involved the topical application of a similar combination of antibiotics – both interventions included gentamicin and colistin; the Bergmans study also included vancomycin, the Garcia study also included amphotericin B. The major difference between the studies was that patients without infection in the Garcia study who were randomised to the SDD intervention also received a 3 days intravenous suspension of ceftriaxone, whilst the control group did not receive ceftriaxone. Thus, the Garcia intervention is a combination of SDD + a course of standard IV antibiotic therapy.

The marginal increase in effectiveness of the combined SDD and standard antibiotic intervention over the combined RRR from the SDD alone intervention could be interpreted as being consistent with the results from the three studies that evaluated standard courses of IV antibiotic therapy. Of the three studies, the study by Claridge et al is the most methodologically sound – Wood et al excluded 19 of 59 randomised patients from their final analysis; Kollef et al cut-off their follow-up at 14 days, and it shown above that effectiveness seems to decrease after 14 days. It is also worth noting that the Wood and Kollef studies were both supported by the manufacturers of the respective interventions, whilst Claridge et al do not acknowledge any industrial support. Claridge et al report a RRR of 0.02 compared to RRRs of 0.54 and 0.2 by Wood and Kollef, respectively.

The antibiotic studies can be split into 3 categories – those evaluating SDD antibiotic therapies and those evaluating non-SDD antibiotic therapies, and those evaluating SDD and non-SDD antibiotic therapies. The combined RRR estimates for the SDD
intervention vs the two control groups reported by Bergmans et al were used to represent the effectiveness of SDD. The RRR presented by Garcia represented the effectiveness of an SDD + non-SDD antibiotics intervention. A single estimate of the effectiveness of a non-SDD antibiotic alone intervention was also specified. Based on the above interpretation of the three relevant studies, a subjectively defined mean RRR of 0.1 is defined, with a 95% confidence interval of 0 to 0.4. Thus, the non-SDD intervention included in the cost-effectiveness analysis is effectively representative of a course of aerolised ceftazidime.

**Table 12: Summary effectiveness measures of evaluated antibiotic regimens**

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparators</th>
<th>ARR (95% CI)</th>
<th>RRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wood et al²⁷</td>
<td>Ceftazidime vs placebo</td>
<td>0.35 (0.04 to 0.58)</td>
<td>0.54 (0.06 to 0.89)</td>
</tr>
<tr>
<td>Claridge et al⁵</td>
<td>Ceftazidime vs placebo</td>
<td>0.01 (-0.18 to 0.19)</td>
<td>0.02 (-0.35 to 0.39)</td>
</tr>
<tr>
<td>Kollef et al²³</td>
<td>Iseganan vs placebo</td>
<td>0.04 (-0.02 to 0.09)</td>
<td>0.20 (-0.11 to 0.50)</td>
</tr>
<tr>
<td>Bergmans et al²⁵</td>
<td>SDD alone vs placebo (non-</td>
<td>0.20 (0.08 to 0.32)</td>
<td>0.66 (0.27 to 1.05)</td>
</tr>
<tr>
<td></td>
<td>isolated)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SDD alone vs placebo (isolated)*</td>
<td>0.24 (0.11 to 0.38)</td>
<td>0.70 (0.31 to 1.09)</td>
</tr>
<tr>
<td>Garcia et al²⁹</td>
<td>SDD + non-SDD vs placebo</td>
<td>0.59 (0.37 to 0.73)</td>
<td>0.70 (0.44 to 0.86)</td>
</tr>
</tbody>
</table>

SDD – selective decontamination of the digestive tract
* isolated refers to the placebo group being isolated from patients receiving active medication

The other antibiotic prophylactic trials compared alternative regimens to placebo or standard care, each of which was evaluated separately in the cost-effectiveness model.

4.7 Kinetic bed therapy

The data informing the effectiveness of kinetic bed therapy is derived from two recently conducted meta-analyses. There was significant overlap in the studies included (though not identical), and both studies reported an almost identical odds ratio for the development of nosocomial pneumonia in mechanically ventilated patients. Table 13 presents the results based on the two meta-analyses. The analysis of the cost-effectiveness of kinetic bed therapy is based on the Delaney meta-analysis as this study provided a fuller explanation of the methods used in the review.

**Table 13: Summary effectiveness measures from meta-analyses of kinetic bed therapy**

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparators</th>
<th>ARR (95% CI)</th>
<th>RRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delaney meta-</td>
<td>Kinetic bed vs manual</td>
<td>0.17 (0.11 to 0.22)</td>
<td>0.54 (0.40 to 0.64)</td>
</tr>
<tr>
<td>analysis</td>
<td>turning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goldhill meta-</td>
<td>Kinetic bed vs manual</td>
<td>0.17 (0.12 to 0.23)</td>
<td>0.53 (0.39 to 0.64)</td>
</tr>
<tr>
<td>analysis</td>
<td>turning</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4.8 Body positioning

The evidence on the effectiveness of body positioning was derived from three separate studies, which included different combinations of prone (lying in a face down position), supine (lying in a face up position), and semi-recumbent (supine at elevated angle) body positioning. The results are shown in Table 14.

The two studies that compared a semi-recumbent position versus a supine position specified similar target positions for the semi-recumbent position of 45 degrees. Van Nieuwenhoven et al stated that the targeted backrest elevation of 45 degrees for semi-recumbent positioning was not achieved for 85% of the study time, Drakulovic et al did not check whether the targeted semi-recumbent position was achieved during study. The target supine positions differed, with Drakulovic specifying a target elevation of 0 degrees and Van Nieuwenhoven et al aiming for a 10 degree elevation. A systematic review of these two studies found that no conclusions for practice can be drawn from the combination of these studies.\(^{31}\)

The third identified study compared a prone position (face down) with a supine position with a small elevation of 20 degrees. Beuret et al did not monitor the achieved positions.

Table 14: Summary effectiveness measures of evaluated antibiotic regimens

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparators</th>
<th>ARR/ARI (95% CI)</th>
<th>RRR/RRI (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drakulovic et al(^{34})</td>
<td>Semi-recumbent (45°) versus supine (0°)</td>
<td>0.26 (0.10 to 0.42)</td>
<td>0.77 (0.28 to 0.93)</td>
</tr>
<tr>
<td>Van Nieuwenhoven et al(^{35})</td>
<td>Semi-recumbent (45°) versus supine (10°)</td>
<td>0.04 (-0.03 to 0.12)*</td>
<td>0.58 (-0.32 to 2.67)*</td>
</tr>
<tr>
<td>Beuret et al(^{36})</td>
<td>Prone (0°) vs supine (20°)</td>
<td>0.18 (-0.07 to 0.41)</td>
<td>0.48 (-0.17 to 1.05)</td>
</tr>
</tbody>
</table>

* absolute and relative risk increase

Van Nieuwenhoven et al found that a supine body position was less effective than a semi-recumbent position, Drakulovic found the opposite. Due to the differences between the studies, there is no scope for combining the results. Beuret et al found that a prone position was more effective than a supine position. However, discussion with clinical colleagues suggested that lying patients in a prone position may impact on the provision of other forms of ICU care that could impact other patient outcomes. In the absence of further information on these potential effects, and the fact that these interventions were not associated with any identifiable additional costs, it was decided that a modelled cost-effectiveness analysis of alternative bed positions would have limited value and was not undertaken at this stage.
4.9 Care bundles

Two relevant studies were identified that reported on the effectiveness of alternative bundles of interventions aimed at reducing the incidence of VAP. Both were non-randomised ‘before and after’ studies that observed the effects of introducing care bundles on VAP incidence in ICU wards. Berriel-Cass et al monitored the impact of a care bundle based on the IHI specified bundle with the addition of a template for oral care. The study by Cocanour et al evaluated the more comprehensive care bundle, including 11 additional components to the bundle specified by the IHI. This study also found that the care bundle was only effective when accompanied by a compliance audit and feedback system. The effectiveness estimates are presented in Table 15.

Cocanour et al presented data on the rate of VAP cases per 1,000 ventilator days and the number of VAP cases for each of the 18 months, which were analysed to estimate the total number of ventilator days for the baseline and intervention time periods. However, the data presented seems to be in error as the estimated number of ventilator days per month ranged from 0 to over 8,000. Hence, the mean rates over the respective 6 and 8 months for the baseline and intervention (+audit) periods were estimated, with the uncertainty in the effectiveness of the more intensive care bundle represented by the upper and lower 95% confidence intervals of the monthly rates.

Berriel-Cass et al report only the aggregate rates of VAP per 1,000 ventilator days, which decline from 8.2 to 3.3 following the introduction of the care bundle.

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparators</th>
<th>ARR (95% CI)*</th>
<th>RRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocanour et al^42</td>
<td>After bundle vs before bundle</td>
<td>20.14 (11.80 to 31.84)</td>
<td>0.70 (0.48 to 0.98)</td>
</tr>
<tr>
<td>Berriel-Cass et al^43</td>
<td>After bundle vs before bundle</td>
<td>4.9</td>
<td>0.60^</td>
</tr>
</tbody>
</table>

* absolute risk reduction in rate per 1,000 ventilator days
^ no range given, so confidence interval estimated as plus and minus 50% of mean RRR

4.10 VAP attributable costs and outcomes

This section describes the findings from an accompanying review of the literature that identified studies reporting the costs and outcomes associated with the incidence of VAP. The objectives of this review were to identify estimates of VAP attributable mortality and VAP attributable resource use during the hospital episode in which the VAP occurred, and post-discharge. The following two sections address these separate phases.

4.11 In-hospital costs and outcomes

Estimates of resource use included duration on mechanical ventilation, ICU LoS, and total hospital LoS. The published literature was searched for papers describing the costs and consequences of VAP. No UK-based studies were identified. To inform estimates of the additional costs incurred by VAP patients, data from the available
literature were extracted that described additional resource use, to which UK relevant unit costs could be applied to estimate aggregate costs.

The model does not describe differential costs for patients who die in-hospital as a result of VAP and those that survive to discharge because data from the literature do not inform this distinction and only provide aggregate additional resource use estimates for patients with VAP.

Two broad data sources were identified. Firstly, some of the studies that informed the effectiveness of the prevention interventions reported relevant secondary outcomes to the primary outcome of the avoidance of VAP. These studies present the aggregate mortality/resource use estimates for all patients in the intervention and control groups (i.e. combining patients who did and did not develop VAP). Secondly, studies specific to the treatment and effects of VAP were identified.

Secondary outcomes presented by the prevention effectiveness studies are shown in Table 16. None of the reporting studies reported a significant reduction in any of the secondary outcomes. In the largest study, a meta-analysis of studies evaluating kinetic bed therapy, Delaney et al found a significant reduction in the incidence of nosocomial pneumonia. However, they found no significant reduction in mortality, duration of mechanical ventilation, intensive care unit stay, or hospital stay. Two of the three other studies that reported significant reductions in the incidence of VAP and presented mortality data showed non-significant decreases in mortality (though the mean RRRs were higher than reported by Delaney). The third study reported a small increase in mortality.

No significant differences in LoS were observed. The largest decline in ICU LoS (2.9 days) was observed in the intervention group assigned to a prone body position, despite this study not identifying a significant decrease in VAP incidence. The two meta-analyses of kinetic bed therapy identified a significant decrease in VAP incidence and a decrease in ICU LoS, though Delaney et al noted an increase in hospital LoS. One of the two other significant studies reported a small increase in ICU LoS, the other a small decrease.
### Table 16: Primary and secondary outcomes reported by prevention studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparison</th>
<th>VAP INCIDENCE</th>
<th>MORTALITY</th>
<th>LENGTH OF STAY (days)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>ARR/ARI</td>
<td>RRR/RRI</td>
<td>ICU</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hospital</td>
</tr>
<tr>
<td>Claridge et al5</td>
<td>Ceftazidime vs placebo</td>
<td>0.01 (-0.18 to 0.19)</td>
<td>0.02 (-0.35 to 0.39)</td>
<td>0.02 (-0.11 to 0.14)†</td>
</tr>
<tr>
<td>Bergmans et al25</td>
<td>SDD alone vs placebo</td>
<td>0.22 (0.12 to 0.32)</td>
<td>0.68 (0.38 to 0.84)</td>
<td>0.09 (-0.05 to 0.20)</td>
</tr>
<tr>
<td>Garcia et al29</td>
<td>SDD + non-SDD vs placebo</td>
<td>0.59 (0.37 to 0.73)</td>
<td>0.70 (0.44 to 0.86)</td>
<td>-</td>
</tr>
<tr>
<td>Drakulovic et al34</td>
<td>Semi-recumbent vs supine</td>
<td>0.26 (0.10 to 0.42)</td>
<td>0.77 (0.28 to 0.93)</td>
<td>-</td>
</tr>
<tr>
<td>Van Nieuwenhoven et al35</td>
<td>Semi-recumbent vs supine</td>
<td>0.04 (-0.03 to 0.12)†</td>
<td>0.58 (-0.32 to 2.67)†</td>
<td>0.02 (-0.10 to 0.13)</td>
</tr>
<tr>
<td>Beuret et al36</td>
<td>Prone vs supine</td>
<td>0.18 (-0.06 to 0.43)</td>
<td>0.48 (-0.31 to 0.79)</td>
<td>0.18 (-0.08 to 0.44)</td>
</tr>
<tr>
<td>Delaney meta-analysis</td>
<td>Kinetic bed vs manual turning</td>
<td>0.17 (0.11 to 0.22)</td>
<td>0.54 (0.40 to 0.64)</td>
<td>0.002 (-0.05 to 0.06)</td>
</tr>
<tr>
<td>Goldhill meta-analysis</td>
<td>Kinetic bed vs manual turning</td>
<td>0.17 (0.12 to 0.23)</td>
<td>0.53 (0.39 to 0.64)</td>
<td>0.01 (-0.04 to 0.07)</td>
</tr>
</tbody>
</table>

* Difference in mean/median LoS: Intervention group LoS minus Control group LoS (i.e. a negative difference indicates lower LoS in the intervention group), 95% Cis presented for means
† absolute/relative risk increase; all other studies found risk reductions
Table 17 presents the summary findings from the literature review of studies reporting attributable costs and/or outcomes of VAP. The ten papers form which potentially relevant data were extracted contain a decision modelling paper, a quantitative systematic review, three matched case control studies, four non-matched case control studies, and randomised controlled trial (RCT) of alternative treatment options for VAP. Matched studies were preferred to non-matched studies, as the patient characteristics tables from the non-matched studies showed some potentially significant differences between the cases and controls. The derivation of the parameter values used to populate the decision model was not clearly defined and so this source was also discounted. The RCT did not present comparative data for VAP and non-VAP patients, though it did not find a significant difference in mortality between the empiric treated and culture directed treated patients.

Regarding mortality, the matched case control studies all reported similar findings of virtually no difference between VAP and non-VAP matched patients. The only meta-analysis identified a non-significant increase in mortality in VAP patients, though the positive odds ratio of 1.64 was dominated by the results of 1 study from which a RR of 1.375 was estimated. The meta-analysis included the studies by Rello et al and Papazien et al, but did not include the Cocanour et al and Hugonnet et al, which reported no difference and an insignificant decrease in mortality in VAP patients.

Of the five matched case control studies, there is most uncertainty regarding methods around the Cunnion study that reports a significant positive rate of VAP attributable mortality. This was a retrospective study and the reported success of the matching process appears poor with significant differences (p≤0.05) in the following risk factors for VAP: percentage on MV ≥ 1 day; on MV ≥ 2 days; Glasgow Coma scale score; APACHE III score; nasogastric intubation; and hyperalimentation. There were also differences in the mean number of days at risk (cases 6.85, controls 5.66 days). The other four studies presents varying details of the matching results, but none appear as divergent as the Cunnion study.

However, as the sample size in the Cunnion study is small, the five matched case control studies were combined to estimate VAP attributable mortality, resulting in a mean value of 0.8% (95% CI -2.37 to 4.16%).

Regarding LoS, the matched case control studies and the meta-analysis are in general agreement that VAP increases ICU LoS. The two case control studies reporting differences in aggregate hospital LoS are also in agreement, with both reporting mean differences of around 10 days.
<table>
<thead>
<tr>
<th>Study</th>
<th>Mortality</th>
<th>Length of Stay</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safdar et al</td>
<td>Odds ratio 1.64 (95% CI 0.86 – 3.14)</td>
<td>Mean VAP attributable ICU LoS = 6.1 (95% CI 5.32-6.87)</td>
<td>Quantitative systematic review, mortality and LoS based on 4 and 3 studies, respectively</td>
</tr>
<tr>
<td>Cocanour et al</td>
<td>VAP = 14.3% Non VAP = 14.3%</td>
<td>MV days; ICU: VAP = 17.7 ± 2.0, Non VAP = 5.8± 1.0; VAP = 21.6 ± 2.2, Non VAP = 6.4± 1.1</td>
<td>Matched patients</td>
</tr>
<tr>
<td>Rello et al</td>
<td>VAP = 30.5% Non VAP = 30.4%</td>
<td>ICU: VAP = 11.7 ± 11.0, No VAP = 5.6 ± 6.1 days</td>
<td>Matched patients</td>
</tr>
<tr>
<td>Rello et al</td>
<td>VAP = 30.5% Non VAP = 30.4%</td>
<td>Hospital: VAP = 25.5 ± 22.8, no VAP = 14.0 ± 14.6</td>
<td>Matched patients</td>
</tr>
<tr>
<td>Hugonnet et al</td>
<td>VAP = 37.1% Non VAP = 38.1%</td>
<td>Mean VAP attributable MV duration; ICU LoS; hospital LoS = 5.1 (95% CI 2.2-8.0); 7.2 (4.1-10.4); 10 days</td>
<td>Matched patients</td>
</tr>
<tr>
<td>Papazian et al</td>
<td>VAP = 41.1% Non VAP = 41.1%</td>
<td>-</td>
<td>Matched patients</td>
</tr>
<tr>
<td>Cunnion et al</td>
<td>VAP = 55% Non VAP = 40%</td>
<td>-</td>
<td>Matched patients</td>
</tr>
<tr>
<td>I.Kappstein et al</td>
<td>Non-matched: VAP = 26.9% Non VAP = 12.5%</td>
<td>Matched excluding patients who died: VAP attributable ICU LoS = 10.13 days</td>
<td>Non-matched or excluded dying patients</td>
</tr>
<tr>
<td>R.H.Erbay et al</td>
<td>VAP =70.3% Non VAP = 35.5%</td>
<td>ICU (median): VAP = 8, No VAP = 2.5 days</td>
<td>Patients not matched, some differences in patient characteristics</td>
</tr>
<tr>
<td>E.Apostolopoulou</td>
<td>VAP = 13.3% Non VAP = 21.3%</td>
<td>Additional 255.8 nursing care hours for 45 patients due to VAP</td>
<td>Patients not matched, and only presents additional nurse time</td>
</tr>
<tr>
<td>D.Ost et al</td>
<td>VAP attributable mortality with correct antibiotics 15% (0-40)</td>
<td>VAP attributable ICU; hospital: 11.8 (range 5-23) and 9.9 (3.3-18) for patients treated with correct antibiotics</td>
<td>Model parameters estimated from literature review</td>
</tr>
<tr>
<td>Warren et al</td>
<td>VAP mortality = 64/127 (50%) Non VAP mortality = 237/692 (34%)</td>
<td>ICU : VAP = 26 days Non VAP = 4 days</td>
<td>Patients not matched</td>
</tr>
<tr>
<td>Baker et al</td>
<td>Empiric treated VAP = 25% (11/44) Culture directed treated VAP 21% (n=6/28)</td>
<td>Presented data includes VAP and non-VAP patients</td>
<td>Randomised trial of empiric vs culture directed VAP treatment</td>
</tr>
</tbody>
</table>
To use the data sources describing the aggregate impact of VAP requires a key assumption that all cases of VAP have similar costs and outcomes, i.e. similar probabilities of in-hospital mortality. The data from the prevention effectiveness studies incorporates the potential for differences in the distribution of VAP severity across cases of VAP occurring in the presence and absence of a prevention intervention.

The argument that studies may not have been powered to detect significant differences in these secondary outcomes is dented by the analyses derived from a meta-analysis that increases power, and given the magnitude of the reduction in the odds of pneumonia one might expect to detect a significant difference in secondary outcomes that occur at relatively high frequency and within a relatively short time frame. Also, the observed results for the secondary outcomes are not consistently in the right direction – mortality and LoS is increased in the intervention group in more than one study, including the meta-analysis.

Alternatively, analyses based on the aggregate mean RRR for mortality, and mean differences in LoS were undertaken to estimate VAP attributable parameter values for mortality and LoS, respectively. These analyses are reported in Tables 18 and 19. Using the observed event rates for VAP reported by each of the studies reporting secondary outcomes, the analyses estimate the VAP attributable parameter values that predict the observed aggregate RRR for mortality, and the aggregate differences in ICU LoS presented by each study. A constant estimate of other cause (non-VAP attributable) mortality of 25% was assumed.

In the analyses for which positive estimates of VAP attributable mortality or LoS could be estimated (i.e. in which VAP incidence, and mortality or LoS, was lower in the intervention group), the estimates of VAP attributable mortality ranged from 1% to 92%. In the latter case, the other cause mortality had to be reduced to 8% as the observed RRR could not be predicted with a 25% other cause mortality rate. VAP attributable ICU LoS ranged from 3 to 16 days, and no positive estimates of VAP attributable hospital LoS could be derived.

The combined interpretation of the VAP attributable mortality rates derived from the prevention intervention studies (direct), and from the VAP-specific assessment studies (indirect), is that VAP appears to have, if any, only a minor additional impact on in-hospital mortality. The model uses the estimates of VAP attributable mortality derived from the 5 matched case control studies (9.7%).

There was slightly less agreement between the direct and indirect studies regarding VAP attributable LoS. The two direct studies that reported aggregate hospital LoS found an increased LoS in patients receiving the prevention intervention, though in one case the intervention was found to be less effective in preventing VAP than the control. In 3 out of 5 studies, ICU LoS was reduced in the study arm with the lowest VAP incidence rate. In these 3 studies the VAP attributable ICU LoS was between 3 and 16 days, which incorporate all of the estimates of VAP attributable ICU LoS of
stay in the four most relevant indirect studies. The model assumes mean (95% CI) values for VAP attributable hospital LoS and ICU LoS of 10 (0 to 12) and 6.1 (0 to 16) days, respectively.
<table>
<thead>
<tr>
<th>Study</th>
<th>Comparators</th>
<th>Cases of VAP</th>
<th>At risk</th>
<th>Proportion VAP</th>
<th>VAP attributable mortality</th>
<th>Other cause mortality</th>
<th>Aggregate mortality</th>
<th>Aggregate mortality RRR</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Claridge et al&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Ceftazidime</td>
<td>21</td>
<td>53</td>
<td>0.396</td>
<td>0.050</td>
<td>0.250</td>
<td>0.270</td>
<td>0.012</td>
<td>-0.145</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>24</td>
<td>52</td>
<td>0.462</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mortality increased in intervention group</td>
</tr>
<tr>
<td>Bergmans et al&lt;sup&gt;13&lt;/sup&gt;</td>
<td>SDD alone</td>
<td>9</td>
<td>87</td>
<td>0.103</td>
<td>0.29</td>
<td>0.250</td>
<td>0.295</td>
<td>0.186</td>
<td>0.188</td>
</tr>
<tr>
<td></td>
<td>Combined controls</td>
<td>45</td>
<td>139</td>
<td>0.324</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van Nieuwenhoven et al&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Semi-recumbent</td>
<td>13</td>
<td>112</td>
<td>0.116</td>
<td>0.050</td>
<td>0.250</td>
<td>0.256</td>
<td>-0.008</td>
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<td></td>
<td>Supine</td>
<td>8</td>
<td>109</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>VAP incidence higher in intervention group</td>
</tr>
<tr>
<td>Beuret et al&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Prone</td>
<td>5</td>
<td>25</td>
<td>0.200</td>
<td>0.920</td>
<td>0.080</td>
<td>0.264</td>
<td>0.391</td>
<td>0.393</td>
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<tr>
<td></td>
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<td>10</td>
<td>26</td>
<td>0.385</td>
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<td></td>
<td></td>
<td></td>
<td>Observed RRR could not be predicted without reducing other cause mortality</td>
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<tr>
<td>Delaney meta-analysis</td>
<td>Kinetic bed</td>
<td>67</td>
<td>470</td>
<td>0.143</td>
<td>0.010</td>
<td>0.250</td>
<td>0.251</td>
<td>0.007</td>
<td>0.007</td>
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<tr>
<td></td>
<td>Manual turning</td>
<td>153</td>
<td>497</td>
<td>0.308</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goldhill meta-analysis</td>
<td>Kinetic bed</td>
<td>63</td>
<td>413</td>
<td>0.153</td>
<td>0.080</td>
<td>0.250</td>
<td>0.262</td>
<td>0.050</td>
<td>0.050</td>
</tr>
<tr>
<td></td>
<td>Manual turning</td>
<td>153</td>
<td>470</td>
<td>0.326</td>
<td></td>
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</table>
## Table 19: Estimating VAP attributable ICU LoS from prevention effectiveness studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparators</th>
<th>Cases of VAP</th>
<th>At risk</th>
<th>Proportion VAP</th>
<th>VAP attributable ICU LoS</th>
<th>Aggregate ICU LoS</th>
<th>Additional LoS with intervention</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bergmans et al(^{25})</td>
<td>SDD alone</td>
<td>9</td>
<td>87</td>
<td>0.103</td>
<td>3.000</td>
<td>0.310</td>
<td>-0.661</td>
<td>-0.683</td>
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<tr>
<td></td>
<td>Combined controls</td>
<td>45</td>
<td>139</td>
<td>0.324</td>
<td></td>
<td>0.971</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Garcia et al(^{39})</td>
<td>SDD + non-SDD</td>
<td>15</td>
<td>131</td>
<td>0.115</td>
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<td>1.317</td>
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<tr>
<td>Drakulovic et al(^{34})</td>
<td>Semi-recumbent</td>
<td>3</td>
<td>39</td>
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<td>0.500</td>
<td>0.038</td>
<td>-0.132</td>
<td>0.400</td>
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<tr>
<td></td>
<td>Supine</td>
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<td>47</td>
<td>0.340</td>
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<tr>
<td>Van Nieuwenhoven et al(^{35})</td>
<td>Semi-recumbent</td>
<td>13</td>
<td>112</td>
<td>0.116</td>
<td>0.500</td>
<td>0.058</td>
<td>0.021</td>
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<tr>
<td></td>
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<td>109</td>
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<tr>
<td>Beuret et al(^{36})</td>
<td>Prone</td>
<td>5</td>
<td>25</td>
<td>0.200</td>
<td>16.000</td>
<td>3.200</td>
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<td></td>
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<td>6.154</td>
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<tr>
<td>Hospital LoS</td>
<td>Cases of VAP</td>
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<tr>
<td>Van Nieuwenhoven et al(^{35})</td>
<td>Semi-recumbent</td>
<td>13</td>
<td>112</td>
<td>0.116</td>
<td>0.500</td>
<td>0.058</td>
<td>0.021</td>
<td>3.000</td>
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<tr>
<td></td>
<td>Supine</td>
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<td>0.073</td>
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<td></td>
</tr>
<tr>
<td>Bergmans et al(^{15})</td>
<td>SDD alone</td>
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<td>0.500</td>
<td>0.052</td>
<td>-0.110</td>
<td>1.500</td>
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<td>139</td>
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<td>0.162</td>
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</tbody>
</table>
4.12 Post-discharge costs and outcomes

Previous cost-effectiveness analyses of alternative treatment options for VAP have estimated QALYs gained post-discharge for survivors of VAP.\textsuperscript{73,74} These studies used the same methodology of assuming survivors of a serious septic condition had their life expectancy reduced by 50\%.\textsuperscript{75} These studies seemingly divided by two the expected survival of members of the general population (of the same age as the evaluated cohort of patients) to estimate survival in VAP patients post-discharge.

The additional element of a cost-effectiveness analysis of interventions aimed at preventing VAP is that it is necessary to estimate post-discharge survival for ventilated ICU patients who did not develop VAP. This survival period is likely to be lower than that of the (age-matched) general population due to the fact that they have obviously experienced a serious illness that required ventilation in an ICU.

Quartin et al investigated the relative contributions of sepsis and co-morbidities to long-term mortality in patients with systemic sepsis (pneumonia is one of six defined categories of sepsis)\textsuperscript{76}

Sepsis patients had been identified from a treatment study for sepsis. Inclusion criteria included probable sepsis according to the presence of the systemic inflammatory response syndrome being unlikely to die of a disorder other than sepsis within 14 days. Control patients were defined as all patients discharged from the same 10 hospitals as the sepsis patients over a 1 year period, excluding those with an index admission that indicated either infection or a primary psychiatric diagnosis or who had been screened for inclusion in the sepsis treatment study.

A Cox proportional hazards model assessed the significance of underlying diseases, infection history, inpatient days in the preceding year, age, race, and sex on survival, as well as two-way interactions where appropriate. The validity of the proportional hazards assumption was tested by dividing the follow-up period into 7 intervals, for each of which separate models were developed.

Analyses investigating the possibility that sepsis may be a marker for more advanced stages of identified co-morbidities found that only gastrointestinal tract disorders were independently associated with a greater risk of death in septic patients than in the control population, and then only during the 91- through 180-day interval (relative risk, 1.82).

1,505 and 91,830 sepsis and control patients were included in the analyses, respectively. The survival model underestimated the numbers of deaths in the septic population, though adjusting the model for different influences of comorbid conditions in septic patients only slightly increased the apparent effect of sepsis. The reference case analysis predicted that sepsis cost the average patient 2.36 years of life and the average 30-day survivor 1.32 years of life during the 8-year follow-up period.
Extrapolating beyond 8 years, sepsis reduced the mean remaining life span from 7.66 years to 2.50 years overall, and from 8.03 years to 4.08 years in 30-day survivors. Discounted at 3.5% per annum, the respective lifetime survival durations are 7.12 and 3.86 years.

The estimated mortality effect of sepsis in 30-day survivors over the extrapolated time horizon is used to inform the relevant VAP model input parameters. It is assumed that survival to 30 days is a reasonable proxy for survival to discharge. Thus, each VAP patient who survives to discharge in the cost-effectiveness model is assumed to lose 3.26 life years (7.12 – 3.86 years) as a result of VAP. The model included three gradation of sepsis severity (septic shock (15%), severe sepsis (45%), and uncomplicated sepsis (40%)), though the survival duration results did not differentiate between these categories. Hence, an additional assumption is that the distributions of sepsis severity and existing co-morbidities in the Quartin population are similar to the distributions amongst patients with VAP in the UK.

To adjust the life years gained for health-related quality of life, utility weights are attached to the VAP and non-VAP survival periods.

Hamel et al undertook a utility study of patients with acute respiratory failure (ARF). Participants included patients with ARF upon hospital admission, as well as patients developing hospital acquired ARF in ICUs. Utility weights were estimated at baseline and at 6 months using time-trade off questions. Hamel et al assumed that the utilities reported by the 225 interviewed patients at 6 months represented those of all surviving patients, and this is the same assumption made in the current analysis. The mean utility weight was 0.88 ±0.22.

The utility weight of 0.88 is reflective of the impact of VAP, plus all the other co-morbidities that the VAP patients may have been experiencing. Non-VAP patients are individuals who have been on MV in an ICU ward and so are likely to have co-morbidities, so an assumption of a utility weight of 1 for the non-VAP cohort would likely overestimate the difference between the cohorts. Therefore, a mean utility weight of 0.95 (with a similar standard error to the VAP group) is assumed for the non-VAP group post-discharge.

The final input to the model was the costs incurred by patients in the post-charge period. Two studies presented estimates in US dollars of the post-discharge costs incurred by VAP patients. These studies estimated annual health care costs of between $16,000 and $19,000. However, as for the utility weights, it is necessary to estimate the corresponding costs in the non-VAP. No data on such costs were identified. It was considered that VAP patients may incur higher annual costs, but that non-VAP patients have a longer survival period. In the absence of any useable data, a neutral aggregate cost difference between the two cohorts over the remainder of their lifetime was assumed.
4.13 Unit costs

This section describes the data sources used to estimate the unit costs that were applied to the resources used as interventions for the prevention of VAP, as well as in the treatment of VAP (as described in the previous sections).

The cost of individual items listed in care bundles like aprons and gloves etc was provided by Western General Hospital, Edinburgh, Rotherham District General Hospital and Sheffield Teaching Hospitals NHS Trust.


The cost of pharmacists time was provided by Curtis and Netton (2005) [http://www.pssru.ac.uk/uc/uc2005contents.htm](http://www.pssru.ac.uk/uc/uc2005contents.htm) accessed 30/07/07.

The cost of drugs making up the oral care interventions and other items like chlorhexidine washes were sourced from the British National Formulary (BNF) [http://www.bnf.org](http://www.bnf.org) on 30/07/07.

We costed the individual items in the two oral decontamination studies; however, we used the costs listed in these studies as there was uncertainty round the estimates we generated. We did not cost any specific UK oral decontamination interventions suggested by our advisors as there was no supporting effectiveness data.

4.14 Model analyses

The main analyses modelled the VAP rates for the different interventions by applying the estimated relative risk (RR) of VAP to the baseline VAP rate. The same, independently estimated VAP attributable in-hospital mortality, and ICU and hospital LoS parameters were then applied to all VAP cases in each intervention arm of the model. Similarly, the same post-discharge effects were applied to all surviving VAP patients. Likewise, the same post-discharge effects were applied to all surviving non-VAP patients. This set of analyses incorporated the assumption that all cases of VAP have similar effects.

A secondary set of analyses was undertaken using data on in-hospital mortality in the intervention and control arms of prevention studies that reported these results. The three studies that reported mortality covered the SDD alone intervention and two meta-analyses of kinetic bed therapy. Two of the three studies that reported such outcomes also presented differences in ICU LoS between the intervention and control groups and these data were used to estimate cost differences, in addition to mortality differences. Effects following discharge were estimated using a proportionately weighted combination of VAP and non-VAP QALYs, based on the relative risks of VAP in the different interventions groups.

Table 20 presents the whole set of input parameters used in the cost-effectiveness analyses. The ranges were used to populate probability distributions that represented...
the uncertainty around each input parameter. The uncertainty around the RR, the unit cost, baseline VAP incidence, other cause mortality, and post-discharge survival input parameters were represented by log normal distributions as such distributions are bounded at zero and have long tails that account for the possibility of large value outliers increasing the mean sampled value. VAP attributable mortality, ICU and hospital LoS were represented by normal distributions as these parameters were not bounded by zero. Utility weights were described using beta distributions as utility weights are bounded by 1, and in this analysis it was unlikely that a utility weight of less than zero would be feasible.

The probability distribution informed a probabilistic sensitivity analysis, which involved sampling a large number of input parameters values (5,000). Summary measures of cost-effectiveness were derived the resulting dataset of estimated cost and QALYs. These included mean values and credible intervals around the cost and QALYs output parameters, as well as around the incremental cost per QALY gained. Cost-effectiveness acceptability frontiers were also derived. These frontiers describe the probability that the intervention with the highest mean net benefits (estimated using the mean total cost and QALY outputs) at alternative QALY values is the most cost-effective intervention (estimated as the proportion of iterations in the probabilistic sensitivity analysis in which that intervention has the highest net benefits. Net benefits are estimated as the number of QALYs gained multiplied by the assumed value of a QALY (varied from £0 to £50,000) minus the costs incurred by patients receiving each intervention.
Table 20: Model input parameters

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
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<td><strong>VAP incidence RRs</strong></td>
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<td>non-SDD antibiotics</td>
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<td>1.00</td>
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<td>SDD antibiotics</td>
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<tr>
<td><strong>Hospital mortality RRs</strong></td>
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<td>Kinetic bed therapy (Goldhill M-A)</td>
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<tr>
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</tr>
<tr>
<td>SDD antibiotics</td>
<td>£21.40</td>
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<tr>
<td>Baseline VAP probability</td>
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<tr>
<td>VAP attributable mortality</td>
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<td>Other cause mortality</td>
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<td>0.32</td>
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<td>VAP attributable ICU LoS</td>
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<td>VAP attributable hospital LoS</td>
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<td>Non-ICU unit cost (per day)</td>
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<td>Post-discharge costs</td>
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<td>Post-discharge survival (VAP)</td>
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<td>Kinetic bed therapy (Delaney M-A)</td>
<td>0.05</td>
<td>-0.18</td>
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4.15 Results

Table 21 presents the results from the primary analysis in which the costs and effects of all VAP cases were assumed to be equal and only data describing the impact of the interventions on the incidence of VAP were derived from the intervention studies. These results show that all of the interventions dominate the no intervention option based on the mean results. Across the interventions, the SDD + non-SDD antibiotic regimen is shown to dominate all other interventions based on the mean results as it has the lowest aggregate costs (£320) and the highest mean QALY gain (4.66).

However, the probabilistic sensitivity shows that there is extreme uncertainty around the estimated incremental cost-effectiveness ratios (ICERs) with three of the six interventions having ICER credible intervals that range from the intervention dominating no intervention at the lower end to the intervention being dominated by no intervention at the upper interval. The three interventions that are not dominated at the upper interval are the SDD + non-SDD regimen, the kinetic bed therapy intervention, and standard care bundle, which have very low ICERs at the upper interval.

Figure 2 presents the cost-effectiveness acceptability frontier. This shows the probability that the intervention with the highest mean net benefits at consecutive values of a QALY (i.e. values that society is assumed to be willing to pay to gain additional QALYs) is the most cost-effective intervention. The curve is unusual as it shows that the SDD + non-SDD option (which consistently has the highest mean net benefits) only has around a 30% probability of being the most cost-effective option. This result is observed because the net benefits are not normally distributed, which is primarily because the observed RRs for the interventions are not normally distributed.

The mean RRs for three of the interventions are very similar (SDD alone, SDD + non-SDD, and the more extensive care bundle (the “care bundle plus”), but the 95% CI for the RR for the SDD + non-SDD option is much narrower than the other two CIs: 0.14 to 0.56 compared to 0.027 to 0.656 and 0.02 to 0.56. The log normal distribution is the most commonly used distributional form to describe RRs, but as this distribution has a long tail it means that the mean values of distributions with wider intervals will be higher than distributions with narrower intervals. This was the case in this evaluation. The median sampled values were similar, but the mean sampled values were 0.32, 0.46, and 0.43 for the SDD + non-SDD, SDD alone, and the care bundle plus options, respectively. The impact of the specified distributions, and the fact that they were sampled independently (i.e. no correlation was assumed) on the outputs is that in only around one third of iterations was the SDD + non-SDD antibiotic intervention found to be the most cost-effective option.
Table 21: Model outputs from primary analysis

<table>
<thead>
<tr>
<th>Output</th>
<th>No intervention</th>
<th>non-SDD antibiotics</th>
<th>SDD antibiotics</th>
<th>SDD + non-SDD antibiotics</th>
<th>Kinetic bed therapy</th>
<th>Care bundle standard</th>
<th>Care bundle plus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention costs (95% CI)</td>
<td>£0.00 (£0.00 to £0.00)</td>
<td>£33.74 (£33.74 to £33.74)</td>
<td>£21.48 (£17.21 to £25.77)</td>
<td>£72.48 (£68.21 to £76.77)</td>
<td>£104.94 (£100.27 to £109.77)</td>
<td>£30.95 (£19.81 to £44.37)</td>
<td>£112.78 (£88.55 to £143.17)</td>
</tr>
<tr>
<td>VAP in-hospital costs (95% CI)</td>
<td>£1000 (-£92 to £2303)</td>
<td>£908 (-£77 to £2161)</td>
<td>£446 (-£18 to £1882)</td>
<td>£320 (-£27 to £890)</td>
<td>£465 (-£42 to £1102)</td>
<td>£425 (-£25 to £1116)</td>
<td>£428 (-£22 to £1912)</td>
</tr>
<tr>
<td>Post-discharge costs (95% CI)</td>
<td>£0 (£0 to £0)</td>
<td>£0 (£0 to £0)</td>
<td>£0 (£0 to £0)</td>
<td>£0 (£0 to £0)</td>
<td>£0 (£0 to £0)</td>
<td>£0 (£0 to £0)</td>
<td>£0 (£0 to £0)</td>
</tr>
<tr>
<td>Total costs (95% CI)</td>
<td>£1000 (-£92 to £2303)</td>
<td>£942 (-£44 to £2195)</td>
<td>£467 (£3 to £1901)</td>
<td>£392 (£45 to £961)</td>
<td>£570 (£64 to £1209)</td>
<td>£456 (-£3 to £1146)</td>
<td>£541 (£93 to £2025)</td>
</tr>
<tr>
<td>QALYs (95% CI)</td>
<td>4.50 (3.45 to 5.75)</td>
<td>4.52 (3.46 to 5.77)</td>
<td>4.63 (3.51 to 5.95)</td>
<td>4.66 (3.53 to 6.01)</td>
<td>4.63 (3.51 to 5.95)</td>
<td>4.62 (3.55 to 5.96)</td>
<td>4.64 (3.50 to 5.96)</td>
</tr>
<tr>
<td>ICER compared to no intervention (upper 95% CI)*</td>
<td>Dominates (Dominated)</td>
<td>Dominates (Dominated)</td>
<td>Dominates (Dominated)</td>
<td>Dominates (£276)</td>
<td>Dominates (£1,253)</td>
<td>Dominates (£570)</td>
<td>Dominates (Dominated)</td>
</tr>
</tbody>
</table>
### Table 22: Model outputs from secondary analysis

<table>
<thead>
<tr>
<th>Outputs</th>
<th>No intervention</th>
<th>SDD antibiotics</th>
<th>Kinetic bed therapy (Delaney M-A)</th>
<th>Kinetic bed therapy (Goldhill M-A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention costs</td>
<td>£0.00 (£0.00 to £0.00)</td>
<td>£21.52 (£17.26 to £25.77)</td>
<td>£104.96 (£100.24 to £109.73)</td>
<td>£104.96 (£100.24 to £109.73)</td>
</tr>
<tr>
<td>VAP in-hospital costs</td>
<td>£0 (£0 to £0)</td>
<td>-£1078 (-£1634 to -£519)</td>
<td>-£84 (-£326 to £149)</td>
<td>-£84 (-£326 to £149)</td>
</tr>
<tr>
<td>Post-discharge costs</td>
<td>£0 (£0 to £0)</td>
<td>£0 (£0 to £0)</td>
<td>-£84 (-£326 to £149)</td>
<td>-£84 (-£326 to £149)</td>
</tr>
<tr>
<td>Total costs</td>
<td>£0 (£0 to £0)</td>
<td>-£1056 (-£1615 to -£497)</td>
<td>£21 (-£222 to £254)</td>
<td>£21 (-£222 to £254)</td>
</tr>
<tr>
<td>QALYs</td>
<td>4.51 (3.48 to 5.79)</td>
<td>4.99 (3.68 to 6.59)</td>
<td>4.67 (3.53 to 6.11)</td>
<td>4.76 (3.57 to 6.23)</td>
</tr>
<tr>
<td>ICER (compared to no intervention) (upper 95% CI)</td>
<td>Dominates (£11,876)</td>
<td>Dominates (Dominated)</td>
<td>Dominates (Dominated)</td>
<td>Dominates (Dominated)</td>
</tr>
</tbody>
</table>
The probability of cost-effectiveness does not vary greatly with the assumed value of a QALY because the cost savings due to reduced ICU LoS are a more significant factor influencing cost-effectiveness than the QALY gain. The QALY gain is primarily due to the differential survival modelled for VAP and non-VAP survivors as the VAP attributable mortality rate was close to zero.

Closer inspection of the data show that the probability that a ‘no intervention’ option being cost-effective is less than 3% when a QALY value of £0 is assumed. When a positive QALY value is assumed the probability of no intervention having the highest net benefits drops to less than 1%.

**Figure 2: Primary analysis: cost-effectiveness acceptability frontier**

The secondary analysis incorporated more data that were available from some of the interventions studies. It used data describing mortality rates in the intervention and control groups, as well as ICU and hospital LoS in the two groups, where available. Costs in the intervention groups were estimated as additional to the no intervention arm so the costs for the no intervention group are zero. The results are presented in Table 22, which show that both the SDD alone antibiotic regimen and Kinetic bed therapy dominate no intervention based on the mean ICERs. Of the two evaluated interventions the SDD option dominates both of the Kinetic bed therapy analyses.

The probabilistic sensitivity shows that there is extreme uncertainty around the estimated ICERs from the Kinetic bed therapy analyses having ICER credible intervals that range from the intervention dominating no intervention at the lower end
to the intervention being dominated by no intervention at the upper interval. The SDD alone regimen is not dominated and has a relatively low ICER at the upper interval.

Unlike the primary analysis, the SDD alone regimen (the intervention with the highest mean net benefits) does have a high probability of being the most cost-effective option, as shown by the cost-effectiveness acceptability curve in Figure 3. This is because it is only being compared to one other intervention, rather than five other interventions in the primary analysis.

**Figure 3: Secondary analysis: cost-effectiveness acceptability frontier**

![Cost-effectiveness acceptability curve](image)

### 4.16 Discussion

The results of the cost-effectiveness analysis of interventions aimed at preventing VAP in ICU patients undergoing MV shows that an intervention is very likely to be cost-effective. There are three main interventions that have the highest probabilities of being the most cost-effective option. These are an SDD alone antibiotic regimen, a SDD + non-SDD antibiotic regimen, and the more extensive care bundle (as defined by Cocanour et al\(^2\)).

The analysis was subject to a number of assumptions that led to some limitations. An important issue is whether the effectiveness of the interventions varies with duration of MV - does the relative risk of VAP in the presence of an intervention increase over time as the effectiveness of an intervention decreases, for example, how long do prophylactic antibiotics retain their effectiveness? If so, does the daily probability of VAP increase with duration of MV, for example, does VAP occur as a result of build up of pathogens or is it a result of any contact with an infectious pathogen? Three studies presented mean days at risk, and three studies reported median days at risk. It was not possible to investigate the relationships between duration of MV and intervention effectiveness or VAP incidence.
There is also a potential issue around the impact of the baseline VAP incidence rate (in the control groups of the intervention studies). A higher baseline rate may provide greater scope for improvement. This is a common issue in many economic evaluations of drug therapies, which is dealt with by assuming that whilst the absolute risk is likely to differ by baseline risk, the relative risk (RR) is more likely to remain constant. Some studies present analyses that show the difference in RR is not significantly different across studies with alternative baseline risks. However, the studies included in these analyses are generally comparing exactly the same comparators (e.g. the same intervention versus the same control). In the case of interventions aimed at preventing VAP, there are no similar studies. No statistical analysis is possible, though Figure 4 presents a scatterplot of the studies that were considered for inclusion in the cost-effectiveness analysis, plotting the baseline VAP incidence against the estimated mean RRR. No significant relationship between baseline incidence and RRR is apparent.

Figure 4: Scatterplot of the baseline VAP incidence against the estimated mean RRR

The other key assumption in the primary analysis was that all cases of VAP, and patients without VAP, had the same subsequent cost and QALY effects, respectively. This issue was explored further in the secondary analyses, which incorporated estimates of in-hospital mortality and LoS derived directly from the intervention and control groups of three different intervention studies. Comparing the results from the primary and secondary analyses for these three interventions shows that the direct approach (secondary analyses) led to an increase in the QALY gained compared to no intervention for all three interventions. The cost difference was also increased for the SDD intervention, though not for the Kinetic bed therapy option. These analyses
indicate that the primary analyses may underestimate the cost-effectiveness of the interventions.

Other issues include the applicability of the evaluated interventions to the UK, for example, are the defined antibiotic regimens reflective of potential UK practice? Could the items in the defined care bundles be implemented in the UK? Were the strains of VAP observed in the intervention studies relevant to the UK? It was also considered infeasible to evaluate the cost-effectiveness of manual bed positioning interventions. Clinical advice indicated that a prone (face down) body position is extremely unusual and has other implications for patient care within an ICU that may make it unsuitable as an intervention for preventing VAP. The effectiveness data on the semi-recumbent body positioning was contradictory and so this intervention was not tested in the cost-effectiveness model.

More minor issues include the data sources used to estimate the effects of VAP. The most appropriate study design for estimating the additional mortality and costs associated with VAP would be a prospective observational design. Such a study would collect data on resources used by a cohort of ventilated ICU patients, from which analyses could estimate hospital mortality and costs as a function of VAP incidence and other relevant patient characteristics (e.g. patient age, sex). Studies identified in the literature review were retrospective observational studies that reported resource use in VAP patients, and matched patients without VAP. These studies may be subject to some additional biases compared to prospective studies, but they still provide a relatively strong source of data for estimating costs associated with VAP.

The eligibility criteria of the intervention studies varied with respect to the inclusion of comatose patients, with two studies only including comatose patients. Presumably risk of VAP may be higher in such patients, but it is not clear whether the interventions would have differential relative effectiveness in comatose and non-comatose patients. All studies eligibility criteria defined expected intubation of at least 2 days (and in some cases longer). This again is likely to increase the risk of VAP in included patients relative to all ICU patients undergoing MV, though the impact on RR is unknown.
5. Conclusions

5.1 Prophylactic antibiotics
Ceftazidime has been evaluated in two RCTs, whilst the smaller RCT showed a significant reduction in the incidence of VAP, the larger RCT did not. There is no evidence to support the routine use of ceftazidime for prophylaxis. Ampicillin-sulbactam, orabase with gentamicin, colistin, and vancomycin, and gentamicin, polymyxin E and amphotericin B all showed a statistical significant reduction in the incidence of VAP, but further research on the complications caused by antibiotic use is needed before firm recommendations can be made.

5.2 Body position
A semi recumbent patient position is a low-cost and practical intervention and while the large trial did not find a statistically significant reduction in the incidence of VAP, a smaller, earlier trial did. This may have been due to the larger trial not achieving a targeted backrest elevation of 45 degrees. As discussed in the larger trial and in a number of articles, a backrest elevation of 45 degrees is not always achieved.

5.3 Kinetic bed therapy
The two meta-analyses on kinetic bed therapy both report a statistically significant reduction in the incidence of VAP, however, doubts have been raised regarding the quality of the trials used. Further high-quality research is required before a definite recommendation can be made.

5.4 Care bundles
Non randomised studies indicate that the use of care bundles, whether the IHI model or a modified version, can reduce VAP rates. Adherence to all elements of a particular care bundle could be problematic. Furthermore, no evidence was presented in the two studies that would assist in the identification of which care bundle component is the most beneficial. For care bundles to work effectively, the various professionals in an ICU will need education on a care bundle and be prepared to adapt their working practice to implement all components of a care bundle.

5.5 Economic conclusions
Whilst better and more UK-specific data would improve the quality of the presented analyses, there does seem to be sufficient evidence to conclude that some form of intervention to prevent VAP would be a cost-effective use of NHS resources.

5.6 Research recommendations

5.6.1 Prophylactic antibiotics
Further research is required on the use of prophylactic antibiotics to reduce the incidence of VAP and the long-term effects prolonged antibiotic use.

5.6.2 Body position
Large, robust and methodically sound RCTs are needed to evaluate the effect of semi recumbent position at 45 degrees on the incidence of VAP, and maintaining an elevation of 45 degrees.
5.6.3 *Kinetic bed therapy*
Robust and methodically sound RCTs are needed to evaluate the effect of Kinetic bed therapy on the reduction of VAP.

5.6.4 *Care bundles*
RCTs are needed to evaluate the effect of care on VAP rates, and if possible, which particular component or components has the most beneficial effect.
Appendix 1: Search strategies

Search strategy clinical effectiveness

Epidemiology search strategy
Database: Ovid MEDLINE(R) <1950 to April Week 1 2007>
Search Strategy:

--------------------------------------------------------------------------------
1. Pneumonia, Ventilator-Associated/
2. ventilator-associated pneumonia.tw.
3. ventilator-acquired pneumonia.tw.
4. or/1-3
5. Pneumonia/
6. Cross Infection/
7. 5 and 6
8. Ventilators, Mechanical/
9. 7 and 8
10. 4 or 9
11. exp Epidemiology/
12. exp Natural History/
13. epidemiology.tw.
14. natural history.tw.
15. incidence.tw.
16. exp Incidence/
17. prevalence.tw.
18. exp Prevalence/
19. or/11-18
20. 10 and 19

Search terms for the ventilator associated pneumonia (1-10) were combined with ‘epidemiology’ search terms (11-18).

Prevention strategies search strategy

1. Pneumonia, Ventilator-Associated/
2. ventilator-associated pneumonia.tw.
3. ventilator-acquired pneumonia.tw.
4. or/1-3
5. Pneumonia/
6. Cross Infection/
7. 5 and 6
8. Ventilators, Mechanical/
9. 7 and 8
10. 4 or 9
11. Primary Prevention/
12. prevent$.tw.
13. antibiotic$.tw.
14. antiseptic.tw.
15. iodine.tw.
16. oral decontaminat$.tw.
Search terms for ventilator acquired pneumonia (1-9) were combined with general prevention (11-12) and specific prevention strategy (13-16) terms.

**Cost effectiveness searches**

To retrieve papers on cost-effectiveness and comparative costs of the different prevention strategies searches were conducted in Medline, CINAHL, Embase, NHS Economic Evaluations Database (EED) and OHE Health Economic Evaluations Database (HEED). Search terms for ventilator associated pneumonia and prevention strategies given above were utilised. Search filters designed to retrieve economic evaluations, were applied to the Medline CINAHL and Embase searches. An example of the Medline (Ovid) search filter is provided below:

1. Economics/
2. exp "Costs and Cost Analysis"/
3. economic value of life/
4. exp economics hospital/
5. exp economics medical/
6. economics nursing/
7. exp models economic/
8. Economics, Pharmaceutical/
9. exp "Fees and Charges"/
10. exp budgets/
11. ecs.
12. (cost or costs or costed or costly or costing$).tw.
13. (economic$ or pharmacoeconomic$ or price$ or pricing$).tw.
14. quality adjusted life years/
15. (qaly or qaly$).af.
16. or/1-15

**Focused prevention strategy searches**

Database: Ovid MEDLINE(R) <1950 to May Week 4 2007>

Search Strategy: 

1. Pneumonia, Ventilator-Associated/
2. ventilator-associated pneumonia.tw.
3. ventilator-acquired pneumonia.tw.
4. 1 or 2 or 3
5. Pneumonia/
6. Cross Infection/
7. 5 or 6
8. Ventilators, Mechanical/
9. 7 and 8
10. 4 or 9
11. Primary Prevention/
12. prevent$.tw.
13. body position$.tw.
The ventilator associated pneumonia terms (1-9) were combined with general prevention terms (11-12) and terms for the specific prevention strategies: body position (13-18), prophylactic antibiotics (20-21), kinetic bed therapy (23-27) and care bundle (29-30).

To retrieve cost effectiveness papers the above strategy was combined with search filters designed to retrieve economic evaluations as discussed above.
Appendix 2: QUOROM trial flow chart

Clinical effectiveness review

- Potentially relevant citations identified through electronic searches and hand searching: n = 1189
  - Papers rejected at the title stage: n = 644
  - Abstracts screened and inspected: n = 545
    - Papers rejected at the abstract stage: n = 405
  - Full copies retrieved and inspected: n = 140
    - Full papers excluded: n = 125
  - Publications meeting inclusion criteria: n = 15
    - Citations meeting inclusion criteria:
      - Prophylactic antibiotics = 7
      - Body position = 4
      - Kinetic bed therapy = 2
      - Care bundles = 2
Appendix 3: Antiseptic oral decontamination

Chan et al\textsuperscript{22} also undertook a meta-analysis of antiseptic agents as part of their systematic review to evaluate the effect of oral decontamination on the incidence of VAP and mortality in mechanically ventilated adults. The review by Chan et al\textsuperscript{22} was well carried out and robust. The authors included seven trials of antiseptic oral decontamination, six which evaluated chlorhexidine versus placebo (five trials) or standard treatment (one trial), and one trial of providine iodine in the meta analysis of antiseptics.

Although the meta-analysis of four trials (1098 patients) that tested antibiotic oral decontamination did not show a statistically significant reduction, the analysis of the seven trials (2144 patients) that tested the effect of antiseptic oral decontamination on VAP showed a significant reduction (relative risk 0.56, 0.39 to 0.81; \textit{P}=0.002; \textit{I}^2=48.2\%).

The authors concluded that in mechanically ventilated patients, antiseptic oral decontamination prophylaxis reduces the incidence of ventilator associated Pneumonia, but that more evidence is needed before firm conclusions can be made on the effect of antibiotic oral decontamination. The authors also stated that their results should be interpreted in light of the moderate heterogeneity of trial results and possible publication bias.
### Appendix 4: Quality assessment

#### Quality assessment summary

#### Prophylactic antibiotics

<table>
<thead>
<tr>
<th>Assessment criteria</th>
<th>Claridge et al(^8)</th>
<th>Kollef et al(^23)</th>
<th>Bergmans et al(^25)</th>
<th>García et al(^29)</th>
<th>Wood et al(^27)</th>
<th>Acquarolo et al(^28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was the method used to assign participants to the treatment groups really random?</td>
<td>Y</td>
<td>Y</td>
<td>U</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>What method of assignment was used?</td>
<td>CR</td>
<td>CR</td>
<td>U</td>
<td>CR</td>
<td>CR</td>
<td>CR</td>
</tr>
<tr>
<td>Was the allocation of treatment concealed?</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>What method was used to conceal treatment allocation?</td>
<td>CG</td>
<td>CG</td>
<td>U</td>
<td>OE</td>
<td>OE</td>
<td>OE</td>
</tr>
<tr>
<td>Was the number of participants who were randomised stated?</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Were details of baseline comparability presented?</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Was baseline comparability achieved?</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Were the eligibility criteria for study entry specified?</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Were any co-interventions identified that may influence the outcomes for each group?</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Were the outcome assessors blinded to the treatment allocations?</td>
<td>U</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>U</td>
<td>U</td>
</tr>
<tr>
<td>Were the individuals who administered the intervention blinded to the treatment allocation?</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>U</td>
<td>U</td>
<td>N</td>
</tr>
<tr>
<td>Were the participants who received the intervention blinded to the treatment allocation?</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>U</td>
</tr>
<tr>
<td>Was the success of the blinding procedure assessed?</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Were at least 80% of the participants originally included in the randomised process followed up in the final analysis?</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Were the reasons for withdrawal stated?</td>
<td>U</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Was an intention-to-treat analysis included?</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>

**Abbreviations:**

- \( Y \) = yes
- \( N \) = no
- \( U \) = unclear
- \( CG \) = computer-generated
- \( CR \) = Central randomisation
- \( N/A \) = not applicable
- \( OE \) = opaque envelopes
# Body position

<table>
<thead>
<tr>
<th>Assessment criteria</th>
<th>Drakulovic et al.⁴</th>
<th>Van Nieuwenhoven et al.⁵</th>
<th>Beuret et al.⁶</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was the method used to assign participants to the treatment groups really random?</td>
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<td>Y</td>
<td>U</td>
</tr>
<tr>
<td>What method of assignment was used?</td>
<td>CG</td>
<td>CR</td>
<td>U</td>
</tr>
<tr>
<td>Was the allocation of treatment concealed?</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>What method was used to conceal treatment allocation?</td>
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<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Was the number of participants who were randomised stated?</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Were details of baseline comparability presented?</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Was baseline comparability achieved?</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Were the eligibility criteria for study entry specified?</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Were any co-interventions identified that may influence the outcomes for each group?</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Were the outcome assessors blinded to the treatment allocations?</td>
<td>U</td>
<td>U</td>
<td>U</td>
</tr>
<tr>
<td>Were the individuals who administered the intervention blinded to the treatment allocation?</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Were the participants who received the intervention blinded to the treatment allocation?</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Was the success of the blinding procedure assessed?</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Were at least 80% of the participants originally included in the randomised process followed up in the final analysis?</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Were the reasons for withdrawal stated?</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Was an intention-to-treat analysis included?</td>
<td>N</td>
<td>Y</td>
<td>N</td>
</tr>
</tbody>
</table>

**Abbreviations:**

- Y = yes;
- N = no;
- U = unclear;
- CG = computer-generated;
- CR = Central randomisation
- N/A = not applicable
References


56. Koontz, C. S., Chang, M. C., Meredith, J. W., Koontz, C. S., Chang, M. C., and Meredith, J. W. Effects of empiric antibiotic administration for suspected


78. ITU and additional hospital stay data for 2005 was sourced from NHS reference costs. *NHS* 2007.
79. The cost of pharmacists time was provided by Curtis and Netton (2005). PSSRU 2007.

80. The cost of drugs making up the oral care interventions and other items like chlorhexidine washes were sourced from the British National Formulary (BNF). BNF 2007.