

CHLORHEXIDINE IN THE PREVENTION OF VENTILATOR ASSOCIATED PNEUMONIA: A SYSTEMATIC REVIEW

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Declaration

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ABSTRACT

Background

Ventilator-Associated Pneumonia (VAP) is a hospital acquired infection, not present or incubating at the time of admission and developing in patients during the process of care within the hospital setting. Between nine and twenty-seven percent of patients who are mechanically ventilated will develop ventilator-associated pneumonia. Mortality rates for ventilated patients who develop ventilator-associated pneumonia are estimated to be between 33-50%. The Institute for Healthcare Improvements (IHI) in 2006 recommended the use of 'care bundles' to reduce VAP but no statistically significant decline has been noted.

Despite the completion of an extensive literature search for purposes of this review, no statistical data on nosocomial infections or nosocomial pneumonia relevant to South Africa was found. Mechanical ventilation, a support therapy used in approximately one third of patients, significantly increases the patient's risk of developing this nosocomial pneumonia. Critically ill patients are by virtue of their critical illness more prone to the development of infections, especially ventilator-associated pneumonia. Consistent evidence suggests that oropharyngeal colonization can be associated with the development of VAP. Studies focusing on standard oral care, with or without the concurrent use of chlorhexidine, have not provided sufficient evidence for the use of chlorhexidine in VAP prevention. Chlorhexidine is an antiseptic agent, which when tested, proved to reduce total respiratory tract infections by up to 69% (DeRiso *et al*, 1996:1558).

Objective: The aim of this study was to systematically appraise and review evidence on the effectiveness of chlorhexidine in reducing the incidence of ventilator-associated pneumonia in adult patients. The secondary aim was to systematically summarize evidence on the use of chlorhexidine in reducing mortality.

Methodology: An extensive literature search of studies published in English was undertaken. Electronic databases searched were CENTRAL, CINAHL, EMBASE and MEDLINE. Reference lists of articles, textbooks and conference summaries were examined. Literature searches were

conducted using Medical Subject Headings (MeSH). These included: Ventilator-associated pneumonia, chlorhexidine, VAP and oral care. Eight randomized controlled trials, investigating the efficacy of Chlorhexidine in ventilator-associated pneumonia prevention in adults met the inclusion criteria. The effect measure of choice was Risk ratio with 95% confidence intervals for dichotomous data using the random effects (Mantel-Haenszel) model; (p -value of 0.05). Heterogeneity was assessed using the Cochrane Q statistic and I^2 .

Results: Eight randomized controlled trials met the inclusion criteria for this review. Pooled risk ratio for the incidence of ventilator-associated pneumonia was 0.64 (95% CI; 0.44-0.91; p =0.18). Treatment with chlorhexidine decreased the risk of ventilator-associated pneumonia by 36%. There was no evidence of Chlorhexidine reducing mortality.

Conclusions: Chlorhexidine is a cost effective safe treatment in the prevention of VAP. The use of 2% chlorhexidine may be more effective in reducing the incidence of VAP. No studies were found conducted in developing countries. More rigorously designed trials using 2% chlorhexidine are recommended.

OPSOMMING

Agtergrond

Ventilator-Geassosieerde Longontsteking (VAP) is 'n hospitaal verkry infeksie, nie teenwoordig met toelating nie. Ventilator-geassosieerde longontsteking word ontwikkel in pasiënte tydens die proses van sorg in die hospitaal. Tussen nege en sewe en twintig persent van pasiënte wat meganies geventileer word kry ventilator-geassosieerde pneumonie. Sterftesyfers vir geventileerde pasiënte wat ventilator-geassosieerde pneumonie ontwikkel is na raming tussen 33-50%. Die Institute for Healthcare Improvements (IHI) het in 2006 die gebruik van 'sorg bundels' aanbeveel om VAP te verminder, maar geen statisties beduidende daling is aangeteken nie.

Ten spyte van 'n uitgebreide literatuur soek, is geen statistiese data op nosokomiale infeksies of nosokomiale longontsteking toepaslik tot Suid-Afrika gevind nie. Meganiese ventilasie, 'n ondersteuningsterapie wat gebruik word in ongeveer een derde van die pasiënte, verhoog aansienlik die pasiënt se risiko vir die ontwikkeling van hierdie nosokomiale longontsteking. Kritiek siek pasiënte is op gronde van hul kritieke toestand meer geneig tot die ontwikkeling van infeksies, veral ventilator-geassosieerde pneumonie. Konsekvente bewyse dui daarop dat orofaringeale kolonisasie kan met die ontwikkeling van VAP geassosieer word. Studies wat fokus op standaard mond sorg, met of sonder die gelyktydige gebruik van chlorhexidine, het nie voldoende bewyse vir die gebruik van chlorhexidine in VAP voorkoming nie. Chlorhexidine is 'n antiseptiese agent, wat wanneer in een verewekansigde gekontroleerde studies (VGS) getoets was die totale respiratoriese kanaal infeksies verminder deur tot 69%.

Doel: Die doel van hierdie sistematiese literatuuroorsig was om stelselmatig te evalueer en bewyse oor die effektiwiteit van chlorhexidine in die vermindering en voorkoms van ventilator-geassosieerde pneumonie in volwasse pasiënte te hersien. Die sekondêre doel was om stelselmatig bewyse op te som op die gebruik van chlorhexidine in die vermindering van sterfte.

Metodiek: 'n Uitgebreide literatuursoektog van studies wat in Engels gepubliseer is was onderneem. CENTRAL, CINAHL, EMBASE en MEDLINE was deursoek. Naslaanlyste van artikels, handboeke en konferensie opsommings is ondersoek. Die literatuur soektog is uitgevoer met behulp van Medical Subject Headings (MeSH). Dit sluit in: ventilator-geassosieerde

pneumonie, chlorhexidine, VAP en mond sorg. Agt verewekansigde gekontroleerde studies (VGS), wat die doeltreffendheid van Chlorhexidine in ventilator-geassosieerde pneumonie voorkoming in volwassenes ondersoek, was ingesluit vir hierdie studie. Die effek mate van keuse was risiko ratio (RR) met 95% vertrouensintervalle met behulp van die ewekansige effekte (Mantel-Haenszel) model; ($p = 0.05$). Heterogeniteit is bepaal deur gebruik te maak van die Cochran Q- statistiek en I^2 .

Hoof resultate: Agt verewekansigde gekontroleerde studies (VGS) het die insluiting kriteria vir hierdie oorsig gepas. Gepoelde risiko ratio vir die voorkoms van ventilator-geassosieerde pneumonie: Risiko Ratio (RR) was 0.64 (95% CI; 0.44-0.91; $p=0.18$).

Gevolgtrekkings: Behandeling met chlorhexidine het die risiko van ventilator-geassosieerde pneumonie met 36% gedaal. Daar was geen bewyse van Chlorhexidine op die vermindering van mortaliteit nie. Chlorhexidine is 'n koste-effektiewe veilige behandeling in die voorkoming van VAP. Die gebruik van 2% chlorhexidine kan moontlik meer effektief wees in die vermindering van die voorkoms van VAP. Meer streng ontwerp studies met 2% chlorhexidine word aanbeveel.

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List of Abbreviations

VAP	-Ventilator -Associated Pneumonia
ICU	-Intensive care unit
HAI	-Hospital Acquired Infection
WHO	-World Health Organisation
CDC	-Centres for Disease Control and Prevention
AACN	-American Association of Critical Care Nurse
DVT	-Deep vein thrombosis
HOB	-Head of bed elevation
PUD	-Peptic ulcer disease
IHI	-Institute for health care improvement
RCT	-Randomized controlled trial
LTFU	-Loss to follow up
RevMan 5.1	-Review Manager (version 5.1)
CENTRAL	-Cochrane Central Register of Controlled Trial
CINHAL	-Cumulative Index of Nursing and Allied Health

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PART A

CHLORHEXIDINE IN THE PREVENTION OF VENTILATOR ASSOCIATED PNEUMONIA: A SYSTEMATIC REVIEW

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Janet Bell

Abstract

Purpose: The aim of this review was to evaluate the evidence on the effectiveness of Chlorhexidine in the prevention of Ventilator-associated pneumonia (VAP) in critically ill, adult patients.

Methodology: An extensive literature search of studies published in English was undertaken between June 2010 and June 2011. Electronic Databases searched were CENTRAL, CINAHL, EMBASE and MEDLINE. Reference lists of articles, textbooks and conference summaries were examined and hand searching was performed. Literature searches were done by use of Medical Subject Headings (MeSH) terms, these included: Ventilator-associated pneumonia, chlorhexidine, VAP and oral care.

Selection Criteria: Eight randomized controlled trials, investigating the efficacy of Chlorhexidine in ventilator-associated pneumonia prevention in adults met the inclusion criteria.

Analysis: Data on ventilator-associated pneumonia was extracted as dichotomous variables. The effect measure of choice was Risk ratio with 95% confidence intervals for dichotomous data using the random effects (Mantel-Haenszel) model; (p -value of 0.05). Heterogeneity was assessed using the Cochrane Q statistic and I^2 .

Results: Eight randomized controlled trials met the inclusion criteria for this review. Pooled risk ratio for the incidence of ventilator-associated pneumonia was 0.64 (95% CI; 0.44-0.91; p = 0.18).

Conclusion: Treatment with chlorhexidine decreased the risk of ventilator-associated pneumonia by 36%. There was no evidence of effect of chlorhexidine on mortality.

INTRODUCTION

Background

Ventilator-Associated Pneumonia (VAP) is a hospital acquired infection. This infection, which was not present or incubating at the time of admission, develops in patients during the process of care within the hospital setting (WHO, 2010: N.P).

In 2009, the hospital acquired infection (HAI) burden was reported in the USA as 1.7 million, resulting in 99,000 deaths per annum and \$26-33 billion in added healthcare costs. Implementing evidence-based prevention strategies can result in up to a 70% or greater reduction in HAI's (Healthcare-Associated Infections: State Plans, 2009: N.P). In 2008, the burden of HAI's in Europe was reported as ranging between 3.5-14.8% (average: 7.1%). These infections added an extra 16 million days of hospital stay with 37 000 attributable deaths (ECDC, 2008: N.P). When considering direct costs alone, the annual economic impact was estimated to be about EUR 7 billion per year (ECDC, 2008: N.P). Between nine and twenty-seven percent of patients who are mechanically ventilated will develop VAP. Mortality rates for those patients who develop VAP are high with between 33-50% of ventilated patients developing this condition (American Thoracic Society, 2005:390). Despite recommendations by the Institute for Healthcare Improvements in 2006 to utilise the bundle methodology to reduce VAP, the incidence of VAP has not shown a statistically significant decline. No statistical data on nosocomial infections or nosocomial pneumonia relevant to South Africa or developing countries was found following an extensive literature search.

Description of the condition

VAP can occur in critically ill patients who are mechanically ventilated for periods longer than 48 hours (Augustyn, 2007:32). VAP is associated with the Intensive Care Unit (ICU) setting and the pathogenesis involves the entry of bacteria to the patient's lower respiratory tract and overwhelming of the patient's defences (Powers, 2006:48B).

VAP can be identified in patients presenting with chest radiographic examinations showing new or progressive infiltrate, consolidation, cavitations, or pleural effusions. In addition, the patient presents with at least one of the following symptoms: new onset of purulent sputum or a change

in colour of sputum, increased temperature, increased or decreased white cell count, organisms cultured from blood, isolation of an etiological agent obtained by transtracheal aspirate, bronchial brushing or biopsy (CDC, 2006).

Hospital-acquired infections/nosocomial infections, and therefore VAP, impact the consumers of health care (patients) negatively by providing a gateway for more serious illnesses to develop and by prolonging a patient's stay in a health care facility (WHO, 2010:N.P). Inadvertently this can contribute to long term disability and results in a high personal cost to the patient and their family (WHO, 2010:N.P). Furthermore ventilator-associated pneumonia contributes to mortality within populations and is an additional financial burden to the health care consumer and the health care facility (WHO, 2010:N.P). Ventilator-associated pneumonia (VAP) in patients who are already critically ill prolongs hospitalization, delays recovery and significantly increases the risk of complications and death (Pruitt & William, 2005:36).

Mechanical ventilation is used as a support therapy in approximately one third of patients in intensive care units (Munro & Grap, 2004:27). Patients requiring mechanical ventilation are at risk of developing ventilator-associated pneumonia (Munro & Grap, 2004:27). The risks associated with mechanical ventilation and predisposing patients to ventilator-associated pneumonia are:

- re-intubation
- self extubation
- contamination of ventilator circuits
- poor humidification
- supine positioning
- presence / absence of naso-gastric tubes (Morton *et al*, 2005: 546).

Critically ill patients are immune-compromised by virtue of their critical illness (Munro & Grap, 2004:27). Consistent evidence suggests that oropharyngeal colonization is the most important pathogenic mechanism in the development of VAP and that dental plaque may serve as a reservoir for organisms (Pobo *et al*, 2009:437). Garrouste-Orgeas, Chevret and Arlet, *et al*, as cited by Schleder, (2004:50) concluded in their studies that bacteria may invade the lower

respiratory tract by micro- or bolus aspiration of oropharyngeal organism, inhalation of aerosols containing bacteria, or haematogenous spread from a distant site (Schleder, 2004:50). Experts believe aspiration to be one of most significant causes of hospital acquired pneumonia (Schleder, 2004:50). Factors identified as leading to nosocomial pneumonia are oropharyngeal colonization, gastric colonization, aspiration and compromised lung defences (Morton *et al*, 2005: 546).

Several strategies have been researched intensively and proposed as key factors in the prevention of ventilator- associated pneumonia (IHI, 2006:N.P). VAP is one of the six interventions that the Institute for Healthcare Improvement (IHI) included in the 100,000 Lives Campaign, a national initiative taken to improve patient care, reduce the prevalence and number of hospital acquired infections and improve patient outcomes by the use of ‘Bundles’ (IHI, 2006). Bundles, also referred to globally as “care bundles”, are groups of disease-specific interventions which are evidence-based and regarded as ‘best’ practices’ (IHI, 2006). Individual practice interventions can add to the improvement of the patient but when used collectively, as a ventilator bundle, have proven to be most effective in reducing complications associated with ventilation and significantly reducing the incidence of VAP in ventilated patients (IHI, 2006).

The interventions in the VAP prevention bundle include elevation of the head of bed (HOB) to between 30 and 45 degrees, deep vein thrombosis (DVT) prophylaxis, daily ‘sedation vacations’ or assessment of readiness to extubate and peptic ulcer disease (PUD) prophylaxis (IHI, 2006:N.P). Oral care was not emphasized as a crucial component of the ventilator bundle. In 2010, the AACN issued a practice alert as a recommendation and guideline to nurses emphasising the benefits of oral care and focused specifically on oral care within mechanically ventilated patients. Amongst several studies done to prove the importance of oral care in mechanically ventilated patients, Mori, Hirasawa, *et al* concluded in their study that oral care decreased the incidence of VAP in ICU patients (Mori *et al*, (2006:230).

Dental plaque is a reservoir for pathogens (Heo, Haase, Less, Gill, & Scannapieco, 2008:1568). Several organisms which primarily colonize dental plaque are present in nasal and oral secretions (Augustyn, 2007:33). Aspiration of bacteria containing secretions, from the oro-pharynx to the lungs, can lead to the development of chest infections (Heo, Haase, Less, Gill, & Scannapieco,

2008:1568). Entry routes for these organisms to the lungs are by micro-aspiration of bacteria laden secretions, which pool above the endotracheal cuff of intubated patients (Augustyn, 2007:33). This leads to colonization of the respiratory tract (Augustyn, 2007:33).

Risk factors contributing to the development of VAP are:

- a decreased level of consciousness
- patients' body position
- underlying medical conditions
- the presence of an endotracheal tube
- ventilator circuits
- naso-gastric/oro-gastric tubes
- poor infection control practices by staff (Augustyn, 2007:33).

The American Association of Critical Care Nurses (AACN), in recognition of the lack of nursing guidelines or protocols for the prevention of ventilator –associated pneumonia, in 2008 issued a practice alert (AACN, 2008:N.P.). This practice alert would guide critical care nurses as to the proven strategies to prevent VAP in mechanically ventilated patients (AACN, 2008:N.P.).

How chlorhexidine might work

Fourrier *et al* (2005:1732) confirmed findings of a high level of concordance between bacteria isolated from dental plaque and those found in the lung. Sequential sampling of dental plaque from ICU patients showed that more than 50% of patients acquiring a respiratory infection are previously colonized at the gingivodental level by the same pathogens (Fourrier *et al*, 2005:1732). Fourrier *et al*, (2005:1733) state that teeth should be considered a substantial reservoir for respiratory pathogens of which decontamination of the oropharynx with the use of antiseptic solutions could reduce the incidence of acquired respiratory infections.

Chlorhexidine is a cationic chlorophenyl bis-biguanide antiseptic agent. Chlorhexidine has been used as an oral disinfectant in mechanically ventilated patients because of its ability to bind to oral tissues with subsequent slow release of antiseptic properties and thus a long period of anti-bacterial action (Scannapieco *et al*, 2009:2). The trial by DeRiso *et al* (1996), reported findings of a 69% reduction in the total respiratory tract infections within their chlorhexidine treated group (DeRiso *et al*, 1996:1558). In a literature review, O'Reilly (2003:108) demonstrated that

using chlorhexidine as an adjunct to mechanical plaque removal suppresses the colonization of dental plaque by potential pathogens.

Poor oral hygiene and exposure of the oral cavity can compromise the immune components of saliva (Munro & Grap, 2009:429). Saliva contains a wide variety of specific and innate immune components and as it circulates in the oral cavity, provides a form of mechanical removal of plaque and microorganisms (Munro & Grap, 2004:27). A reduction in the amount of saliva leads to microbial overgrowth in the oropharynx, followed by dental plaque accumulation and the development of dental caries (Munro & Grap, 2004:27). Exposed oropharyngeal and nasopharyngeal cavities may lead to a dry mouth, also known as xerostomia (Munro & Grap, 2004:27). The majority of mechanically ventilated patients may have equipment or devices, such as endotracheal tubes in place which keep the oropharyngeal and nasopharyngeal cavities continuously open. Other contributors to the development of xerostomia in critically ill patients are:

- Psychological factors such as anxiety and stress
- Pharmacological agents, physiological contributors such as dehydration associated with fluid imbalances
- Underlying diseases such as Sjogren syndrome.

Once xerostomia develops, dental plaque accumulates reducing the amount of salivary immune factors within the oral cavity. Powers (2006:48D) states that micro aspiration of bacteria from the oropharyngeal cavity can precipitate the development of VAP.

Significance of this research

Historically dental plaque and associated microbes are removed using two known methods: mechanical interventions (including tooth brushing and rinsing of the oral cavity) and pharmacological interventions (including use of antiseptic and antimicrobial agents).

Studies focusing on standard oral care, with or without the concurrent use of chlorhexidine, have not provided sufficient evidence for the use of chlorhexidine in VAP prevention. Although VAP prevention requires a multi-disciplinary and multi-faceted approach, oral care is primarily a nursing led intervention. Oral care has not been sufficiently focused on as a part of VAP

prevention. Nursing research, protocols and interventions to prevent ventilator-associated pneumonia are lacking.

Aims:

The primary aim of this study was to systematically appraise and review evidence on the effectiveness of chlorhexidine in reducing the incidence of ventilator-associated pneumonia in adult patients. The secondary aim was to systematically summarize evidence on the use of chlorhexidine in reducing mortality.

Criteria for selection of studies:

Inclusion Criteria

Types of studies:

General eligibility criteria for articles required that the studies were:

- Published in English
- Randomized controlled trials or quasi-experimental studies using comparative groups
- Investigating chlorhexidine as an oral decontaminant in the prevention of VAP

Types of interventions: Studies were included if they investigated the use of chlorhexidine versus tooth brushing, placebo or other comparators as oral care interventions to reduce VAP in adult mechanically ventilated patients. Studies included therefore had to have an experimental or treatment group with chlorhexidine and a comparative without chlorhexidine.

Types of participants: The settings for selected studies were intensive care units where mechanical ventilation was being performed. Study participants were mechanically ventilated adult patients (18 years or older, legally able therefore to provide consent for research purposes), with valid consent for study. In the selected studies all participants were 18 years and older as the studies focused on adult intensive care units.

Types of outcome measures: The primary outcome of interest was reduction of the incidence of VAP in mechanically ventilated adult patients. The secondary outcome was a reduction in mortality.

Exclusion criteria

Studies were excluded when VAP was not investigated as an outcome even when chlorhexidine was used. Exclusion criteria within the individual included studies were similar. Patients under the age of 18 years were excluded. Other exclusion criteria within individual studies were a clinical diagnosis of pneumonia at start of study, extubated patients, edentulous patients, patients with a known allergy and hypersensitivity to chlorhexidine.

Exclusion criteria for this review were a high attrition rate of greater than 20%, unavailability of the full text article and incomplete study or outcome data within the included studies.

Dealing with missing data: Where pertinent data was missing from the included trials, the authors concerned were contacted. Missing data was regarded as the absence of any results adding weight to the study, reports on study outcomes or details on methodology applied throughout trials.

Methodology

Search Methods for identification of studies

Electronic searches

An extensive literature search of published clinical trials reporting on VAP prevention, with the use of chlorhexidine in oral care, was undertaken. Peer-reviewed publications were searched between June 2010 and July 2011. Sources for relevant studies included the following databases: the Cochrane Central Register of Controlled Trials (CENTRAL), the Cumulative Index of Nursing and Allied Health (CINAHL) and MEDLINE from inception to present. Literature searches were done by use of Medical Subject Headings (MeSH). The MeSH terms used for the search included: Ventilator-associated pneumonia, VAP, chlorhexidine, hospital acquired pneumonia, nosocomial infections, mechanically ventilated patients, intensive care, mouthwash, mouth care, oral care, oral hygiene and dental care. In total 73 articles were retrieved electronically of which eight of these were trials chosen for inclusion in this systematic review.

Searching for other resources

Reference lists of all relevant articles and textbooks were searched for further relevant studies. Experts in critical care nursing, critical care medicine, infection control, microbiology and dentistry were consulted to identify other studies. Hand searching (pearling) of reference lists of all potentially eligible papers (n=8) was performed. Summaries from conference proceedings were examined.

Data Collection and Analysis

Selection of studies

The above-mentioned search strategies were independently employed by the two reviewers and initially the title of the articles were considered. Titles that were relevant to the study were identified by searching with the use of the following keywords: ventilator-associated pneumonia, chlorhexidine, oral care, mouth care, nosocomial pneumonia. Irrelevant titles were discarded if they never contained any of the search words.

Thereafter the article abstracts of relevant titles were retrieved and reviewed independently by two reviewers with consideration of the inclusion criteria as described in a previous section. Full texts of relevant articles meeting the inclusion criteria were obtained, reviewed and analyzed for methodological quality. The reviews were conducted independently by the two reviewers, Olivia Snyders (OS) and Oswald Khondowe (OK). In case of disagreements not being resolved by discussion, the third reviewer Janet Bell (JB) was available for consultation.

Data extraction and management

Selection of studies: A data extraction tool was developed and utilized to collect information from the studies relevant for this review. A pilot study was conducted to determine the feasibility of the study and to test the search range, assessment and extraction tools. The data extraction tool included baseline characteristics such as study id, citation, methodology, setting, population and sample size, loss to follow up (LTFU) and country where the study was conducted. The two reviewers (OS and OK) extracted all relevant data from the studies as per the data extraction tool.

Assessment of risk of bias in included studies: Methodological quality was assessed by two reviewers (OS & OK) using the Cochrane quality assessment form. The quality assessment form

is freely available on the Cochrane website (The Cochrane Collaboration, 2009: N.P.). The assessment tool addressed the following elements of randomized controlled trials:

- External validity (ability to generalize findings),
- Internal validity (adequate sequence generation, allocation concealment, blinding of participants, incomplete outcome data, selective outcome reporting and other biases).

Measures of treatment effect: The effect measure of choice was risk ratio with 95% confidence intervals for dichotomous data and weighted mean difference using the random effects model (Mantel-Haenszel method). The *p* value was set at 0.05.

Unit of analysis: All included studies randomized participants to a treatment group or a control group.

Dealing with missing data: Where pertinent data was missing from the included trials, the authors concerned were contacted. Missing data was regarded as the absence of any results adding weight to the study, reports on study outcomes or details on methodology applied throughout trials.

Assessment of heterogeneity: Pooled effect sizes of risk ratio (RR) were estimated using (Mantel-Haenszel) random effects model and 95 % Confidence intervals (CI) were presented. Heterogeneity was calculated by use of $I^2 = [Q-df / Q] \times 100 \%$, where *Q* is the Chi-squared statistic and *df* is its degrees of freedom. This describes the percentage of the variability in effect estimates which is due to heterogeneity rather than chance. A value of less than 40 % was considered as not important. An I^2 value of 40 to 60 was considered moderate heterogeneity and more than 60 to 75 as substantial heterogeneity. Values of 75% and above were regarded as considerable heterogeneity.

Assessment of reporting biases: Reporting bias was not identified in any of the included studies.

Data synthesis: All relevant data were entered into a statistical analysis software package known as Review Manager (version 5.1, Cochrane Collaboration: N.P.) for analyses. The effect measure of choice was risk ratio with 95% confidence intervals for dichotomous data and weighted mean difference with 95% confidence intervals for continuous data using the random effects (Mantel-Haenszel) model.

Studies drawn for inclusion in this systematic review were all different with regard to several aspects, i.e. trial settings, varying ages, varying methods of treatment application, etc. These

differences could therefore impact the treatment effect, which in this case would vary between studies. Using the random effects model allows for the distribution of effect sizes and ultimately a combined estimate and the average of a distribution of values. Forest plots were used to demonstrate the effect of interventions.

Subgroup analysis and investigation of heterogeneity: Subgroup analysis was completed on trials after identifying clinical diversity. In this systematic review, subgroup analysis was conducted with respect to the differing concentrations of chlorhexidine used within these included trials.

Sensitivity analysis: Data was entered into RevMan 5.1. and a sensitivity analysis was performed.

Reliability and Validity: Reliability, validity and quality assessment of study data was ensured by piloting and using a standardized data extraction form (The Cochrane Collaboration, 2009: N.P.). Both reviewers (OS & OK) performed research tasks independently. They (OS & OK) have attended research methodology and systematic review workshops and undergone other relevant training. OK has previously conducted and published systematic reviews in peer reviewed journals.

Ethical approval: Ethical approval to conduct this review was obtained from the Health Research Ethics Committee at the Stellenbosch University.

RESULTS

Results of search: The results of the search are shown in Figure 1. Of the 86 titles and abstracts identified, 94.2% (81) were from electronic searches and the remaining 5.8% (5) were identified from manual reference checks. The reviewers excluded 71 articles because the titles were not relevant to the review. After reading the abstracts of the remaining 15 studies, 4 studies were excluded for failing to report outcomes as VAP. Full articles were retrieved for the 11 studies and appraised for methodological quality. Three articles were excluded following this process. Meta-analysis was performed on 8 studies.

Description of selected studies: The studies included in this review (n=8) were all randomized controlled trials. The trials collectively enrolled a total of 1930 patients of which 947 received chlorhexidine (treatment group) as varying oral formulations.

Studies Included: The eight studies included in this review are DeRiso *et al* (1996), Fourrier *et al* (2000), Fourrier *et al* (2005), Houston *et al* (2002), Koeman *et al* (2006), Pobo *et al* (2009), Scannapieco *et al* (2009) and Tantipong *et al* (2007).

Studies excluded: Three studies were excluded after critical appraisal of methodologies (n=3). The trial conducted by Munro and Grap *et al* (2009) was excluded after repeated, unsuccessful attempts to contact the authors for information. The full text article of a trial by MacNaughton *et al* (2004) could not be located. The trial by Grap *et al* (2004) was excluded after the full text review revealed an attrition rate of 50%.

Studies Included in review

Characteristics of included studies (Table 1)

Trials Settings: All trials were conducted within critical care settings where patients are dependent on nursing care to meet their hygiene needs and more specifically, oral care needs (See Table 1). These settings included cardiothoracic intensive care units (n=2), trauma intensive care units (n=1), medical intensive care units (n=1) and mixed medical-surgical intensive care units (n=4). Some studies were single-centre (n=5) focused while others were multi-centre (n=3).

Intervention group: The chlorhexidine preparations varied amongst the experimental groups. The majority of the included trials used chlorhexidine in the form of an oral solution. The trial by Pobo *et al* (2009) used chlorhexidine digluconate. Chlorhexidine digluconate differs from chlorhexidine gluconate only on a molecular binding level. This difference is insignificant and does not affect the potency or effect of chlorhexidine. Chlorhexidine digluconate was regarded as included in the subgroup analysis done on the variance of concentration levels of chlorhexidine. Amongst the treatment group variance was noted in the concentrations of the chlorhexidine used. The majority of trials used chlorhexidine 0.12% (n=4), while others (n=2) used chlorhexidine 0.2% and chlorhexidine 2% concentrations (n=2).

Comparison group: The comparison groups received, placebos in the form of oral solution, gel or pastes with a similar taste, smell or consistency as the chlorhexidine (n=5). The comparison

groups also received power tooth brushing (n=1), normal saline oral rinse (n=1) or phenolic rinse, Listerine, (n=1).

Loss to Follow-up: Loss to follow-up was low among the included trials, ranging from 0% to 16.5%.

Diagnostic criteria: Diagnostic measures used to diagnose ventilator-associated pneumonia included semi-quantitative microbiology techniques and quantitative microbiology techniques.

Risk of Bias in included studies (Table 2)

Methodological assessment: computerized randomization was the most frequently used method amongst the trials (n=5). Other means of randomization included block randomization stratified by site (n=1), stratified randomization according gender and hospital location (n=1) and consecutive randomization by medical record numbers (n=1). Allocation concealment was achieved in most of the trials by having pharmacy staff complete the randomization schedule. Other methods of allocation concealment included opaque sealed envelopes and web-based subject identity number. There was no mention of blinding of participants or allocation concealment in the trial by Houston *et al* (2002).

Results of pooling trials:

The use of chlorhexidine was supported in the 8 trials with a risk ratio of 0.64 (95% CI; 0.44 - 0.91; $p = 0.18$). The pooled results showed evidence of the effectiveness of chlorhexidine in reducing ventilator-associated pneumonia, as the test for overall effect is reflected as $Z = 2.47$ ($p = 0.01$). Figure 2 shows a good overlap of confidence intervals although most individual studies did not show benefit in the use of chlorhexidine in reducing ventilator-associated pneumonia.

Subgroup analysis: Subgroup analyses were performed on the three common strengths of chlorhexidine to determine their effect on the results (Figure 3). In the chlorhexidine 0.12% group, 32 of 574 patients developed VAP associated with a risk ratio of 0.70. In the chlorhexidine 0.2% trials, 18 of 144 patients had developed VAP associated with a risk ratio of 0.62.

In the chlorhexidine 2% trials 18 of the 229 patients in the chlorhexidine treatment group were found to develop VAP, the risk ratio was 0.53 (95% CI; 0.31-0.91; $p = 0.11$). Chlorhexidine 2% therefore demonstrated a better treatment effect.

Mortality

Results of all 8 trials were available for pooling and analysis of mortality (Figure 4). DeRiso *et al*, (1996:1559) reported findings of a reduction in mortality within their chlorhexidine 0.12% treatment group, the reduction being 1.16% as compared to 5.56% in the comparison groups. These findings are also reflected within the pooled analysis (figure 4) performed for this review. Mortality was a secondary outcome of interest when doing this review therefore the effect of chlorhexidine on mortality was now explored. In this systematic review, mortality appeared to be unaffected by chlorhexidine with a risk ratio of 1.12 (95% CI; 0.86-1.46; $p = 0.18$).

Cost effectiveness of chlorhexidine:

Tantipong *et al*, reported findings of cost effectiveness with use of chlorhexidine 2%, the mean cost per patient calculated to be ten times less than the cost of antibiotics needed to treat an episode of VAP (Tantipong *et al*, 2008:135). Koeman *et al* (2002:1352) also found chlorhexidine to be an extremely cost effective safe intervention in VAP prevention especially when considering the absence of known side effects in their trial.

Side effects associated with chlorhexidine use:

Side effects related to 2% chlorhexidine oral solution use was observed and reported in 9.8% of participants in the trial by Tantipong *et al*, (2008:133). These side effects were reported to be mild, reversible and affecting mainly the oral mucosa, observed in 10 of the 102 patients randomized to the chlorhexidine treatment group. Tantipong *et al*, however reported observing this irritation after personnel responsible for administering the treatment were found to be vigorously rubbing the oropharyngeal mucosa with gauze soaked 2% chlorhexidine (2008:135). Personnel were instructed therefore to clean the oropharyngeal mucosa gently, after which the incidence of irritation was reduced (Tantipong *et al*, 2008:135).

DISCUSSION

Eight randomized controlled trials met the inclusion criteria. Using the random effects (Mantel-Haenszel) model, the pooled risk ratio was 0.64 (95% CI; 0.44 - 0.91; $p = 0.18$). The probability of mechanically ventilated patients acquiring ventilator-associated pneumonia with the use of chlorhexidine is 36% less likely than in controls and heterogeneity was not of concern as $I^2=31\%$. As stated earlier in this review, when assessing heterogeneity an I^2 value of less than 40 is considered not important. These findings were consistent with a previous meta-analysis done by Chlebicki and Safdar, (2007:598) who found a pooled relative ratio of 0.70 (95% CI; 0.48-1.04; $p = 0.08$).

In another meta-analysis done by Chan *et al* (2007), pooled analysis of the seven trials that tested the effect of antiseptic oral decontamination on ventilator-associated pneumonia showed a significant reduction with a relative risk of 0.56 (0.39 to 0.81; $p = 0.002$; $I^2=48.2\%$).

Heterogeneity is a problem inherent in all systematic reviews since it involves the pooling of several trials to obtain an overall effect by the combination of trials. Within individual trials homogeneity of comparison and treatment groups were satisfactory.

In this systematic review, individual trial interventions differed, i.e. Different trial settings, differing chlorhexidine dosage, concentrations and method of administration of treatments, diagnostic criteria and exclusion criteria. Subgroup analysis was performed where these differences were observed. Use of random effects model for analysis proved useful also within this systematic review by ensuring heterogeneity was adequately addressed.

In this systematic review, chlorhexidine 0.12% and chlorhexidine 0.2% failed to show any significant effect.

However, chlorhexidine 2% demonstrated a more significant effect on the incidence of VAP when using a random effects analysis, with a risk ratio 0.53 (95% CI; 0.31-0.91; $p = 0.63$). There was no evidence of heterogeneity in the subgroup analysis of studies that used chlorhexidine 2% and results from the overall test of heterogeneity was 0 % ($I^2= 0\%$; $df =1$; $p=0.62$; $Chi^2= 0.24$). A meta-analysis recently undertaken by Labeau, Van de Vyver, Brusselaers, Vogelaers and Blot (2011:6), in their subgroup analysis done on the varying concentrations of chlorhexidine, for chlorhexidine 2% produced a risk ratio 0.53 (95% CI; 0.31-0.91; $p = 0.62$). The results for

Labeau *et al*, were identical and consistent with the findings for subgroup analysis done for this systematic review. Chlorhexidine 2% may provide a better reduction of VAP within high risk patients (those from mixed and medical intensive care units). Ironically chlorhexidine 0.12 % and chlorhexidine 0.2% were used in the majority of trials and showed no effect in reducing VAP (Figure 3). These results support the use of 2% chlorhexidine versus 0.12% chlorhexidine and 0.2% chlorhexidine for reducing VAP. Findings of this study support therefore that chlorhexidine 2% may provide a better reduction of VAP within high risk patients (those from mixed and medical intensive care units).

Methodological bias could not be overlooked, especially in those trials which we found to be at high risk for bias. In terms of adequate sequence generation, the study by Houston *et al*, (2002) was considered high risk because trial participants were randomized by consecutive medical record numbers, adding predictability to the randomization process. Houston *et al* (2002) also failed to report on concealment or blinding procedures making the detection of bias difficult and therefore marked as ‘unclear’ within the methodological quality/ risk of bias assessment prepared for this systematic review (Table 2). Pobo *et al* (2009) also was considered high risk for methodological bias as that trial was prematurely ended by the steering committee after no differences were found between treatment and comparison groups.

In consideration of these methodological concerns, the above-mentioned trials were entered into RevMan 5.1 and a sensitivity analysis was completed (Appendices: Figure 5). Sensitivity analysis resulted in a more favourable effect of chlorhexidine by overall use in the remaining population, with a risk ratio of 0.57 (95% CI; 0.40-0.81; p= 0.39). Chan *et al*, in their systematic review and meta-analysis showed consistency with this review and previous works emphasizing that unblinded designs and trials considered to be of lower methodological quality tend to yield greater treatment effects (2007:8).

In the trial by Tantipong *et al* (2007), randomization was stratified by gender and hospital location. Methods of allocation based on patient characteristics such as date of birth or gender, are usually not reliably random. This is due to this method of randomization being predictable and not easily concealed, reducing the guarantee that allocation has indeed been random and no

potential subjects have been excluded by foreknowledge of the intervention. To strengthen their allocation sequence however, Tantipong *et al* (2007) also randomized by hospital location, therefore the study was still regarded as having low risk for bias.

Trial settings within the included studies contributed to heterogeneity of results. The trials which had been conducted within cardiothoracic intensive care units had a low incidence of VAP (7 of 443 in the chlorhexidine groups and 18 of 471 in the comparison group). These observations and findings were consistent with those of Chlebicki and Safdar (2007) and Labeau *et al* (2011) in their meta-analyses. One could further argue that because the trials done by DeRiso *et al* (1996) and Houston *et al* (2002) were performed in cardio-thoracic intensive care units, they achieved better effect from the use of chlorhexidine. Cardiac patients, especially those planning to have elective surgery, such as valve surgery, generally have a better physiological status and better co-morbid conditions with the duration of ventilation rarely exceeding 24 to 48 hours. Benefit to the participants would therefore be more impressive and significant. Subgroup analysis in this review was attempted using the random effects model and pooling data from only these two trials revealing a risk ratio of 0.41 (95% CI; 0.17-0.98; $p = 0.72$).

In the mixed medical populations, the period of ventilation and intubation usually exceeds 24-48 hours, patients generally have more underlying co-morbidities and multi-medical problems making these patients more prone to developing VAP as well as other infections. Length of stay together with length of ventilation can be extended due to this. These observations are consistent with the rationale of Chan, Ruest, Mead and Cook (2007:8) who also found a greater treatment effect in the non- medical intensive care settings.

Mortality was unaffected by the use of chlorhexidine with a risk ratio of 1.12 (95% CI; 0.69 – 1.45; $p = 0.18$ and $I^2 = 31\%$ indicating moderate clinical heterogeneity. These findings again were consistent with recent findings by Chlebicki and Safdar (2007), Chan *et al* (2007) and Labeau *et al* (2011). Clinical diversity, causing heterogeneity amongst trials, was apparent and could be linked again to the lack of effect of chlorhexidine on mortality.

Heterogeneity therefore may also be directly linked to the effect of chlorhexidine on mortality. Mixed ICU patients and medical patients generally tend to have more co-morbidity's and

produce higher figures for mortality. The trial by DeRiso *et al*, (1996), as an individual trial found a reduction on mortality. Again, these findings may have been directly related to the underlying heterogeneity associated with trial setting and the risks for mortality being lower within the cardio-thoracic populations.

A formal cost analysis of chlorhexidine was not yet undertaken but individual trials have reported chlorhexidine to be a cost-effective alternative in comparison to the cost of treating an episode of VAP, or in comparison to the use of prophylactic antibiotic therapy. Side effects were minimal within the individual trials included in this meta-analysis therefore chlorhexidine may prove to be a safer alternative to prophylactic antibiotics.

Summary of main results

Eight studies included in this review contributed to overall completeness of this systematic review. This review was conducted thoroughly and effort made to identify all literature relevant to this study. The evidence can be applied to settings similar to the ones in the included trials. None of these studies have however been conducted in developing countries.

The evidence by way of literature review, statistical analysis and interpretation was of a good standard in all included articles and within the consulted meta-analyses referenced. Special care was taken to ensure high quality of studies included in order to obtain results that can be generalized to other populations.

Although an extensive study was conducted, only studies in English were considered.

Inter-observer agreement among study reviewers was satisfactory. Trials were independently reviewed and agreement was reached between the reviewers. The third reviewer was not called upon as all disagreements were resolved through discussion.

Authors' Conclusions:

The need to conduct this review arose from considering the impact, complexities and the lack of proven preventative strategies for VAP. The results of this systematic review have the potential to provide guidance to nurses and other health care workers who are in the front line of the fight against nosocomial / hospital-acquired infections, allowing them to improve clinical practice.

Ventilator-associated pneumonia is a leading cause of death in hospitalized patients. Few studies have reported on nursing interventions to prevent VAP. The use of chlorhexidine in South Africa is not routine and needs to be studied in South African populations. Recent, reliable data and statistics relevant to developing countries, in particular South Africa, appear to be rare and unavailable. Allegranzi (2010:N.P.), at the World Health Organisation (WHO) inaugural infection control webinar series in 2010, emphasized that the lack of national policies, programs and guidelines together with a lack of data collection, monitoring and evaluation are constraints in Africa and in other developing countries . Reducing VAP may contribute to reducing the burden suffered by a health system that is struggling to cope with the burden of disease upon healthcare systems.

Chlorhexidine in this review, proved to be beneficial for the prevention of ventilator-associated pneumonia. Results however need to be interpreted with the view of moderate heterogeneity. It is recommended that more studies be done on the optimal concentration, administration procedures, dosage and cost-effectiveness of chlorhexidine use as a focus of future more rigorously designed trials. Unlike the chlorhexidine effect on the incidence of VAP, evidence on mortality did not show any effect with the use of chlorhexidine. Chlorhexidine was found further to be a cost effective, safe treatment in the prevention of VAP. The use of 2% chlorhexidine may be more effective in reducing the incidence of VAP but due to the few trials that it was tested in, further research may be recommended. More evidence is needed from developing countries.

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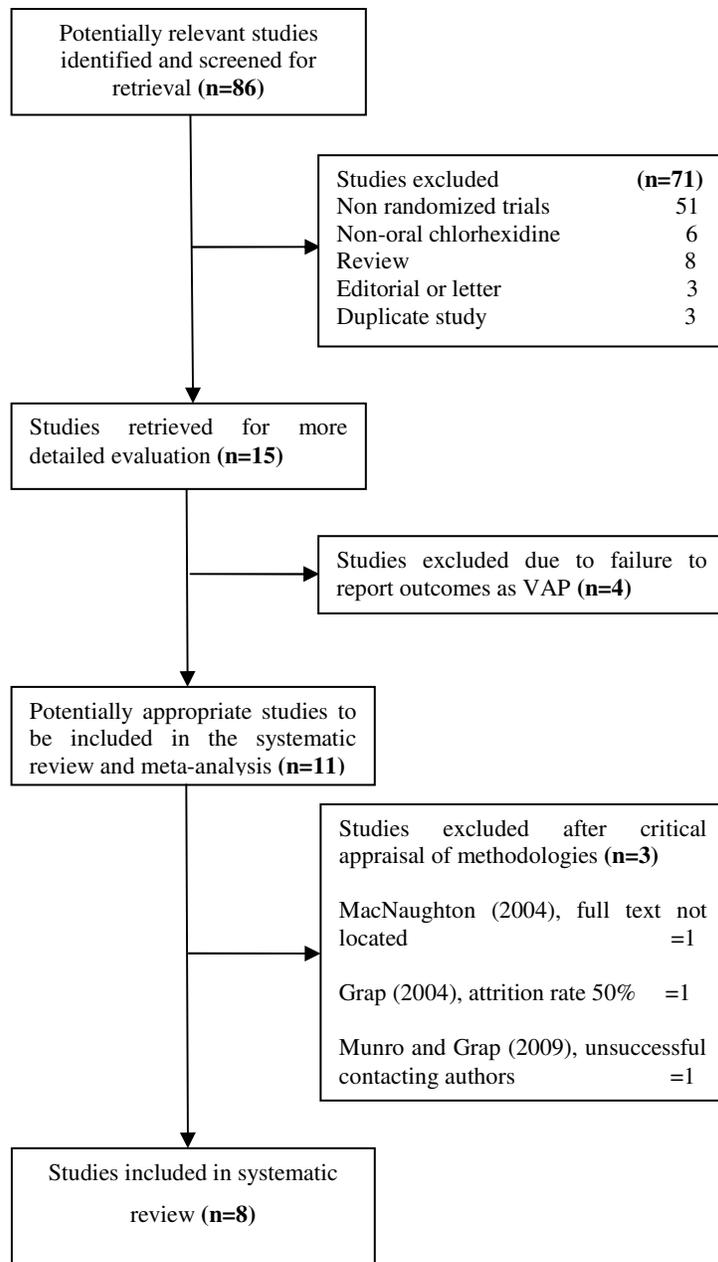


Figure 1: Flow diagram of included studies

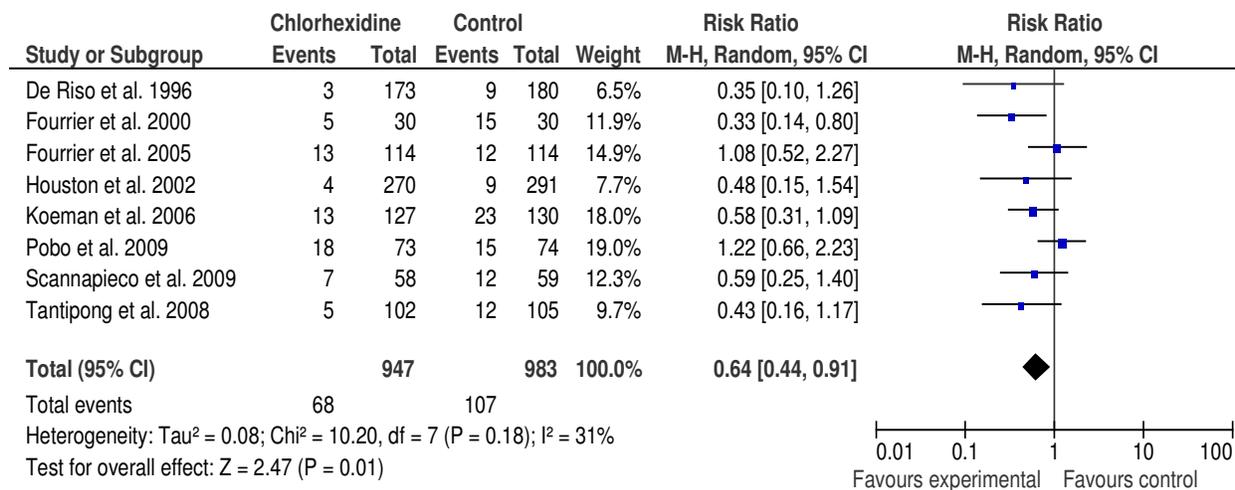
Table 1: Characteristics of included studies

Study –Author, Year, study no.	Population	Intervention	Comparison	Chlorhexidine dosing schedule	Loss to Follow-up
DeRiso 1996	Cardio-thoracic (open heart surgery)	Chlorhexidine gluconate 0.12%	Placebo	0.5 ounces/15ml of Chlorhexidine 0.12% solution used as rinse pre-operatively; twice daily post-operatively until discharge.	None
Fourrier 2000	Medical-surgical ICU	Chlorhexidine 0.2%	Standard oral care with bicarbonate isotonic serum rinse	After mouth rinsing and oropharyngeal aspiration, gel 3 times a day during ICU stay	None
Fourrier 2005	Medical-surgical ICU	Chlorhexidine gluconate 0.2%	Placebo	Oral gel applied three times daily during ICU stay for 28days.	One (0.87%) secondarily excluded (early antibiotics therapy)
Houston 2002	Cardio-thoracic (open heart surgery)	Chlorhexidine gluconate 0.12%	Listerine	15 ml oral rinse post-operatively and twice daily for 10days until death, extubation, tracheostomy or diagnosis of pneumonia.	7.7% due to death and tracheostomy
Koeman 2006	Mixed ICU's	Chlorhexidine 2%	Placebo	Approximately 2cm of paste to buccal cavity, until VAP diagnosed death or extubation.	1.55% due to consent:1 in placebo group and 2 in Chlorhexidine group
Pobo 2009	Medical-surgical ICU	Chlorhexidine digluconate 0.12%	Power Tooth-	Gauze containing 20ml Chlorhexidine digluconate 0.12% to all oral surfaces or 10ml Chlorhexidine injected into oral cavity, 8hrly, for 28 days. Power tooth brushing 8hrly.	2.7% Early introduction (<48hrs) of antibiotic since randomization.
Scannapieco 2009	Trauma ICU	Chlorhexidine gluconate 0.12%	Placebo	Chlorhexidine 0.12% solution or Control twice daily as oral topical treatment, for up to 21 days, until ICU discharge or death.	16.57% secondary to death, tracheostomy.
Tantipong 2007	ICU and general medical ward	Chlorhexidine 2% oral	Normal Saline	15 ml of Chlorhexidine solution or normal saline 4 times per day until extubation.	None

Table 2: Methodological quality/ Risk of bias assessment

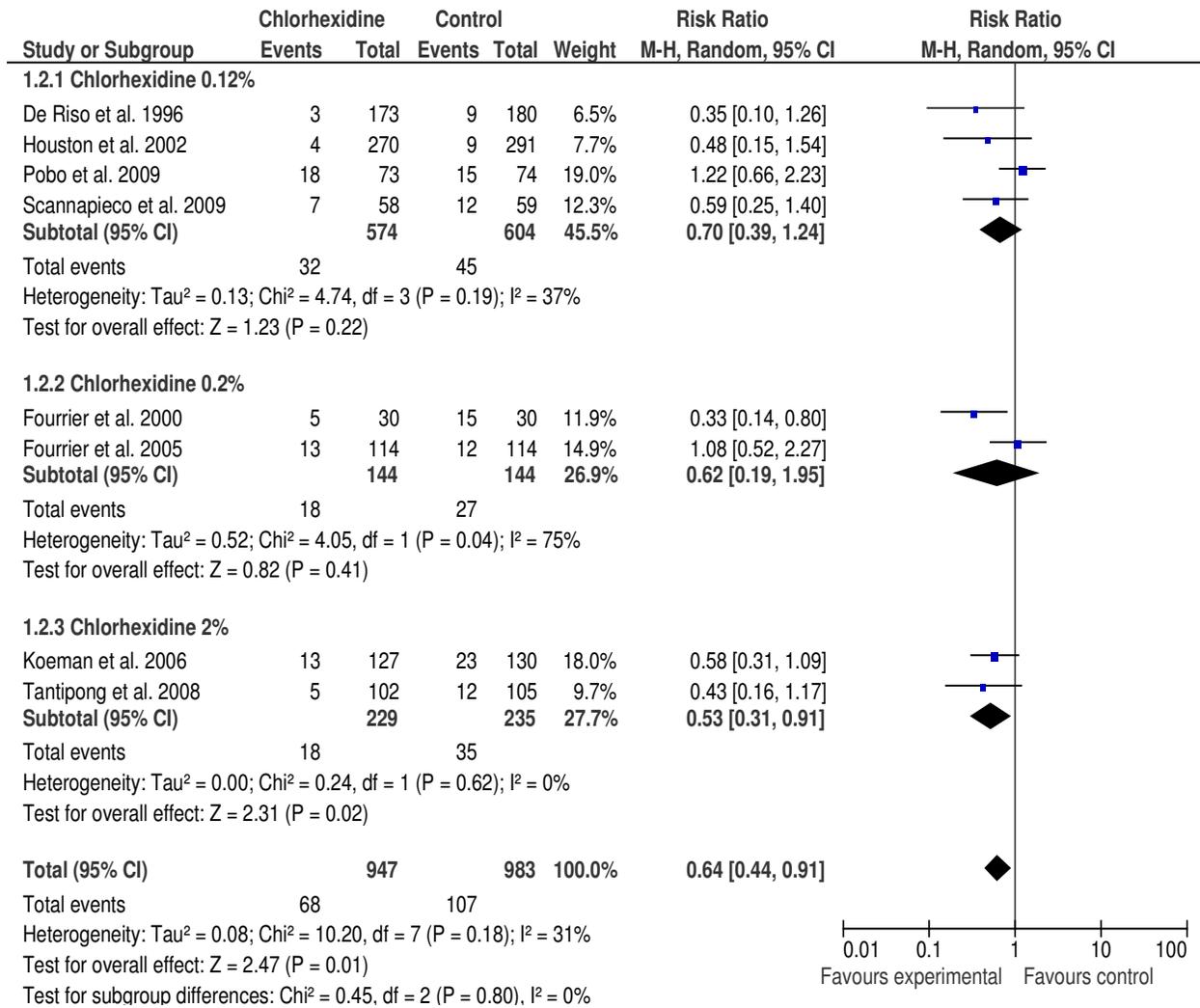
Study –Author, Year,	Adequate sequence generation	Allocation Concealment	Blinding of participants, personnel and outcome	Incomplete outcome data	Selective outcome reporting	Other Biases/ potential threats
DeRiso 1996	Low risk Computer-driven random number generated	Low risk Randomization by the pharmacy.	Low risk Placebo prepared and dispensed by pharmacy-placebo and treatment identical.	Low risk All participants randomized were analyzed	Low risk All relevant outcomes fully reported on	Low risk Nil noted
Fourrier 2000	Low risk Computer – generated balanced randomization table	Low risk blinded physicians in charge from results, dental bacteriologists from treatment allocation code.	Low risk hygiene nurse and physicians blinded to treatment given	Low risk Intention treat(ITT) to Analysis reported	Low risk All relevant outcomes fully reported on	Low risk Nil noted
Fourrier 2005	Low risk Block randomization stratified by site	Low risk Randomization lists held in sealed envelopes in pharmacy.	Low risk Investigators blinded to patient assignments.	Low risk (ITT)analysis used-one Secondary exclusion.	Low risk All relevant outcomes fully reported on	Low risk Nil noted
Houston 2002	High risk Consecutively randomized by medical record numbers	Unclear	Unclear	Low risk All outcomes fully reported on	Low risk All relevant outcomes fully reported on	Unclear
Koeman 2006	Low risk Randomly assigned by computerized randomization stratified by hospital/ centre	Low risk Experimental and placebo pastes produced and labeled by clinical pharmacy.	Low risk Intensivists blinded to trail randomization.	Low risk ITT employed; exclusions were low due	Low risk All relevant outcomes fully reported on	Low risk Nil noted
Pobo 2009	Low risk Randomization by computer-generated list	Low risk Randomized by means of opaque sealed envelopes	Low risk Investigators and attending physicians blind to group assignment.	Low risk All participants randomized were analyzed	Low risk All relevant outcomes fully reported on	High risk Trial prematurely stopped by steering committee
Scannapieco 2009	Low risk Randomized by web-based subject enrollment system with protocol specification files	Low risk Web-based (computer generated) randomization preparing individual treatment	Low risk Assignment of treatments blinded to outcome assessors, statisticians and care providers.	Low risk ITT analysis employed	Low risk All relevant outcomes fully reported on	Low risk Nil noted
Tantipong 2007	Low risk Stratified randomization according to sex and hospital location	Low risk Executed by pharmacy.	Low risk Blinding of data collectors and outcome assessors.	Low risk All outcomes reported on.	Low risk All relevant outcomes fully reported on	Low risk Nil noted

***Unclear** = lack of information or unknown risk of bias



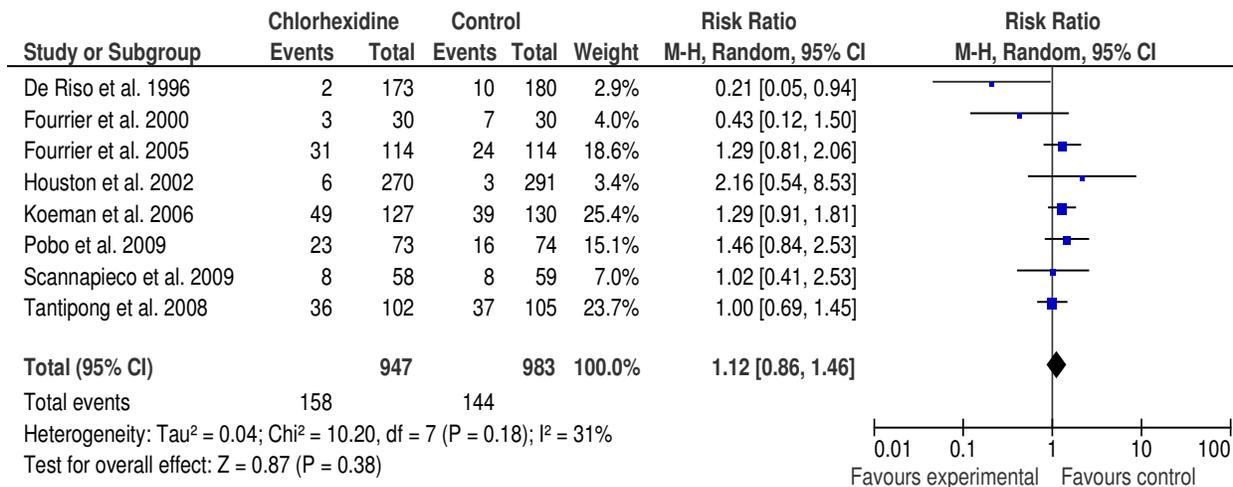
(Random effects - relative risk (95% confidence interval))

Figure 2- Random effects analysis: Risk of Ventilator-Associated Pneumonia (VAP)



(Random effects - relative risk (95% confidence interval))

Figure 3: Subgroup analysis of ventilator-associated pneumonia (VAP) per chlorhexidine level of therapeutic concentration



Random effects - relative risk (95% confidence interval)

Figure 4: Random effects analysis –overall effect of chlorhexidine on mortality.

PART B

APPENDICES

Appendix 1

List of included studies:

DeRiso, A.J., Ladowski, J.S., Dillon, T.A., Justice, J.W. & Peterson, A.C. 1996, "Chlorhexidine gluconate 0.12% oral rinse reduces the incidence of total nosocomial respiratory infection and nonprophylactic systemic antibiotic use in patients undergoing heart surgery", *Chest*, vol. 109, no. 6, pp. 1556.

Fourrier, F., Dubois, D., Pronnier, P., Herbecq, P., Leroy, O., Desmettre, T., Pottier-Cau, E., Boutigny, H., Di Pompéo, C. & Durocher, A. 2005, "Effect of gingival and dental plaque antiseptic decontamination on nosocomial infections acquired in the intensive care unit: A double-blind placebo-controlled multicenter study*", *Critical Care Medicine*, vol. 33, no. 8, pp. 1728.

Fourrier, F., Duvivier, B., Boutigny, H., Roussel-Delvallez, M. & Chopin, C. 1998, "Colonization of dental plaque: a source of nosocomial infections in intensive care unit patients", *Critical Care Medicine*, vol. 26, no. 2, pp. 301.

Houston, S., Hougland, P., Anderson, J.J., LaRocco, M., Kennedy, V. & Gentry, L.O. 2002, "Effectiveness of 0.12% chlorhexidine gluconate oral rinse in reducing prevalence of nosocomial pneumonia in patients undergoing heart surgery", *American Journal of Critical Care*, vol. 11, no. 6, pp. 567.

Koeman, M., van der Ven, A.J.A.M., Hak, E., Joore, H.C.A., Kaasjager, K., de Smet, A.G.A., Ramsay, G., Dormans, T.P.J., Aarts, L.P.H.J. & de Bel, E.E. 2006, "Oral decontamination with chlorhexidine reduces the incidence of ventilator-associated pneumonia", *American journal of respiratory and critical care medicine*, vol. 173, no. 12, pp. 1348.

- Pobo, A., Lisboa, T., Rodriguez, A., Sole, R., Magret, M., Treffler, S., Gómez, F. & Rello, J. 2009, "A randomized trial of dental brushing for preventing ventilator-associated pneumonia", *Chest*, vol. 136, no. 2, pp. 433.
- Scannapieco, F., Yu, J., Raghavendran, K., Vacanti, A., Owens, S., Wood, K. & Mylotte, J. 2009, "A randomized trial of chlorhexidine gluconate on oral bacterial pathogens in mechanically ventilated patients", *Critical Care*, vol. 13, no. 4, pp. R117.
- Tantipong, H., Morkchareonpong, C., Jaiyindee, S. & Thamlikitkul, V. 2008, "Randomized controlled trial and meta-analysis of oral decontamination with 2% chlorhexidine solution for the prevention of ventilator-associated pneumonia", *infection control and hospital epidemiology*, vol. 29, no. 2, pp. 131-136.

Appendix 2

List of excluded studies:

Grap, M.J., Munro, C.L. & Elswick, R. 2004, "Duration of action of a single, early oral application of chlorhexidine on oral microbial flora in mechanically ventilated patients: a pilot study", *Heart & Lung: The Journal of Acute and Critical Care*, vol. 33, no. 2, pp. 83-91.

Munro, C.L., Grap, M.J., Jones, D.J., McClish, D.K. & Sessler, C.N. 2009, "Chlorhexidine, toothbrushing, and preventing ventilator-associated pneumonia in critically ill adults", *American journal of critical care*, vol. 18, no. 5, pp. 428.

MacNaughton, P., Bailey, J., Donlin, N., Branfield, P., Williams, A. & Rowswell, H. 2004, "A randomized controlled trial assessing efficacy of oral chlorhexidine in ventilated patients", *European Society of Intensive Care Medicine, 17th Annual Congress, Berlin, Germany. Intensive Care Med*, pp. S5.

Appendix 3

Data Extraction Forms

Data extraction form 01

1. Source

Study ID	01
Reviewer	Olivia Snyders; Oswell Khondowe
Author & Year	DeRiso, A.J., Ladowski, J.S., Dillon, T.A., Justice, J.W. & Peterson, A.C. 1996
Journal	<i>Chest</i> , vol. 109, no. 6, pp. 1556.
Title	"Chlorhexidine gluconate 0.12% oral rinse reduces the incidence of total nosocomial respiratory infection and nonprophylactic systemic antibiotic use in patients undergoing heart surgery"
Country	Indiana, USA

2. Eligibility

(Tick in the appropriate space)

2.1 Types of studies

RCT	<input checked="" type="checkbox"/>
Quasi-experimental	<input type="checkbox"/>
Other specify	<input type="checkbox"/>
Published study	<input checked="" type="checkbox"/>

2.2 Types of participants

Adult Ventilated Patients	<input checked="" type="checkbox"/>
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2.3 Types of intervention

(Tick appropriate intervention provide details on other treatment in space provided)

Chlorexidine vs Placebo	<input checked="" type="checkbox"/>	
Chlorexidine Vs Standard Care	<input type="checkbox"/>	

2.4 Types of outcomes

Incidence of VAP	<input checked="" type="checkbox"/>
Mortality	<input checked="" type="checkbox"/>

2.5 Lost to follow up <15%

Equation	N/A	<input checked="" type="checkbox"/> Y	<input type="checkbox"/> N
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2.5.1 Reasons for LTFU

N/A

2.5.2 Other reasons for exclusion

Intra-operative death; pre-operative infection or intubation; heart and lung transplant recipients;
Pregnancy; known hypersensitivity to chlorhexidine;
Concurrent participation in another research project;

3. Methodology

3.1 Study design

RCT	✓	Single centre	✓
Quasi-experimental	-	Multi centre	-

3.2 Study duration

Month & Year	10 months –no dates provided
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3.3 Eligibility criteria

Adults (> 18yrs); Consent obtained;
Coronary artery bypass grafting (CABG), valve surgery, septal surgery, cardiac tumour excision, combined CABG and valve surgery requiring cardiopulmonary bypass,

Methodological quality/Risk of bias assessment

(Answer the domain-question with a ‘Yes’ signifying low risk of bias, ‘No’ signifying high risk of bias, and ‘Unclear’ signifying either lack of information or unknown risk of bias)

3.4 Cochrane Collaboration ‘Risk of Bias’ Tool

Entry	Judgement	Description
Adequate sequence generation?	YES	Computer-driven random number generated
Allocation concealment?	YES	Randomization by the pharmacy staff.
Blinding of participants, personnel and outcome assessors?	YES	Described only as a double-blind, placebo-controlled study.
Incomplete outcome data addressed?	YES	All outcomes reported on
Free of selective outcome reporting?	YES	-
Free of other bias?	YES	-

3.5 Participants

Total number	353
Total number analyzed	353
Number of VAP cases	12
Mortality	12
High risk?	No
Setting	Cardio-thoracic ICU
Diagnostic criteria	New or progressive pulmonary infiltrate, fever, leukocytosis, purulent tracheal secretions.
Age	Mean 64yrs (male); mean 63 yrs (female)
Sex	M= 242 ; F = 111
Country	USA
Date of study	1996

*Mean±SD.

3.6 Interventions

Experimental group				
Type	Route	Dose	Timing	Side effect
Chlorhexidine Gluconate 0.12%	Oral , rinse	15ml rinse	pre-operatively; twice daily post- operatively until discharge	none
Control group				
Type	Route	Dose	Timing	Side effect
Placebo	Oral, rinse	15ml rinse	pre-operatively; twice daily post- operatively until discharge	none

3.7 Outcomes relevant to this review

(Tick yes or no)

1. Incidence of Ventilator Associated Pneumonia	YES	✓
2. Mortality	YES	✓

3.8 Outcome definitions

1. Incidence of Ventilator Associated Pneumonia	YES	✓
2. Mortality	YES	✓

4. Results

Number of patients: 353		
	Randomized	Analyzed
Experimental	173	173
Control	180	180
Total	353	353

4.1 Summary data for each intervention group

1. Incidence of VAP	Event	No event	Total
Experimental group	3	170	173

Control group	9	164	173
1. Mortality	Event	No event	Total
Experimental group	2	171	173
Control group	10	163	173

4.2 Continuous Data : N/A

4.3 Estimate of effect with confidence interval/*P*-value

1. Incidence of VAP	RR	CI 95%	<i>P</i> -value
Experimental group versus Control group	0.35	0.10 – 1.26	0.18
1. Mortality	RR	CI 95%	<i>P</i> -value
Experimental group versus Control group	0.21	0.05 – 0.94	0.18

4.4 Subgroup analysis

Concentration: 0.12% chlorhexidine gluconate
Settings: Cardiothoracic ICU

4.5 Miscellaneous

Funding source	Grant: August Tomusk Foundation, Indiana
Key conclusions	Chlorhexidine decreases total respiratory infection rate and need for non-prophylactic antibiotic use in patients undergoing heart surgery; Cost saving; impacts favourably on mortality
Other comments from authors	Ease of administration
Reference to other relevant studies	YES
Correspondence required	X
Comments from reviewers	-
1. Subgroup analysis needed-concentration	2. Study older than 10 years but part of review and not literature review, feasible.
3. Setting favourable for positive effect=+-subanalysis	4.

Data extraction form 02

1. Source

Study ID	02
Reviewer	Olivia Snyders and Oswell Khondowe
Author & Year	Fourrier, F., Duvivier, B., Boutigny, H., Roussel-Delvallez, M. & Chopin, C. 1998,
Journal	<i>Critical Care Medicine</i> , vol. 26, no. 2, pp. 301.
Title	"Colonization of dental plaque: a source of nosocomial infections in intensive care unit patients"
Country	France

2. Eligibility

(Tick in the appropriate space)

2.1 Types of studies

RCT	<input checked="" type="checkbox"/>
Quasi-experimental	<input type="checkbox"/>
Other specify	<input type="checkbox"/>
Published study	<input checked="" type="checkbox"/>

2.2 Types of participants

Adult Ventilated Patients	<input checked="" type="checkbox"/>
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2.3 Types of intervention

(Tick appropriate intervention provide details on other treatment in space provided)

Chlorexidine vs Bicarbonate rinse	<input type="checkbox"/>	<input type="checkbox"/>
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2.4 Types of outcomes

Incidence of VAP	<input checked="" type="checkbox"/>
Mortality	<input checked="" type="checkbox"/>

2.5 Lost to follow up <15%

Equation	None	<input checked="" type="checkbox"/>	N
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2.5.1 Reasons for LTFU

No LTFU

2.5.2 Other reasons for exclusion

Edentulous Patients; <18yrs;
No consent;

3. Methodology

3.1 Study design

RCT	✓	Single centre	✓
Quasi-experimental		Multi centre	

3.2 Study duration

Month & Year	June 1997 to July 1998
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3.3 Eligibility criteria

>18yrs; Consent
Medical condition suggest ICU stay of 5 days requiring mechanical ventilation

Methodological quality/Risk of bias assessment

(Answer the domain-question with a 'Yes' signifying low risk of bias, 'No' signifying high risk of bias, and 'Unclear' signifying either lack of information or unknown risk of bias)

3.4 Cochrane Collaboration 'Risk of Bias' Tool

Entry	Judgement	Description
Adequate sequence generation?	Yes	Computer –generated balanced randomization table
Allocation concealment?	Yes	Blinded physicians in charge from results, dental bacteriologists
Blinding of participants, personnel and outcome assessors?	Yes	Hygiene nurse and physicians blinded to treatment given
Incomplete outcome data addressed?	Yes	Intention to treat(ITT) Analysis reported; All outcomes addressed
Free of selective outcome reporting?	Yes	No evidence of publication bias
Free of other bias?	Yes	--

3.5 Participants

Total number	60
Total number analyzed	60
Number of VAP cases	20
Mortality	10
High risk?	no
Setting	Medical-surgical ICU
Diagnostic criteria	Temperature>38°C or < 36°C; presence of infiltrate on chest radiography; leukocytosis or leucopenia;positive quantitative culture of tracheal aspirate(10 ⁶ CFU/ml) and/or positive culture of BAL (10 ⁶ CFU/ml).
Age	Treatment mean=51.2; Control mean=50.4
Sex	Treatment (m/f)= 19/11; Control (m/f)= 19/11

Country	France
Date of study	June 1997-July 1998

*Mean±SD.

3.6 Interventions

Experimental group				
Type	Route	Dose	Timing	Side effect
Chlorhexidine 0.2% dental gel	Oral- oropharyngeal surfaces	-	3x day	none
Control group				
Type	Route	Dose	Timing	Side effect
Bicarbonate isotonic serum	Oral rinse	-	4xday	none

3.7 Outcomes relevant to this review

(Tick yes or no)

3. Incidence of Ventilator Associated Pneumonia	YES	✓
4. Mortality	YES	✓

3.8 Outcome definitions

3. Incidence of Ventilator Associated Pneumonia	YES	✓
4. Mortality	YES	✓

4. Results

Number of patients: 60		
	Randomized	Analyzed
Experimental	30	30
Control	30	30
Total	60	60

4.1 Summary data for each intervention group

1. Incidence of VAP	Event	No event	Total
Experimental group	5	25	30
Control group	15	15	30

1. Mortality	Event	No event	Total
Experimental group	3	27	30
Control group	7	23	30

4.2 Continuous Data-N/A

4.3 Estimate of effect with confidence interval/*P*-value

1. Incidence of VAP	RR	CI 95%	<i>P</i> -value
Experimental group versus Control group	0.33	0.14 – 0.80	
1. Mortality	RR	CI 95%	<i>P</i> -value
Experimental group versus Control group	0.43	0.12 – 1.50	0.18

4.4 Subgroup analysis

Chlorhexidine concentration 0.2%
Setting- medical –surgical ICU

4.5 Miscellaneous

Funding source	Not mentioned
Key conclusions	Antiseptic oral decontamination may reduce incidence of VAP
Other comments from authors	Results need further confirmation
Reference to other relevant studies	Yes
Correspondence required	No
Comments from reviewers	For inclusion
1.ITT analysis performed	2.
3.	4.

Data extraction form 03

1. Source

Study ID	03
Reviewer	Olivia Snyders and Oswell Khondowe
Author & Year	Fourrier, F., Dubois, D., Pronnier, P., Herbecq, P., Leroy, O., Desmettre, T., Pottier-Cau, E., Boutigny, H., Di Pompéo, C. & Durocher, A. 2005, ,
Journal	<i>Critical Care Medicine</i> , vol. 33, no. 8, pp. 1728.
Title	"Effect of gingival and dental plaque antiseptic decontamination on nosocomial infections acquired in the intensive care unit: A double-blind placebo-controlled multicenter study*"
Country	France

2. Eligibility

(Tick in the appropriate space)

2.1 Types of studies

RCT	<input checked="" type="checkbox"/>
Quasi-experimental	<input type="checkbox"/>
Other specify	<input type="checkbox"/>
Published study	<input checked="" type="checkbox"/>

2.2 Types of participants

Adult Ventilated Patients	<input checked="" type="checkbox"/>
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2.3 Types of intervention

(Tick appropriate intervention provide details on other treatment in space provided)

Chlorexidine vs Placebo	<input checked="" type="checkbox"/>	
Chlorexidine Vs Standard Care	<input type="checkbox"/>	<input type="checkbox"/>

2.4 Types of outcomes

Incidence of VAP	<input checked="" type="checkbox"/>
Mortality	<input checked="" type="checkbox"/>

2.5 Lost to follow up <15%

Equation		Y	<input checked="" type="checkbox"/>
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2.5.1 Reasons for LTFU

Secondary exclusion- oral antibiotic therapy required (n=1)

2.5.2 Other reasons for exclusion

Tracheostomy at inclusion,
Hospitalisation >48hrs
Randomization after D0 (within 24hrs of randomization)
Completely edentulous, facial trauma, post surgical patients with ‘specific oropharyngeal care’
Known allergy to chlorhexidine

3. Methodology

3.1 Study design

RCT	✓	Single centre	
Quasi-experimental		Multi centre	✓

3.2 Study duration

Month & Year	Jan 2001-Sept 2002
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3.3 Eligibility criteria

Adult > 18yrs and medical condition suggesting ICU stay at least 5days
Requiring mechanical ventilation by orotrachela or nsao tracheal intubation
Hospitalisation <48hrs

Methodological quality/Risk of bias assessment

(Answer the domain-question with a ‘Yes’ signifying low risk of bias, ‘No’ signifying high risk of bias, and ‘Unclear’ signifying either lack of information or unknown risk of bias)

3.4 Cochrane Collaboration ‘Risk of Bias’ Tool

Entry	Judgement	Description
Adequate sequence generation?	Yes	Block randomization stratified by site
Allocation concealment?	Yes	Randomization lists held in sealed envelopes in pharmacy.
Blinding of participants, personnel and outcome assessors?	Yes	Investigators blinded to patient assignments
Incomplete outcome data addressed?	Yes	All outcomes reported on
Free of selective outcome reporting?	Yes	No evidence of Publication Bias
Free of other bias?	Yes	-

3.5 Participants

Total number	228
Total number analyzed	228
Number of VAP cases	25

Mortality	55
High risk?	No
Setting	Multi-centre, mixed ICU population
Diagnostic criteria	Temperature >38°C or < 36°C; presence of infiltrate on chest radiography; leukocytosis or leucopenia; positive quantitative culture of tracheal aspirate (10 ⁶ CFU/ml) and/or positive culture of BAL (10 ⁶ CFU/ml).
Age	Chlorhexidine mean age (61.1 yrs); Placebo mean age (61 yrs)
Sex	PAD -(m)=72; (f)=41; Placebo (m)=64; (f)=50
Country	France
Date of study	Jan 2001-September 2002

*Mean±SD.

3.6 Interventions

Experimental group				
Type	Route	Dose	Timing	Side effect
Chlorhexidine gluconate 0.2%	Oral gel	After mouth rinse and oro-paryngeal aspiration, gel applied	3x daily during ICU stay and until 28 days of treatment achieved.	Nil reported
Control group				
Type	Route	Dose	Timing	Side effect
Placebo	Oral gel	After mouth rinse and oro-paryngeal aspiration, gel applied	3x daily during ICU stay and until 28 days of treatment achieved.	Nil reported

3.7 Outcomes relevant to this review

(Tick yes or no)

5. Incidence of Ventilator Associated Pneumonia	YES	✓
6. Mortality	YES	✓

3.8 Outcome definitions

5. Incidence of Ventilator Associated Pneumonia	YES	✓
6. Mortality	YES	✓

4. Results

Number of patients: 228		
	Randomized	Analyzed
Experimental	114	113
Control	114	114
Total	228	227

4.1 Summary data for each intervention group

1. Incidence of VAP	Event	No event	Total
Experimental group	13	101	114
Control group	12	102	114

1. Mortality	Event	No event	Total
Experimental group	31	83	114
Control group	24	90	114

4.2 Continuous Data –N/A

4.3 Estimate of effect with confidence interval/*P*-value

1. Incidence of VAP	RR	CI 95%	<i>P</i> -value
Experimental group versus Control group	1.08	0.52- 2.27	0.18
1. Mortality	RR	CI 95%	<i>P</i> -value
Experimental group versus Control group	1.29	0.81 – 2.06	0.18

4.4 Subgroup analysis

Chlorhexidine concentration , 0.2%
Multi-centre trial= Mixed ICU population

4.5 Miscellaneous

Funding source	Supported in part by French Ministry of Health
Key conclusions	PAD prophylaxis insufficient in critically ill patients
Other comments from authors	PAD decrease rate of plaque colonization in ventilated patients (by aerobic pathogens)
Reference to other relevant studies	YES
Correspondence required	No
Comments from reviewers	For inclusion
1.	2.
3.	4.

Data extraction form 04

1. Source

Study ID	04
Reviewer	(OS) and (OK)
Author & Year	Houston, S., Hougland, P., Anderson, J.J., LaRocco, M., Kennedy, V. & Gentry, L.O. 2002, ,
Journal	<i>American Journal of Critical Care</i> , vol. 11, no. 6, pp. 567.
Title	"Effectiveness of 0.12% chlorhexidine gluconate oral rinse in reducing prevalence of nosocomial pneumonia in patients undergoing heart surgery"
Country	Houston, Texas,USA

2. Eligibility

(Tick in the appropriate space)

2.1 Types of studies

RCT	<input checked="" type="checkbox"/>
Quasi-experimental	<input type="checkbox"/>
Other specify	<input type="checkbox"/>
Published study	<input checked="" type="checkbox"/>

2.2 Types of participants

Adult Ventilated Patients	<input checked="" type="checkbox"/>
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2.3 Types of intervention

(Tick appropriate intervention provide details on other treatment in space provided)

Chlorexidine vs Placebo	<input checked="" type="checkbox"/>	
Chlorexidine Vs Standard Care	<input type="checkbox"/>	

2.4 Types of outcomes

Incidence of VAP	<input checked="" type="checkbox"/>
Mortality	<input checked="" type="checkbox"/>

2.5 Lost to follow up <20%

Equation	7.7%	-----	Yes
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2.5.1 Reasons for LTFU

Death and Tracheostomy

2.5.2 Other reasons for exclusion

Death during surgery; pregnancy; lack of consent
Pre-op Respiratory Infection

3. Methodology

3.1 Study design

RCT	✓	Single centre	✓
Quasi-experimental		Multi centre	

3.2 Study duration

Month & Year	Details not provided
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3.3 Eligibility criteria

Adult, >18yrs
Aorta-coronary bypass graft and valve surgery; cardiopulmonary surgery
Consent

Methodological quality/Risk of bias assessment

(Answer the domain-question with a 'Yes' signifying low risk of bias, 'No' signifying high risk of bias, and 'Unclear' signifying either lack of information or unknown risk of bias)

3.4 Cochrane Collaboration 'Risk of Bias' Tool

Entry	Judgement	Description
Adequate sequence generation?	No	Consecutively randomized by medical record numbers-poor method
Allocation concealment?	Unclear	No details provided
Blinding of participants, personnel and outcome assessors?	Unclear	No details provided
Incomplete outcome data addressed?	Unclear	All outcomes reported on
Free of selective outcome reporting?	Yes	No publication bias
Free of other bias?	Yes	Yes

3.5 Participants

Total number	561
Total number analyzed	561
Number of VAP cases	13
Mortality	9
High risk?	No
Setting	Cardio-thoracic (open heart surgery)
Diagnostic criteria	New or progressive infiltrate, CDC tool based on criteria for diagnosing nosocomial pneumonia: Fever and pulmonary infiltrate; nature of trachea-bronchial secretions; degree of leukocytosis; microbial culture results. Semi-quantitative sputum samples at extubation.

Age	Not provided
Sex	Exp Group-(m)=73,(f)=197 ;Comparison-(m)=79,(f)=212
Country	Houston, Texas
Date of study	2002

*Mean±SD.

3.6 Interventions

Experimental group				
Type	Route	Dose	Timing	Side effect
Chlorhexidine gluconate 0.12%	Oral Rinse	15 ml oral rinse post-operatively	twice daily for 10days until death, extubation, tracheostomy or diagnosis of pneumonia.	None
Control group				
Type	Route	Dose	Timing	Side effect
Listerine	Oral Rinse	15 ml oral rinse post-operatively	As above	None

3.7 Outcomes relevant to this review

(Tick yes or no)

7. Incidence of Ventilator Associated Pneumonia	YES	✓
8. Mortality	YES	✓

3.8 Outcome definitions

7. Incidence of Ventilator Associated Pneumonia	YES	✓
8. Mortality	YES	✓

4. Results

Number of patients: 561		
	Randomized	Analyzed
Experimental	270	270
Control	291	291
Total	561	561

4.1 Summary data for each intervention group

1. Incidence of VAP	Event	No event	Total
Experimental group	4	266	270
Control group	9	282	291

1. Mortality	Event	No event	Total
Experimental group	6	264	270
Control group	3	288	291

4.2 Continuous Data –(none)

4.3 Estimate of effect with confidence interval/*P*-value

1. Incidence of VAP	RR	CI 95%	<i>P</i> -value
Experimental group versus Control group	0.48	0.15 - 1.54	0.18
1. Mortality	RR	CI 95%	<i>P</i> -value
Experimental group versus Control group	2.16	0.54-8.53	0.18

4.4 Subgroup analysis

Setting: Cardiothoracic
0.12% chlorhexidine

4.5 Miscellaneous

Funding source	Roderick McDonald Fund, Houston, Texas
Key conclusions	Nosocomial infections lower in peridex group
Other comments from authors	Peridex group effect only significant in patients intubated >24hours
Reference to other relevant studies	YES
Correspondence required	Possibly
Comments from reviewers	Included in other meta-analyses
1.Follow methodology	2.
3.	4.

Data extraction form 05

1. Source

Study ID	05
Reviewer	Olivia Snyders and Oswell Khondowe
Author & Year	Koeman, M., van der Ven, A.J.A.M., Hak, E., Joore, H.C.A., Kaasjager, K., de Smet, A.G.A., Ramsay, G., Dormans, T.P.J., Aarts, L.P.H.J. & de Bel, E.E. 2006
Journal	<i>American journal of respiratory and critical care medicine</i> , vol. 173, no. 12, pp. 1348.
Title	"Oral decontamination with chlorhexidine reduces the incidence of ventilator-associated pneumonia"
Country	Netherlands

2. Eligibility

(Tick in the appropriate space)

2.1 Types of studies

RCT	<input checked="" type="checkbox"/>
Quasi-experimental	<input type="checkbox"/>
Other specify	<input type="checkbox"/>
Published study	<input checked="" type="checkbox"/>

2.2 Types of participants

Adult Ventilated Patients	<input checked="" type="checkbox"/>
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2.3 Types of intervention

(Tick appropriate intervention provide details on other treatment in space provided)

Chlorexidine vs Placebo	<input checked="" type="checkbox"/>	
Chlorexidine Vs Standard Care	<input type="checkbox"/>	

2.4 Types of outcomes

Incidence of VAP	<input checked="" type="checkbox"/>
Mortality	<input checked="" type="checkbox"/>

2.5 Lost to follow up <20%

Equation	1.55%	Y	<input checked="" type="checkbox"/>
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2.5.1 Reasons for LTFU

Consent Withdrawal : Treatment group (n=2); Comparison Group (n=1)

2.5.2 Other reasons for exclusion

Pre-admission immunocompromised status
Pregnant;

Pre-existing condition not allowing oral application of study medication;

3. Methodology

3.1 Study design

RCT	✓	Single centre	
Quasi-experimental		Multi centre	✓

3.2 Study duration

Month & Year	unknown
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3.3 Eligibility criteria

Adult (>18yrs)
Need for mechanical ventilation at least 48hrs
Inclusion within 24hrs of intubation and start of mechanical ventilation

Methodological quality/Risk of bias assessment

(Answer the domain-question with a 'Yes' signifying low risk of bias, 'No' signifying high risk of bias, and 'Unclear' signifying either lack of information or unknown risk of bias)

3.4 Cochrane Collaboration 'Risk of Bias' Tool

Entry	Judgement	Description
Adequate sequence generation?	Yes	Randomly assigned by computerized randomization
Allocation concealment?	Yes	Experimental and placebo pastes produced and labeled by clinical
Blinding of participants, personnel and outcome assessors?	Yes	Experimental and Placebo pastes prepared and labeled by clinical pharmacy
Incomplete outcome data addressed?	Yes	ITT employed; exclusions were low due, Full outcome data provided
Free of selective outcome reporting?	Yes	No evidence of publication bias
Free of other bias?	Yes	----

3.5 Participants

Total number	257
Total number analyzed	257
Number of VAP cases	36
Mortality	88
High risk?	88
Setting	ICU, mixed, multi-centre
Diagnostic criteria	Chest radiography with new, persistent or progressive infiltrate in combination with at least 3 of 4 of the following criteria: Temperature >38 °C or < 35.5°C; Blood Leukocytosis or leucopenia; purulent tracheal aspirate; positive semi-quantitative culture from tracheal aspirates (cutoff ≥ 10 ⁵ cfu/ml). Daily Clinical Pulmonary Infection Scores (CPIS) were done.
Age	Chlorhexidine mean=60.9, Placebo mean=62.1
Sex	Chlorhexidine (m)=66,(f)=61; Placebo(m)=93, (f)=37
Country	Netherlands
Date of study	Feb 2001-March 2003

*Mean±SD.

3.6 Interventions

Experimental group				
Type	Route	Dose	Timing	Side effect
Chlorhexidine 2%	Oral-buccal cavity	Approximately 2cm of paste (0.5gram)	administered to each side of buccal cavity. Study stopped when VAP diagnosed, death, consent withdrawal or extubation.	None
Control group				
Type	Route	Dose	Timing	Side effect
Placebo	Oral-buccal cavity	Approximately 2cm of paste (0.5gram)	administered to each side of buccal cavity. Study stopped when VAP diagnosed, death, consent withdrawal or extubation.	None

3.7 Outcomes relevant to this review

(Tick yes or no)

9. Incidence of Ventilator Associated Pneumonia	YES	✓
10. Mortality	YES	✓

3.8 Outcome definitions

9. Incidence of Ventilator Associated Pneumonia	YES	✓
10. Mortality	YES	✓

4. Results

Number of patients: 257		
	Randomized	Analyzed
Experimental	127	127
Control	130	130
Total	257	257

4.1 Summary data for each intervention group

1. Incidence of VAP	Event	No event	Total
Experimental group	13	114	127
Control group	23	107	130

1. Mortality	Event	No event	Total
Experimental group	49	78	127
Control group	39	91	130

4.2 Continuous Data- None

4.3 Estimate of effect with confidence interval/*P*-value

1. Incidence of VAP	RR	CI 95%	<i>P</i> -value
Experimental group versus Control group	0.58	0.31 – 1.09	0.18
1. Mortality	RR	CI 95%	<i>P</i> -value
Experimental group	1.29	0.91 – 1.81	0.18

4.4 Subgroup analysis

Concentration -2% Chlorhexidine
Settings –mixed ICU

4.5 Miscellaneous

Funding source	Not mentioned
Key conclusions	Topical and oral use of Chlorhexidine and Colistin reduced VAP
Other comments from authors	Chlorhexidine probably the preferred preventative strategy of choice
Reference to other relevant studies	YES
Correspondence required	NO
Comments from reviewers	For inclusion
1.ITT employed	2.
3.	4.

Data extraction form 06

1. Source

Study ID	06
Reviewer	Olivia Snyders and Oswell Khondowe
Author & Year	Pobo, A., Lisboa, T., Rodriguez, A., Sole, R., Magret, M., Trefler, S., Gómez, F. & Rello, J. 2009
Journal	<i>Chest</i> , vol. 136, no. 2, pp. 433
Title	"A randomized trial of dental brushing for preventing ventilator-associated pneumonia"
Country	Spain

2. Eligibility

(Tick in the appropriate space)

2.1 Types of studies

RCT	<input checked="" type="checkbox"/>
Quasi-experimental	<input type="checkbox"/>
Other specify	<input type="checkbox"/>
Published study	<input checked="" type="checkbox"/>

2.2 Types of participants

Adult Ventilated Patients	<input checked="" type="checkbox"/>
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2.3 Types of intervention

(Tick appropriate intervention provide details on other treatment in space provided)

Chlorhexidine vs Power Toothbrushing	<input checked="" type="checkbox"/>	
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2.4 Types of outcomes

Incidence of VAP	<input checked="" type="checkbox"/>
Mortality	<input checked="" type="checkbox"/>

2.5 Lost to follow up <15%

Equation	2.7%	Y	<input checked="" type="checkbox"/>
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2.5.1 Reasons for LTFU

Early introduction of antibiotics within 48hrs of randomization

2.5.2 Other reasons for exclusion

Lack of consent; <18 years of age; Chlorhexidine allergy;
Suspicion of Pneumonia at time of intubation; Evidence of massive aspiration during intubation;
Tracheostomy; Intubated patients; moribund patients(expected to die within 72hrs)
Edentulous patients; Pregnancy;

Enrollment in other trials

3. Methodology

3.1 Study design

RCT	✓	Single centre	✓
Quasi-experimental		Multi centre	

3.2 Study duration

Month & Year	
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3.3 Eligibility criteria

>18yrs, Consent
Intubation expected within 48hrs of randomization;
No evidence of Pulmonary infection

Methodological quality/Risk of bias assessment

(Answer the domain-question with a 'Yes' signifying low risk of bias, 'No' signifying high risk of bias, and 'Unclear' signifying either lack of information or unknown risk of bias)

3.4 Cochrane Collaboration 'Risk of Bias' Tool

Entry	Judgement	Description
Adequate sequence generation?	Yes	Randomization by computer-generated list
Allocation concealment?	Yes	Randomized by means of opaque sealed envelopes
Blinding of participants, personnel and outcome assessors?	Yes	Investigators and attending physicians blind to group assignment.
Incomplete outcome data addressed?	Yes	All participants randomized were analyzed ; All relevant outcomes reported on
Free of selective outcome reporting?	Yes	No evidence of Publication Bias
Free of other bias?	No	Trial prematurely stopped by steering committee

3.5 Participants

Total number	147
Total number analyzed	143
Number of VAP cases	33
Mortality	39
High risk?	Yes
Setting	Medical-surgical ICU
Diagnostic criteria	Presence of new or progressive pulmonary opacities on chest radiography, purulent respiratory secretions, fever (>38°C), Leukocytosis > 10,000cells/ml, quantitative respiratory samples with at least one pathogenic organism (protected specimen brush

	yielding $\geq 10^3$ or tracheal aspirates yielding 10^5 cfu/mL).
Age	Std group: mean age 52.6 TBgroup: mean=55.3
Sex	Std group(m)=46,(f)=27 TBgrouping (m)=49,(f)=25
Country	Spain
Date of study	Unknown; 30month period

*Mean±SD.

3.6 Interventions

Experimental group				
Type	Route	Dose	Timing	Side effect
Power Toothbrushing	Oral	Use of Power Toothbrush	8hrly	None
Control group				
Type	Route	Dose	Timing	Side effect
Standard care with chlorhexidine	Oral	20ml Chlorhexidine to oral surfaces	8hrly	None

3.7 Outcomes relevant to this review

(Tick yes or no)

11. Incidence of Ventilator Associated Pneumonia	YES	✓
12. Mortality	YES	✓

3.8 Outcome definitions

11. Incidence of Ventilator Associated Pneumonia	YES	✓
12. Mortality	YES	✓

4. Results

Number of patients: 147		
	Randomized	Analyzed
Experimental	74	70
Control	73	73
Total	147	143

4.1 Summary data for each intervention group

1. Incidence of VAP	Event	No event	Total
Experimental group	15	55	70
Control group	18	55	73

1. Mortality	Event	No event	Total
Experimental group	16	54	70
Control group	23	50	73

4.2 Continuous Data-None

4.3 Estimate of effect with confidence interval/*P*-value

1. Incidence of VAP	RR	CI 95%	<i>P</i> -value
Experimental group versus Control group	1.22	0.66 – 2.23	0.18
1. Mortality	RR	CI 95%	<i>P</i> -value
Experimental group versus Control group	1.46	0.84 – 2.53	0.18

4.4 Subgroup analysis

Chlorhexidine concentration, 0.12%
Setting-mixed icu

4.5 Miscellaneous

Funding source	Not mentioned
Key conclusions	Addition of mechanical debridement system to the use of chlorhexidine to prevent VAP not effective
Other comments from authors	Larger groups needed
Reference to other relevant studies	Yes
Correspondence required	No
Comments from reviewers	Check methodology
1.	2.
3.	4.

Data extraction form 7

1. Source

Study ID	07
Reviewer	Olivia and Oswell
Author & Year	Scannapieco, F., Yu, J., Raghavendran, K., Vacanti, A., Owens, S., Wood, K. & Mylotte, J. 2009
Journal	<i>Critical Care</i> , vol. 13, no. 4, pp. R117.
Title	"A randomized trial of chlorhexidine gluconate on oral bacterial pathogens in mechanically ventilated patients"
Country	Eirie Country , Buffalo, USA

2. Eligibility

(Tick in the appropriate space)

2.1 Types of studies

RCT	<input checked="" type="checkbox"/>
Quasi-experimental	<input type="checkbox"/>
Other specify	<input type="checkbox"/>
Published study	<input checked="" type="checkbox"/>

2.2 Types of participants

Adult Ventilated Patients	<input checked="" type="checkbox"/>
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2.3 Types of intervention

(Tick appropriate intervention provide details on other treatment in space provided)

Chlorexidine vs Placebo	<input checked="" type="checkbox"/>	
Chlorexidine Vs Standard Care	<input type="checkbox"/>	

2.4 Types of outcomes

Incidence of VAP	<input checked="" type="checkbox"/>
Mortality	<input checked="" type="checkbox"/>

2.5 Lost to follow up <15%

Equation	16.57 %	<input type="checkbox"/>	<input checked="" type="checkbox"/>
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2.5.1 Reasons for LTFU

Death or tracheostomy.

2.5.2 Other reasons for exclusion

Known sensitivity to Chlorhexidine; Pregnancy; <18yrs; legal incarceration; Oral mucocytosis
Immunosuppression; transfer from another ICU ; Re-admission to ICU; "Do not Intubate" Order
No consent; Diagnosis of Thrombocytopenia; Confirmed diagnosis of of ost obstructive pneumonia; witnessed aspiration; intubation > 48hrs since admission

3. Methodology

3.1 Study design

RCT	✓	Single centre	✓
Quasi-experimental		Multi centre	

3.2 Study duration

Month & Year	2009 (March 2004-November 2007)
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3.3 Eligibility criteria

>18years, Consent ; expected intubation within 48hrs from admission;

Methodological quality/Risk of bias assessment

(Answer the domain-question with a 'Yes' signifying low risk of bias, 'No' signifying high risk of bias, and 'Unclear' signifying either lack of information or unknown risk of bias)

3.4 Cochrane Collaboration 'Risk of Bias' Tool

Entry	Judgement	Description
Adequate sequence generation?	Yes	Randomized by web-based subject enrollment
Allocation concealment?	Yes	Web-based (computer generated) randomization
Blinding of participants, personnel and outcome assessors?	Yes	Assignment of treatments blinded to outcome assessors
Incomplete outcome data addressed?	Yes	Outcomes fully reported on.
Free of selective outcome reporting?	Yes	No evidence of reporting bias
Free of other bias?	Yes	-----

Participants

Total number	117
Total number analyzed	117
Number of VAP cases	19
Mortality	16
High risk?	No
Setting	Trauma ICU
Diagnostic criteria	CPIS scores based on following elements: Partial pressure of arterial oxygenation (PaO ₂)/Fraction of inspired oxygen (FiO ₂), Infiltrate on chest radiology, fever, leukocytosis and purulent secretions. CPIS scores of 6 or more triggered BAL sampling of lower airways.
Age	Exp Mean (age)=50.0; Comp Mean(age)=47.6
Sex	(M) = 80 ;(F)= 37
Country	USA
Date of study	2009 (March 2004-November 2007)

*Mean±SD.

3.6 Interventions

Experimental group				
Type	Route	Dose	Timing	Side effect
Chlorhexidine 0.12 % solution	Oral rinse (solution)		2x daily as oral topical treatment with patients followed for up to 21 days, until discharge from ICU or death	None
Control group				
Type	Route	Dose	Timing	Side effect
Placebo	Oral rinse (solution)		2x daily as oral topical treatment with patients followed for up to 21 days, until discharge from ICU or death	None

3.7 Outcomes relevant to this review

(Tick yes or no)

13. Incidence of Ventilator Associated Pneumonia	YES	✓
14. Mortality	YES	✓

3.8 Outcome definitions

13. Incidence of Ventilator Associated Pneumonia	YES	✓
14. Mortality	YES	✓

4. Results

Number of patients: 117		
	Randomized	Analyzed
Experimental	58	58
Control	59	59
Total	117	117

4.1 Summary data for each intervention group

1. Incidence of VAP	Event	No event	Total
Experimental group	7	110	117
Control group	12	105	117

1. Mortality	Event	No event	Total
Experimental group	8	109	117
Control group	8	109	117

4.2 Continuous Data- N/A

4.3 Estimate of effect with confidence interval/*P*-value

1. Incidence of VAP	RR	CI 95%	<i>P</i> -value
Experimental group versus Control group	0.59	0.25 – 1.40	0.18
1. Mortality	RR	CI 95%	<i>P</i> -value
Experimental group versus Control group	1.02	0.41 – 2.53	0.18

4.4 Subgroup analysis

Concentration- 0.12% chlorhexidine
Setting- Trauma ICU (mixed)

4.5 Miscellaneous

Funding source	USPH grant –national institute of dental and craniofacial surgery
Key conclusions	Chlorhexidine did not reduce the total# of potential respiratory pathogensbut did reduce the # of Staph aureas in dental plaqueof trauma ICU patients
Other comments from authors	none
Reference to other relevant studies	Yes, prev meta-analyses
Correspondence required	No
Comments from reviewers	For inclusion
1. ITT analysis	2.
3.	4.

Data extraction form 08

1. Source

Study ID	08
Reviewer	Olivia Snyders and Oswald Khondowe
Author & Year	Tantipong, H., Morkchareonpong, C., Jaiyindee, S. & Thamlikitkul, V. 2008,
Journal	<i>Infection control and hospital epidemiology</i> , vol. 29, no. 2, pp. 131-136.
Title	"Randomized controlled trial and meta-analysis of oral decontamination with 2% chlorhexidine solution for the prevention of ventilator-associated pneumonia"
Country	Bangkok, Thailand

2. Eligibility

(Tick in the appropriate space)

2.1 Types of studies

RCT	<input checked="" type="checkbox"/>
Quasi-experimental	<input type="checkbox"/>
Other specify	<input type="checkbox"/>
Published study	<input checked="" type="checkbox"/>

2.2 Types of participants

Adult Ventilated Patients	<input checked="" type="checkbox"/>
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2.3 Types of intervention

(Tick appropriate intervention provide details on other treatment in space provided)

Chlorhexidine vs Normal Saline	<input checked="" type="checkbox"/>	
Chlorhexidine vs Placebo	<input type="checkbox"/>	

2.4 Types of outcomes

Incidence of VAP	<input checked="" type="checkbox"/>
Mortality	<input checked="" type="checkbox"/>

2.5 Lost to follow up <15%

Equation	-----	N	-
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2.5.1 Reasons for LTFU

None

2.5.2 Other reasons for exclusion

Diagnosis / presence of pneumonia on admission
Chlorhexidine sensitivity

3. Methodology

3.1 Study design

RCT	✓	Single centre	✓
Quasi-experimental		Multi centre	

3.2 Study duration

Month & Year	
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3.3 Eligibility criteria

Adult (>18yrs); Mechanically ventilated hospitalized in ICU;

Methodological quality/Risk of bias assessment

(Answer the domain-question with a 'Yes' signifying low risk of bias, 'No' signifying high risk of bias, and 'Unclear' signifying either lack of information or unknown risk of bias)

3.4 Cochrane Collaboration 'Risk of Bias' Tool

Entry	Judgement	Description
Adequate sequence generation?	Yes	Stratified randomization according to sex and hospital location
Allocation concealment?	Yes	Executed by pharmacy staff
Blinding of participants, personnel and outcome assessors?	Yes	Blinding of to data collectors and outcome assessors.
Incomplete outcome data addressed?	Yes	All outcomes addressed
Free of selective outcome reporting?	Yes	All outcomes reported on
Free of other bias?	Yes	-

3.5 Participants

Total number	207
Total number analyzed	207
Number of VAP cases	17
Mortality	73
High risk?	NO
Setting	ICU-mixed
Diagnostic criteria	Chest radiography with new, persistent or progressive infiltrate in combination with at least 3 of the following criteria: Temperature > 38°C or < 35.5°C, leukocytosis or leucopenia, purulent tracheal aspirate, tracheal aspirate and/or a semi-quantitative sample of tracheal aspirate which was positive for pathogenic bacteria.
Age	Mean :(treatment)=56.5;(Nacl)=60.3
Sex	Male: 101 Female: 106
Country	Bangkok, Thailand
Date of study	Jan 2006-March 2007

*Mean±SD.

3.6 Interventions

Experimental group				
Type	Route	Dose	Timing	Side effect
2% Chlorhexidine	Oral	15ml oral rinse plus toothbrushing	4xday	Irritation of the oral mucosa (n=10)
Control group				
Type	Route	Dose	Timing	Side effect
Normal Saline	oral	oral rinse plus toothbrushing	4xday	Irritation of the oral mucosa (n=1)

3.7 Outcomes relevant to this review

(Tick yes or no)

1. Incidence of Ventilator Associated Pneumonia	YES	✓
2. Mortality	YES	✓

3.8 Outcome definitions

1. Incidence of Ventilator Associated Pneumonia	YES	✓
2. Mortality	YES	✓

4. Results

Number of patients: 207		
	Randomized	Analyzed
Experimental	102	102
Control	105	105
Total	207	207

4.1 Summary data for each intervention group

1. Incidence of VAP	Event	No event	Total
Experimental group	5	97	102
Control group	12	93	105

1. Mortality	Event	No event	Total
Experimental group	36	66	102
Control group	37	68	105

4.2 Continuous Data- N/A

4.3 Estimate of effect with confidence interval/*P*-value

1. Incidence of VAP	RR	CI 95%	<i>P</i> -value
Experimental group versus Control group	0.43	0.16 – 1.17	0.18
1. Mortality	RR	CI 95%	<i>P</i> -value
Experimental group versus Control group	1.00	0.69 – 1.45	0.18

4.4 Subgroup analysis

Chlorhexidine concentration (2% used)
Trial setting (mixed ICU)

4.5 Miscellaneous

Funding source	Thailand research funding & faculty of medicine Siriraj Hospital Thailand
Key conclusions	2% chlorhexidine cost effective strategy to reduce risk of VAP
Other comments from authors	No diff in duration of MV or LOS in ICU or mortality
Reference to other relevant studies	Koeman <i>et al</i> 2002; chlebicki <i>et al</i> (2007); chan <i>et al</i> (2007); Kola <i>et al</i> (2007);
Correspondence required	No
Comments from reviewers	Meta-analysis embedded in article
1.	2.
3.	4.