# Oral hygiene care for critically ill patients to prevent ventilator-associated pneumonia (Review)

**Shi Z, Xie H, Wang P, Zhang Q, Wu Y, Chen E, Ng L, Worthington HV, Needleman I, Furness S**

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[Intervention Review]

# Oral hygiene care for critically ill patients to prevent ventilator-associated pneumonia

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## ABSTRACT

### Background

Ventilator-associated pneumonia (VAP) is defined as pneumonia developing in persons who have received mechanical ventilation for at least 48 hours. VAP is a potentially serious complication in these patients who are already critically ill. Oral hygiene care (OHC), using either a mouthrinse, gel, toothbrush, or combination, together with aspiration of secretions may reduce the risk of VAP in these patients.

### Objectives

To assess the effects of OHC on the incidence of VAP in critically ill patients receiving mechanical ventilation in intensive care units (ICUs) in hospitals.

### Search methods

We searched the Cochrane Oral Health Group's Trials Register (to 14 January 2013), CENTRAL (*The Cochrane Library* 2012, Issue 12), MEDLINE (OVID) (1946 to 14 January 2013), EMBASE (OVID) (1980 to 14 January 2013), LILACS (BIREME) (1982 to 14 January 2013), CINAHL (EBSCO) (1980 to 14 January 2013), Chinese Biomedical Literature Database (1978 to 14 January 2013), China National Knowledge Infrastructure (1994 to 14 January 2013), Wan Fang Database (January 1984 to 14 January 2013), OpenGrey and ClinicalTrials.gov (to 14 January 2013). There were no restrictions regarding language or date of publication.

### Selection criteria

We included randomised controlled trials (RCTs) evaluating the effects of OHC (mouthrinse, swab, toothbrush or combination) in critically ill patients receiving mechanical ventilation.

**Data collection and analysis**

Two review authors independently assessed all search results, extracted data and undertook risk of bias. We contacted study authors for additional information. Trials with similar interventions and outcomes were pooled reporting odds ratios (OR) for dichotomous outcomes and mean differences (MD) for continuous outcomes using random-effects models unless there were fewer than four studies.

**Main results**

Thirty-five RCTs (5374 participants) were included. Five trials (14%) were assessed at low risk of bias, 17 studies (49%) were at high risk of bias, and 13 studies (37%) were assessed at unclear risk of bias in at least one domain. There were four main comparisons: chlorhexidine (CHX mouthrinse or gel) versus placebo/usual care, toothbrushing versus no toothbrushing, powered versus manual toothbrushing and comparisons of oral care solutions.

There is moderate quality evidence from 17 RCTs (2402 participants, two at high, 11 at unclear and four at low risk of bias) that CHX mouthrinse or gel, as part of OHC, compared to placebo or usual care is associated with a reduction in VAP (OR 0.60, 95% confidence intervals (CI) 0.47 to 0.77, P < 0.001, $I^2$ = 21%). This is equivalent to a number needed to treat (NNT) of 15 (95% CI 10 to 34) indicating that for every 15 ventilated patients in intensive care receiving OHC including chlorhexidine, one outcome of VAP will be prevented. There is no evidence of a difference between CHX and placebo/usual care in the outcomes of mortality (OR 1.10, 95% CI 0.87 to 1.38, P = 0.44, $I^2$ = 2%, 15 RCTs, moderate quality evidence), duration of mechanical ventilation (MD 0.09, 95% CI -0.84 to 1.01 days, P = 0.85, $I^2$ = 24%, six RCTs, moderate quality evidence), or duration of ICU stay (MD -0.21, 95% CI -1.48 to 1.89 days, P = 0.81, $I^2$ = 9%, six RCTs, moderate quality evidence). There was insufficient evidence to determine whether there is a difference between CHX and placebo/usual care in the outcomes of duration of use of systemic antibiotics, oral health indices, microbiological cultures, caregivers preferences or cost. Only three studies reported any adverse effects, and these were mild with similar frequency in CHX and control groups.

From three trials of children aged from 0 to 15 years (342 participants, moderate quality evidence) there is no evidence of a difference between OHC with CHX and placebo for the outcomes of VAP (OR 1.07, 95% CI 0.65 to 1.77, P = 0.79, $I^2$ = 0%), or mortality (OR 0.73, 95% CI 0.41 to 1.30, P = 0.28, $I^2$ = 0%), and insufficient evidence to determine the effect on the outcomes of duration of ventilation, duration of ICU stay, use of systemic antibiotics, plaque index, microbiological cultures or adverse effects, in children.

Based on four RCTs (828 participants, low quality evidence) there is no evidence of a difference between OHC including toothbrushing (± CHX) compared to OHC without toothbrushing (± CHX) for the outcome of VAP (OR 0.69, 95% CI 0.36 to 1.29, P = 0.24 , $I^2$ = 64%) and no evidence of a difference for mortality (OR 0.85, 95% CI 0.62 to 1.16, P = 0.31, $I^2$ = 0%, four RCTs, moderate quality evidence). There is insufficient evidence to determine whether there is a difference due to toothbrushing for the outcomes of duration of mechanical ventilation, duration of ICU stay, use of systemic antibiotics, oral health indices, microbiological cultures, adverse effects, caregivers preferences or cost.

Only one trial compared use of a powered toothbrush with a manual toothbrush providing insufficient evidence to determine the effect on any of the outcomes of this review.

A range of other oral care solutions were compared. There is some weak evidence that povidone iodine mouthrinse is more effective than saline in reducing VAP (OR 0.35, 95% CI 0.19 to 0.65, P = 0.0009, $I^2$ = 53%) (two studies, 206 participants, high risk of bias). Due to the variation in comparisons and outcomes among the trials in this group there is insufficient evidence concerning the effects of other oral care solutions on the outcomes of this review.

**Authors' conclusions**

Effective OHC is important for ventilated patients in intensive care. OHC that includes either chlorhexidine mouthwash or gel is associated with a 40% reduction in the odds of developing ventilator-associated pneumonia in critically ill adults. However, there is no evidence of a difference in the outcomes of mortality, duration of mechanical ventilation or duration of ICU stay. There is no evidence that OHC including both CHX and toothbrushing is different from OHC with CHX alone, and some weak evidence to suggest that povidone iodine mouthrinse is more effective than saline in reducing VAP. There is insufficient evidence to determine whether powered toothbrushing or other oral care solutions are effective in reducing VAP.

## PLAIN LANGUAGE SUMMARY

### Oral hygiene care for critically ill patients to prevent ventilator-associated pneumonia

**Review question**

To assess the effects of oral hygiene care on the incidence of ventilator-associated pneumonia (VAP) in critically ill patients receiving mechanical ventilation in intensive care units (ICUs) in hospitals (excluding the use of antibiotics). The aim was to summarise all the available appropriate research in order to facilitate the provision of evidence-based care for these vulnerable patients.

Trials were grouped into four main comparisons.

1. Chlorhexidine antiseptic mouthrinse or gel compared to placebo (treatment without the active ingredient chlorhexidine) or usual care, (with or without toothbrushing).

2. Toothbrushing compared with no toothbrushing, (with or without chlorhexidine).

3. Powered compared with manual toothbrushing.

4. Oral care with other solutions.

**Background**

Critically ill people, who may be unconscious or sedated while they are treated in intensive care units often need to have machines to help them breathe (ventilators). The use of these machines for more than 48 hours may result in VAP. VAP is a potentially serious complication in these patients who are already critically ill.

Keeping the teeth and the mouth clean, preventing the build-up of plaque on the teeth, or secretions in the mouth may help reduce the risk of developing VAP. Oral hygiene care, using a mouthrinse, gel, toothbrush, or combination, together with aspiration of secretions may reduce the risk of VAP in these patients.

**Study characteristics**

This review of existing studies was carried out by the Cochrane Oral Health Group and the evidence is current up to 14 January 2013.

Thirty-five separate research studies were included but only a minority (14%) of the studies were well conducted and described.

All of the studies took place in intensive care units in hospitals. In total there were 5374 participants randomly allocated to treatment. Participants were critically ill and required assistance from nursing staff for their oral hygiene care. In three of the included studies participants were children and in the remaining studies only adults participated. Participants had been hospitalised as medical, surgical or trauma patients. In 13 studies it was not clear which of these three categories the participants belonged to.

**Key results**

Effective oral hygiene care is important for ventilated patients in intensive care. We found evidence that chlorhexidine either as a mouthrinse or a gel reduces the odds of VAP in adults by about 40%. So for example for every 15 people on ventilators in intensive care, the use of oral hygiene care including chlorhexidine will prevent one person developing VAP. However, we found no evidence that chlorhexidine makes a difference to the numbers of patients who die in ICU, to the number of days of mechanical ventilation or the number of days in ICU.

The three studies of children (aged birth to 15 years) showed no evidence of a difference in VAP between the use of chlorhexidine mouthrinse or gel and placebo in children.

Four studies showed no evidence of a difference between toothbrushing (with or without chlorhexidine) and oral care without toothbrushing (with or without chlorhexidine) in the risk of developing VAP. Two studies showed some evidence of a reduction in VAP with povidone iodine antiseptic mouthrinse.

There was not enough research information available to provide evidence of the effects of other mouth care rinses such as water, saline or triclosan.

Only two of the included studies reported any adverse effects of the interventions (mild oral irritation (one study) and unpleasant taste (both chlorhexidine and placebo)), four studies reported that there were no adverse effects and the remaining studies do not mention adverse effects in the reports.

**Quality of the evidence**

The evidence presented is of moderate quality. Only 14% of the studies were well conducted and described.

## SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

**Chlorhexidine (mouthrinse or gel) versus placebo/usual care for critically ill patients to prevent ventilator-associated pneumonia (VAP)**

**Patient or population:** Critically ill patients receiving mechanical ventilation
**Settings:** Intensive care unit (ICU)
**Intervention:** Chlorhexidine (mouthrinse or gel)
**Comparison:** Placebo or usual care

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Control (placebo or usual care) | Chlorhexidine (mouthrinse or gel) | | | | |
| **VAP**<br>Follow-up: mean 1 month | **242 per 1000** | **160 per 1000**<br>(130 to 197) | **OR 0.60**<br>(0.47 to 0.77) | 2402<br>(17 studies) | ⊕⊕⊕○<br>**moderate**[1] | This equates to an NNT of 15 (95% CI 10 to 34) |
| **Mortality**<br>Follow-up: mean 1 month | **239 per 1000** | **257 per 1000**<br>(215 to 303) | **OR 1.10**<br>(0.87 to 1.38) | 2111<br>(15 studies) | ⊕⊕⊕○<br>**moderate**[1] | |
| **Duration of ventilation**<br>Days of ventilation required<br>Follow-up: mean 1 month | The mean duration of ventilation in the control groups ranged from 7 to 18 days | The mean duration of ventilation in the intervention groups was **0.09 higher**<br>(0.84 lower to 1.01 higher) | | 933<br>(6 studies) | ⊕⊕⊕○<br>**moderate**[1] | |
| **Duration of ICU stay**<br>Follow-up: mean 1 month | The mean duration of ICU stay in the control groups ranged from 10 to 24 days | The mean duration of ICU stay in the intervention groups was **0.21 higher**<br>(1.48 lower to 1.89 higher) | | 833<br>(6 studies) | ⊕⊕⊕○<br>**moderate**[1] | |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)
**CI:** confidence interval; **NNT:** number needed to treat; **OR:** odds ratio

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
**Very low quality:** We are very uncertain about the estimate

[1] 2 studies at high risk of bias, 11 at unclear risk of bias and 4 at low risk of bias
[2] Assumed risk is based on the outcomes in the control groups of the included studies

# BACKGROUND

## Description of the condition

Patients in intensive care units in hospital frequently require mechanical ventilation because their ability to breathe unassisted is impaired due to trauma, or as the result of a medical condition or recent surgery. These critically ill patients are also dependent on hospital staff to meet their needs for nutrition and hygiene, including oral hygiene.

Overall the research suggests that oral health deteriorates following admission to a critical care unit (Terezakis 2011). Intubation and critical illness reduce oral immunity, may be associated with mechanical injury of the mouth or respiratory tract, increase the likelihood of dry mouth and the presence of the endotracheal tube may also make access for oral care more difficult (Alhazzani 2013; Labeau 2011). Dental plaque accumulates rapidly in the mouths of critically ill patients and as the amount of plaque increases, colonisation by microbial pathogens is likely (Fourrier 1998; Scannapieco 1992). Plaque colonisation may be exacerbated in the absence of adequate oral hygiene care and by the drying of the oral cavity due to prolonged mouth opening which reduces the buffering and cleansing effects of saliva. In addition, the patient's normal defence mechanisms for resisting infection may be impaired (Alhazzani 2013; Terpenning 2005). Dental plaque is a complex biofilm which, once formed, is relatively resistant to chemical control, requiring mechanical disruption (such as toothbrushing) for maximum impact (Marsh 2010).

One of the complications which may develop in ventilated patients is ventilator-associated pneumonia (VAP). VAP is generally defined as a pneumonia developing in a patient who has received mechanical ventilation for at least 48 hours (ATS Guideline 2005). It is thought that the endotracheal tube, which delivers the necessary oxygen to the patient, may also act as a conduit for pathogenic bacteria which multiply in the oral cavity and move down the tube into the lungs. Micro-aspiration of pharyngeal secretions may also occur around an imperfect seal of the cuff of the endotracheal tube in a ventilated patient. Several studies have shown that micro-aspiration contributes to the development of nosocomial pneumonia (Azoulay 2006; Scannapieco 1992; Mojon 2002).

There is increasing evidence in the literature to suggest a link between colonisation of dental plaque with respiratory pathogens and VAP (Azarpazhooh 2006; Estes 1995; Fourrier 1998; Garrouste-Orgeas 1997; Scannapieco 1992). Scannapieco et al conducted a survey where 65% of 34 patients in intensive care units (ICUs) were found to have respiratory pathogen colonisation in the plaque or oral mucosa or both, compared with only 16% of 25 patients in dental clinics (Scannapieco 1992). Treloar and co-workers reported that 37.5% of oropharyngeal cultures taken from orally intubated patients had the same pathogens as sputum specimens (Treloar 1995). In another study, pathogens from the respiratory tract of patients with hospital-acquired pneumonia genetically matched those from dental plaque (El-Solh 2004).

Ventilator-associated pneumonia is a relatively common nosocomial infection in critically ill patients, with a reported prevalence ranging between 6% and 52% (Apostolopoulou 2003; Edwards 2009) with some indications that incidence is decreasing as understanding of the risk factors and preventative measures improves. A recent study estimated that the attributable mortality of VAP to be 10% (Melsen 2011). Cohort studies (Apostolopoulou 2003; Cook 1998) have found that duration of ICU stay is increased in patients who develop VAP but it is unclear whether this is cause or effect.

Antibiotics, administered either intraorally as topical pastes or systemically have been used to prevent VAP and these interventions are evaluated in other Cochrane systematic reviews (D'Amico 2009; Selim 2010). Topical antibiotic pastes have been shown to be effective but are not widely used because of the risk of developing antibiotic resistant organisms (Panchabhai 2009). However overuse of antibiotics is associated with the development of multidrug resistant pathogens and therefore there is merit in using other approaches for preventing infections such as VAP.

## Description of the intervention

This systematic review evaluates various types of oral hygiene care as a means of reducing the incidence of VAP in critically ill patients receiving mechanical ventilation. Oral hygiene care is promoted in clinical guidelines as a means of reducing the incidence of VAP but the evidence base is limited (Tablan 2004).

Oral hygiene care includes the use of mouthrinses (water, saline, antiseptics) applied either as sprays, liquids or with a swab, with or without toothbrushing (either manual or powered) and toothpaste, to remove plaque and debris from the oral cavity. Oral hygiene care also involves suction to remove excess fluid, toothpaste and debris and may be followed by the application of an antiseptic gel. Antiseptics are broadly defined to include saline, chlorhexidine, povidone iodine, cetylpyridium and possibly others, (but exclude antibiotics).

## How the intervention might work

Patients on mechanical ventilation often have a very dry mouth due to prolonged mouth opening which may be exacerbated by the side effects of medications used in their treatment. In healthy individuals, saliva functions to maintain oral health through its lubricating, antibacterial and buffering properties (Labeau 2011) but patients on ventilators lack sufficient saliva for this to occur, and the usual stimuli for saliva production are absent.

Routine oral hygiene care is designed to remove plaque and debris as well as replacing some of the functions of saliva, moistening and rinsing the mouth. Toothbrushing, with either a man-

ual or powered toothbrush, removes plaque from teeth and gums and disrupts the biofilm within which plaque bacteria multiply (Whittaker 1996; Zanatta 2011). It is hypothesised that using an antiseptic, such as chlorhexidine gluconate or povidone-iodine, as either a rinse or a gel may further reduce the bacterial load or delay a subsequent increase in bacterial load.

However, it is important that during oral hygiene care, the plaque and debris are removed from the oral cavity with care in order to avoid aspiration of contaminated fluids into the respiratory tract. Raising the head of the bed, and careful use of appropriately maintained closed suction systems, together with an appropriately fitted cuff around the endotracheal tube are other important aspects of care of critically ill patients that are not part of this systematic review.

### Why it is important to do this review

Other Cochrane systematic reviews have evaluated the use of topical antibiotic pastes applied to the oral cavity (selective oral decontamination D'Amico 2009), the use of probiotics (Hao 2011) and systemic antibiotics (Selim 2010) to prevent VAP. Other published reviews have evaluated aspects of oral hygiene care, such as toothbrushing (Alhazzani 2013) or use of chlorhexidine (Pineda 2006), and broader reviews have noted the lack of available evidence (Berry 2007; Shi 2004). Clinical guidelines recommend the use of oral hygiene care but there is a lack of available evidence as a basis for specifying the essential components of such care (Muscedere 2008; Tablan 2004). The goal of this Cochrane systematic review was to evaluate all oral hygiene care interventions (excluding the use of antibiotics) used in ICU for patients on ventilators to determine the effects of oral hygiene care on the development of VAP. We planned to summarise all the available research in order to facilitate the provision of evidence-based care for these vulnerable patients.

## OBJECTIVES

To assess the effects of oral hygiene care on prevention of VAP in critically ill patients receiving mechanical ventilation in hospital settings.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We included in the review all randomised controlled trials (RCTs) of oral hygiene care interventions.

#### Types of participants

Critically ill patients in hospital settings receiving mechanical ventilation, without ventilator-associated pneumonia or respiratory infection at baseline. Trials where only some of the participants were receiving mechanical ventilation were included if

- the outcome of ventilator-associated pneumonia was reported,
- data for those who had been treated with mechanical ventilation for a minimum of 48 hours and then developed nosocomial pneumonia were available.

Trials where participants were undergoing a surgical procedure that involved mechanical ventilation (e.g. cardiac surgery) were only included in this review if the oral hygiene care was given during the period of mechanical ventilation which had a minimum duration of 48 hours. Trials where pre-operative patients received a single dose of antibacterial rinse or gargle, and received mechanical ventilation only for the duration of the surgery, with no further mechanical ventilation and oral hygiene care during the post-operative period were excluded.

#### Types of interventions

- Intervention group: received clearly defined oral care procedures such as nurse-assisted toothbrushing, oral and pharyngeal cavity rinse, decontamination of oropharyngeal cavities with antiseptics.
- Control group: received no treatment, placebo, 'usual care' or a different specific oral hygiene care procedure.

Trials where the intervention being evaluated was a type of suction system or variation of method, timing, or place where mechanical ventilation was introduced (e.g. emergency room or ICU) were excluded.

We excluded trials of selective decontamination using topical antibiotics administered to the oral cavity or oropharynx because these interventions are covered in another Cochrane review (D'Amico 2009). Trials of probiotics administered to prevent respiratory infections were also excluded as these are covered in a separate review (Hao 2011).

#### Types of outcome measures

##### Primary outcomes

1. Incidence of VAP (defined as pneumonia developing in a patient who has received mechanical ventilation for at least 48 hours).
2. Mortality (either ICU mortality if these data were available, or 30-day mortality).

### Secondary outcomes

1. Duration of mechanical ventilation or ICU stay or both.
2. Systemic antibiotic use.
3. Colonisation of dental plaque, saliva, oropharyngeal mucosa or endotracheal aspirates by VAP-associated organisms.
4. Oral health indices such as gingival index, plaque index, bleeding index, periodontal index etc.
5. Adverse effects of the interventions.
6. Caregivers' preferences for oral hygiene care.
7. Economic data.

## Search methods for identification of studies

For the identification of studies included or considered for this review, we developed detailed search strategies for each database searched. These were based on the search strategy developed for MEDLINE (OVID) but revised appropriately for each database.

### Electronic searches

We searched the following electronic databases:

- Cochrane Oral Health Group's Trials Register (to 14 January 2013) (Appendix 1)
- The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2012, Issue 12) (Appendix 2)
- MEDLINE via OVID (1946 to 14 January 2013) (Appendix 3)
- EMBASE via OVID (1980 to 14 January 2013) (Appendix 4)
- CINAHL via EBSCO (1980 to 14 January 2013) (Appendix 5)
- LILACS via BIREME Virtual Health Library (1982 to 14 January 2013) (Appendix 6)
- Chinese Biomedical Literature Database (1978 to 14 January 2013) (Appendix 7)
- China National Knowledge Infrastructure (1994 to 14 January 2013) (Appendix 8)
- Wan Fang Database (1984 to 14 January 2013) (Appendix 9)
- OpenGrey (1980 to 14 January 2013) (Appendix 10)
- ClinicalTrials.gov (14 January 2013) (Appendix 11).

The search strategy used a combination of controlled vocabulary and free text terms, details of the MEDLINE search are provided in Appendix 3. The search of EMBASE was linked with the Cochrane Oral Health Group filter for identifying RCTs (Appendix 4). All relevant publications were included irrespective of language.

### Searching other resources

All the references lists of the included studies were checked manually to identify any additional studies.

We contacted the first author of the included studies, other experts in the field and manufacturers of oral hygiene products to request unpublished relevant information.

## Data collection and analysis

### Selection of studies

Two review authors independently examined the title and abstract of each article obtained from the searches. If they disagreed with the inclusion of any study, there was group discussion with other members of the review team until consensus was achieved. Multiple reports from a study were linked and the report with more complete follow-up data was the primary source of data.
Full-text copies of potentially relevant reports were obtained and examined in detail to determine whether the study fulfilled the eligibility criteria. Any queries were once again resolved by discussion. Attempts were made to contact study authors to obtain additional information as necessary.

### Data extraction and management

Two review authors independently extracted data from the included studies into the pre-designed structured data extraction forms. Any disagreements were resolved by discussion. Contents of the data extraction included the following items.
(1) General characteristics of the study
Authors, year of publication, country where the study was performed, funding, language of publication, study duration, citation, contact details for the authors and identifier.
(2) Specific trial characteristics
Basic study design characteristics: sequence generation, allocation sequence concealment, blinding, incomplete outcome data and selective outcome reporting etc were collected and presented in the table of 'Characteristics of included studies'. Verbatim quotes on the first three issues from original reports were adopted.
Participants: total number, setting, age, sex, country, ethnicity, socio-demographic details (e.g. education level), diagnostic criteria of VAP and the presence of co-morbid conditions.
Interventions: we collected details of all experimental and control interventions, such as dosages for drugs used and routes of delivery, format for oral hygiene care, timing and duration of the oral care procedures. In addition, information on any co-interventions administered were also collected.
Outcomes: incidence of VAP or other respiratory diseases and mortality (directly and indirectly attributable), adverse outcomes resulting from the interventions, quantity of pathogenic microorganisms from culture of oropharyngeal materials or tracheal aspirates, indices of the plaque, inflammation of the gum or periodontal tissues etc were collected. All outcome variables were specified in terms of definition, timing, units and scales.

Other results: we also collected summary statistics, sample size, key conclusions, comments and any explanations provided for unexpected findings by the study authors. The lead authors of included studies were contacted if there were issues to be clarified.

### Assessment of risk of bias in included studies

Two review authors assessed the risk of bias of all included studies, independently and in duplicate, using The Cochrane Collaboration's domain-based, two-part tool as described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* ( Higgins 2011). Study authors were contacted for clarification or missing information where necessary. Any disagreements concerning risk of bias were resolved by discussion. A 'Risk of bias' table was completed for each included study. For each domain of risk of bias, we described what was reported to have happened in the study in order to provide a rationale for the second part, which involved assigning a judgement of 'Low risk' of bias, 'High risk' of bias, or 'Unclear risk' of bias.

For each included study, we assessed the following seven domains of risk of bias.

- Random sequence generation (selection bias): use of simple randomisation (e.g. random number table, computer-generated randomisation, central randomisation by a specialised unit), restricted randomisation (e.g. random permuted blocks), stratified randomisation and minimisation were assessed as low risk of bias. Other forms of simple randomisation such as repeated coin tossing, throwing dice or dealing cards were also considered as low risk of bias (Schulz 2002). Where a study report used the phrase 'randomised' or 'random allocation' but with no further information we assessed it as unclear for this domain.
- Allocation concealment (selection bias): use of centralised/ remote allocation, pharmacy-controlled randomisation and sequentially numbered, sealed, opaque envelopes were assessed as low risk of bias. If a study report did not mention allocation concealment we assessed it as unclear for this domain.
- Blinding of participants and personnel (performance bias): participants in included studies were in intensive care and on mechanical ventilation and were therefore unlikely to be aware of the treatment group to which they were assigned. Where no placebo was used, caregivers would be aware of the assigned intervention and it is unclear whether this would introduce a risk of performance bias. If a study was described as double blind, and a placebo was used we assumed that caregivers and outcome assessors were blinded to the allocated treatment. If blinding was not mentioned, and if no placebo was used we assumed that no blinding of caregivers occurred and we assessed this domain as at unclear risk of bias.
- Blinding of outcome assessment (detection bias): if outcome assessor blinding was not mentioned in the trial report we assessed this domain as at unclear risk of bias.
- Incomplete outcome data (attrition bias): where the overall rate of attrition was high the risk of attrition bias was assessed as high. Alternatively if the numbers of participants, and/or the reasons for exclusion were different in each arm of the study, risk of attrition bias was assessed as high. If numbers of participants randomised or evaluated in each arm of the study were not reported we assessed this domain as unclear.
- Selective reporting (reporting bias): if the study did not report outcomes stated in the methods section, or reported outcomes without estimates of variance, we assessed this as at high risk of reporting bias.
- Other bias: any other potential source of bias which might feasibly alter the magnitude of the effect estimate e.g. baseline imbalance between study arms in important prognostic factors (e.g. clinical pulmonary infection scores (CPIS), antibiotic exposure), early stopping of the trial, or co-interventions or differences in other treatment between study arms. Other potential sources of bias were described and risk of bias assessed.

We summarised the risk of bias as follows.

| Risk of bias | Interpretation | In outcome | In included studies |
|---|---|---|---|
| Low risk of bias | Plausible bias unlikely to seriously alter the results | Low risk of bias for all key domains | Most information is from studies at low risk of bias |
| Unclear risk of bias | Plausible bias that raises some doubt about the results | Unclear risk of bias for one or more key domains | Most information is from studies at low or unclear risk of bias |
| High risk of bias | Plausible bias that seriously weakens confidence in the results | High risk of bias for one or more key domains | The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of results |

We presented the risk of bias graphically by: (a) proportion of studies with each judgement ('Low risk', 'High risk', and 'Unclear risk' of bias) for each risk of bias domain (Figure 1), and (b) cross-tabulation of judgements by study and by domain (Figure 2).

**Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies**

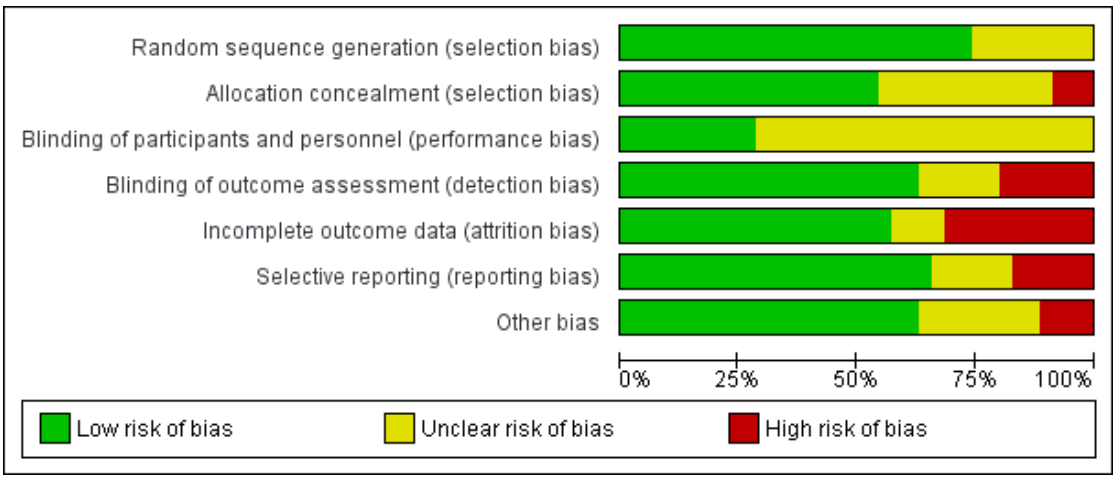
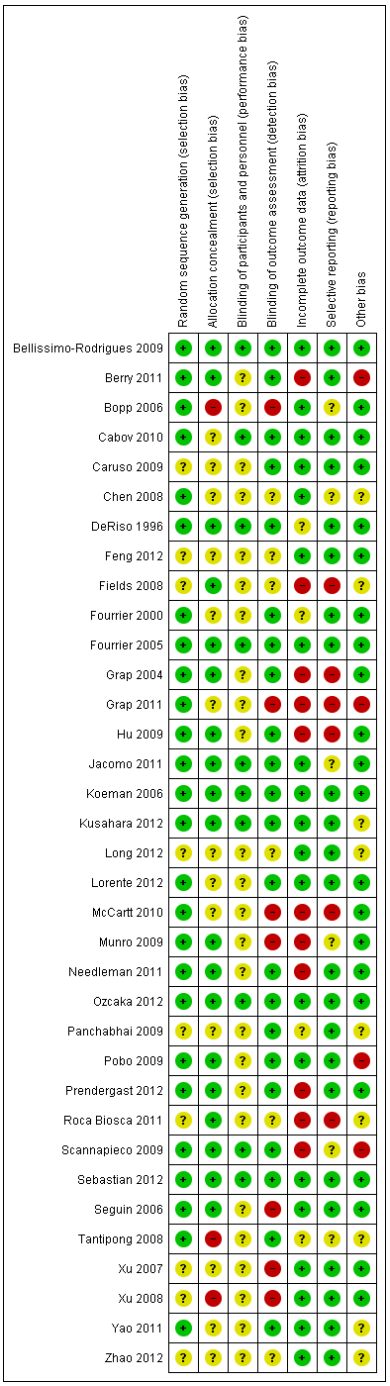


**Figure 2. Risk of bias summary graph: review authors' judgements about each risk of bias item for each included study**



### Measures of treatment effect

For dichotomous outcomes, we computed the effect measure the odds ratio (OR) together with the 95% confidence interval. For continuous outcomes, mean difference (MD) with 95% confidence interval was used to estimate the summary effect.

### Unit of analysis issues

The unit of analysis was the patient. The indices of plaque and gingivitis were measured as mean values for the patients. Episodes of care were also related back to individual patients.

### Dealing with missing data

We contacted the lead author of studies requesting that they supply any missing data. Missing standard deviations were to be obtained using the methods outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

### Assessment of heterogeneity

To detect heterogeneity among studies in a meta-analysis, a $Chi^2$ test with a 0.01 level of significance as the cut-off value was applied. The impact of statistical heterogeneity was quantified using the $I^2$ statistic. The thresholds of $I^2$ recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011)

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity

were used for interpretation of the results. If considerable heterogeneity existed then it was investigated. We used subgroup analyses to investigate possible differences between the studies.

### Assessment of reporting biases

Only a proportion of research projects conducted are ultimately published in an indexed journal and become easily identifiable for inclusion in systematic reviews. Reporting biases arise when the reporting of research findings is influenced by the nature and direction of the findings of the research. We investigated and attempted to minimise potential reporting biases including publication bias, time lag bias, multiple (duplicate) publication bias and language bias in this review.

Where there were more than 10 studies in one outcome we constructed a funnel plot. We planned to investigate the asymmetry in the funnel plot (indicating possible publication bias) by undertaking statistical analysis using the methods introduced by Egger 1997 (continuous outcome) and Rücker 2008 (dichotomous outcome) (such analysis would have been done in STATA 11.0).

### Data synthesis

Meta-analyses were undertaken for the similar comparisons and same outcomes across studies. We decided to use random-effects models providing there were four or more trials in any one meta-analysis. If different scales were used, standardised mean differences were calculated.

### Subgroup analysis and investigation of heterogeneity

One subgroup analysis was proposed a priori when discussing how to structure the data comparisons. It was decided to undertake a subgroup analysis for whether the patients' teeth were cleaned or not as it was hypothesised that antiseptics would be less effective if toothbrushing was not used to disrupt dental plaque biofilm.

### Sensitivity analysis

To determine whether the intervention effects of oral hygiene care were robust, sensitivity analyses were planned to determine the effect of those factors, such as exclusion of some studies with questionable diagnostic criteria for VAP, excluding studies with high risk of bias, or changing assumptions about missing data on the estimates of effect.

If the results did not change substantially in sensitivity analyses, then the conclusion would have been regarded as stable with a higher degree of certainty. Where sensitivity analyses identified particular factors that greatly influenced the conclusions of the review, the plausible causes of the uncertainties would have been explored, and the results would be interpreted with caution.

### Summary of findings

The GRADE system for evaluating quality of the evidence of systematic reviews (Guyatt 2008; Higgins 2011) was adopted using the software GRADEprofiler. The quality of the body of evidence was assessed with reference to the overall risk of bias of the included studies, the directness of the evidence, the inconsistency of the results, the precision of the estimates, and the risk of publication bias. The quality of the body of evidence was classified into four categories: high, moderate, low and very low.

## RESULTS

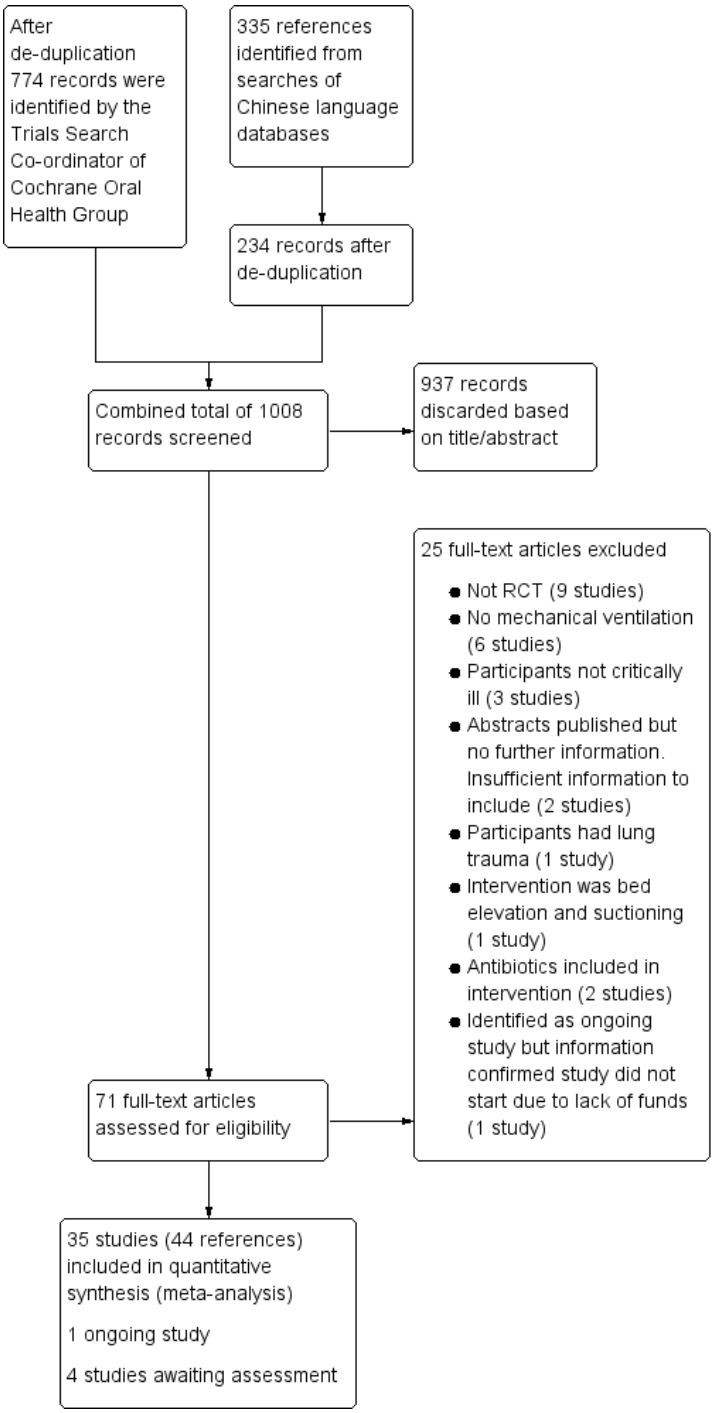
## Description of studies

### Results of the search

After removal of duplicates, the electronic search strategies identified 774 records from English language databases and 234 from Chinese language databases, which were screened by at least two review authors against the inclusion criteria for this review. Of these 937 were discarded and full-text copies of 71 references were requested. These papers were assessed by at least two review authors to determine their eligibility, and from these 35 studies were identified which met the inclusion criteria for this review. One ongoing study was identified and a further four studies are awaiting classification because we have not yet obtained full-text copies or they require translation or both.

The flow diagram is shown in Figure 3.

**Figure 3. Study flow diagram**



## Included studies

We included 35 RCTs in this review.

### Setting

Nine of the included studies were conducted in the USA (Bopp 2006; DeRiso 1996; Fields 2008; Grap 2004; Grap 2011; McCartt 2010; Munro 2009; Prendergast 2012; Scannapieco 2009), seven in China (Chen 2008; Feng 2012; Hu 2009; Long 2012; Xu 2007; Xu 2008; Zhao 2012), four in Brazil (Bellissimo-Rodrigues 2009; Caruso 2009; Jacomo 2011; Kusahara 2012), three in each of France (Fourrier 2000; Fourrier 2005; Seguin 2006) and Spain (Lorente 2012; Pobo 2009; Roca Biosca 2011), two in India (Panchabhai 2009; Sebastian 2012), and one in each of Australia (Berry 2011), Croatia (Cabov 2010), Taiwan(Yao 2011), Thailand (Tantipong 2008), Turkey (Ozcaka 2012), the Netherlands (Koeman 2006), and the United Kingdom (Needleman 2011).

All of the studies took place in intensive care units in hospitals. Most of the studies were two-arm parallel group RCTs, but six studies had three arms (Berry 2011; Grap 2004; McCartt 2010; Scannapieco 2009; Seguin 2006; Xu 2007) and one study had four arms (Munro 2009).

### Participants

In total there were 5374 participants randomly allocated to treatment in 34 RCTs included in this review and the other trial did not state how many patients were included (Fields 2008). The criteria for inclusion in these studies generally specified no prior intubation, no clinically apparent pneumonia at baseline (except for Sebastian 2012, where most of the children admitted to ICU had pneumonia already and criteria of the Centers for Disease Control (CDC) were strictly applied to diagnose subsequent VAP) and an expected requirement for mechanical ventilation for a minimum of 48 hours. Participants were critically ill and required assistance from nursing staff for their oral hygiene care. In three of the included studies participants were children (Jacomo 2011; Kusahara 2012; Sebastian 2012) and in the remaining studies only adults participated.

In four studies (Koeman 2006; McCartt 2010; Munro 2009; Panchabhai 2009) participants were either medical or surgical patients, in another four studies participants were described as trauma patients (Grap 2011; Prendergast 2012; Scannapieco 2009; Seguin 2006), six studies recruited surgical patients only (Chen 2008; DeRiso 1996; Jacomo 2011; Kusahara 2012; Yao 2011; Zhao 2012), eight studies recruited medical patients only (Cabov 2010; Fields 2008; Fourrier 2000; Fourrier 2005; Needleman 2011; Ozcaka 2012; Sebastian 2012; Tantipong 2008) and in the remaining 13 studies it was not clearly stated whether participants were medical, surgical or trauma cases.

### Classification of the interventions

The interventions in the included studies were in three broad groups.

- Chlorhexidine.
    - Chlorhexidine solution (applied as mouthrinse, spray or on a swab).
    - Chlorhexidine gel.
- Toothbrushing.
    - Powered.
    - Manual.
- Other solutions.
    - Saline.
    - Bicarbonate.
    - Povidone iodine.
    - Triclosan.

These interventions were used either singly or in combinations. We evaluated the following comparisons.

1. Chlorhexidine versus placebo/usual care with or without toothbrushing (20 studies: Bellissimo-Rodrigues 2009; Berry 2011; Bopp 2006; Cabov 2010; Chen 2008; DeRiso 1996; Fourrier 2000; Fourrier 2005; Grap 2004; Grap 2011; Jacomo 2011; Koeman 2006; Kusahara 2012; McCartt 2010; Munro 2009; Ozcaka 2012; Panchabhai 2009; Scannapieco 2009; Sebastian 2012; Tantipong 2008).
2. Toothbrushing versus no toothbrushing (in addition to usual care) (eight studies: Bopp 2006; Fields 2008; Lorente 2012; Munro 2009; Needleman 2011; Pobo 2009; Roca Biosca 2011; Yao 2011).
3. Powered toothbrushing versus manual toothbrushing (one study: Prendergast 2012).
4. Other solutions (nine studies).
    i) Saline (Caruso 2009; Hu 2009; Seguin 2006; Xu 2007; Xu 2008).
    ii) Bicarbonate (Berry 2011).
    iii) Povidone iodine (Feng 2012; Long 2012; Seguin 2006).
    iv) Triclosan (Zhao 2012).

Three studies (Berry 2011; Bopp 2006; Munro 2009) are included in two comparisons.

Placebos used included saline (Chen 2008; Feng 2012; Hu 2009; Ozcaka 2012; Seguin 2006; Tantipong 2008; Xu 2007; Xu 2008), potassium permanganate (Panchabhai 2009), half-strength hydrogen peroxide (Bopp 2006), water/alcohol mixture (DeRiso 1996; Jacomo 2011), placebo gel (Fourrier 2005; Koeman 2006;

Kusahara 2012;Sebastian 2012), base solution (Scannapieco 2009) or water (Berry 2011). In one trial the nature of the placebo was not specified (Bellissimo-Rodrigues 2009). In some of these studies the intervention described as placebo may have had some antibacterial activity but this was considered to be negligible compared to the active intervention.

In nine studies the control group received usual/standard care ( Caruso 2009; Fields 2008; Fourrier 2000; Grap 2004; Grap 2011; McCartt 2010; Munro 2009; Seguin 2006; Yao 2011) (for specific details see Characteristics of included studies), and in four studies there was a head to head comparison between two potentially active interventions (Needleman 2011; Pobo 2009; Prendergast 2012; Roca Biosca 2011).

### Measures of primary outcomes

#### Incidence of VAP

The primary outcome of our review is ventilator-associated pneumonia (VAP) defined as pneumonia developing in a person who has been on mechanical ventilation for at least 48 hours. VAP was fully reported by 28 of the included studies (Bellissimo-Rodrigues 2009; Berry 2011; Bopp 2006; Cabov 2010; Caruso 2009; Chen 2008; DeRiso 1996; Feng 2012; Fourrier 2005; Grap 2011; Hu 2009; Jacomo 2011; Koeman 2006; Kusahara 2012; Long 2012; Lorente 2012; Ozcaka 2012; Panchabhai 2009; Pobo 2009; Prendergast 2012; Scannapieco 2009; Sebastian 2012; Seguin 2006; Tantipong 2008; Xu 2007; Xu 2008; Yao 2011; Zhao 2012), one study reported only that there was no difference in VAP between the two arms of the study (Roca Biosca 2011) and in another study it was reported that the VAP rate dropped to zero in the intervention group but the control group event rate was not reported (Fields 2008). Two studies (Fourrier 2000; Hu 2009) reported the outcome of nosocomial pneumonia but it was not clear in the trial reports whether all those who developed this outcome had been on mechanical ventilation for at least 48 hours. One study reported mean CPIS score per group but did not record cases of VAP (McCartt 2010). We sought clarification from the trial authors but to date no further data have been received.

Diagnostic criteria for the outcome of ventilator-associated pneumonia were specified in 21 of the studies which reported the outcome of VAP (60%). Sixteen studies (Berry 2011; Cabov 2010; Caruso 2009; Fourrier 2000; Fourrier 2005; Grap 2004; Grap 2011; Koeman 2006; Kusahara 2012; McCartt 2010; Munro 2009; Pobo 2009; Scannapieco 2009; Seguin 2006; Tantipong 2008; Yao 2011) used Pugin's criteria (Cook 1998; Pugin 1991) which form the basis of the CPIS score, based on the presence of an infiltrate on chest radiograph, plus two or more of the following: temperature greater than 38.5º C or less than 35º C, white blood cell count greater than 11,000/$mm^3$ or less than 4000/$mm^3$, mucopurulent or purulent bronchial secretions, or more than 20% increase in fraction of inspired oxygen required to maintain saturation above 92%. In Ozcaka 2012 no specific criteria were reported, but communication from the author confirmed that patients with new pulmonary infiltrates or opacities on the chest X-ray were pre-diagnosed VAP and lower tracheal mini-bronchoalveolar lavage (mini-BAL) samples were taken and then subjects were diagnosed according to CPIS criteria. Patients who had a score $\geq$ 6 and the presence of $\geq 10^4$ colony-forming units/mL of a target potential respiratory bacterial pathogen (PRP) in mini-BAL were diagnosed VAP.

A further six studies (Bellissimo-Rodrigues 2009; DeRiso 1996; Fields 2008; Jacomo 2011; Panchabhai 2009; Sebastian 2012) used the CDC criteria as described in Horan 2008.

Four studies (Chen 2008; Feng 2012; Xu 2007; Xu 2008) used the criteria of the Chinese Society of Respiratory Diseases: presence of new infiltrates on chest radiographs developed after 48 hours of mechanical ventilation with any two of the following items: (a) temperature greater than 38º C, (b) change in characteristics of bronchial secretions from mucoid to mucopurulent or purulent, (c) white cell count greater than 10,000/$mm^3$, (d) positive culture of tracheal aspirate or positive culture of bronchoalveolar lavage fluid or both, or (e) arterial oxygen tension/inspiratory fraction of oxygen $PaO_2/FiO_2$ decreased over 30% within the period of ventilation.

The study by Hu 2009 reported the outcome of VAP based on clinical examination plus three criteria: chest radiograph, white cell count and culture of the aspirate from lower respiratory tract (but no precise parameters were specified). In Lorente 2012 the diagnosis of VAP was made by an expert panel blinded to the allocated intervention but the diagnostic criteria were not specified. The study by Prendergast 2012 had a single diagnostic criteria of a new or worsening pulmonary infiltrate on chest radiograph. Two studies used positive culture from the lower respiratory tract as criteria for diagnosis of VAP (Long 2012; Zhao 2012).

In the remaining two studies with the outcome of VAP, diagnostic criteria were not reported (Bopp 2006; Roca Biosca 2011) and the study by Needleman 2011 did not report the outcome of VAP.

#### Mortality

Twenty included studies reported the outcome of mortality either as ICU mortality or 30-day mortality (Bellissimo-Rodrigues 2009; Berry 2011; Cabov 2010; Caruso 2009; Fourrier 2000; Fourrier 2005; Jacomo 2011; Kusahara 2012; Long 2012; Lorente 2012; Munro 2009; Ozcaka 2012; Panchabhai 2009; Pobo 2009; Prendergast 2012; Scannapieco 2009; Sebastian 2012; Seguin 2006; Tantipong 2008; Yao 2011). Where ICU mortality was reported we used these data, and where ICU mortality was not reported we used 30-day mortality.

### Measures of secondary outcomes

### Duration of ventilation

There were 15 studies which reported this outcome (Bellissimo-Rodrigues 2009; Caruso 2009; Fourrier 2000; Fourrier 2005; Hu 2009; Koeman 2006; Long 2012; Lorente 2012; Ozcaka 2012; Pobo 2009; Prendergast 2012; Scannapieco 2009; Seguin 2006; Xu 2008; Zhao 2012). The studies by Jacomo 2011 and Sebastian 2012 reported the median duration of ventilation and the range for each group, but these data could not be combined in a meta-analysis.

### Duration of ICU stay

There were 14 studies reporting this outcome (Bellissimo-Rodrigues 2009; Bopp 2006; Caruso 2009; Fourrier 2000; Fourrier 2005; Koeman 2006; Kusahara 2012; Lorente 2012; Ozcaka 2012; Panchabhai 2009; Pobo 2009; Prendergast 2012; Seguin 2006; Zhao 2012). The studies by Jacomo 2011 and Sebastian 2012 reported the median ICU stay and the range for each group, but these data could not be combined in a meta-analysis.

### Systemic antibiotic therapy

There were three studies which reported some measure of systemic antibiotic use. DeRiso 1996 reported the number of patients in each group who required treatment of an infection with systemic antibiotics during their ICU stay, and Fourrier 2005 and Scannapieco 2009 both reported the mean number of days of systemic antibiotic use in the intervention and control groups.

### Microbial colonisation

Oropharyngeal colonisation is considered to be an important source in the pathogenesis of VAP and reducing bacterial colonisation may be a step towards prevention of VAP. Unfortunately only six studies (Cabov 2010; Feng 2012; Grap 2004; Kusahara 2012; Needleman 2011; Zhao 2012) reported data for the outcome of numbers of participants with microbial colonisation of plaque in each treatment group, and each study used a slightly different measure. Additionally, Fourrier 2005 reported the bacteria cultured from dental plaque only for the subgroup of participants who developed a nosocomial infection, and Scannapieco 2009 reported a graph of mean log of potential plaque respiratory pathogens in each group, but we were unable to use these measures in our meta-analysis.

### Oral health indices

Plaque indices were mentioned as outcomes in five studies (Needleman 2011; Ozcaka 2012; Roca Biosca 2011; Scannapieco 2009; Yao 2011). Complete data for plaque indices were available in two studies (Needleman 2011; Ozcaka 2012), were supplied by the corresponding author in one study (Yao 2011), one study (Scannapieco 2009) reported this outcome in graphs only and the other study (Roca Biosca 2011) did not report any estimate of variance so these data could not be used in this review.

### Adverse effects

Only two of the included studies (Bellissimo-Rodrigues 2009; Tantipong 2008) reported adverse effects of the interventions, four studies reported that there were no adverse effects (Berry 2011; Jacomo 2011; Ozcaka 2012; Sebastian 2012) and the remaining studies did not mention adverse effects in the reports.

## Excluded studies

There were 25 excluded studies. Reasons are summarised below.

- Nine studies were excluded because the methods used to allocate participants to interventions were not truly random (Abusibeih 2010; Chao 2009; Genuit 2001; Li 2011; Liwu 1990; McCoy 2012; Pawlak 2005; Santos 2008; Wang 2006).
- In six studies the participants were not receiving mechanical ventilation (Houston 2002; Lai 1997; Liang 2007; Ogata 2004; Segers 2006; Yin 2004).
- In three studies the patients were not critically ill (Epstein 1994; Ferozali 2007; Ueda 2004).
- Two studies were reported as abstracts only and our attempts to find a full publication or obtain sufficient data to enable inclusion in this review were unsuccessful (MacNaughton 2004; Zouka 2010).
- Guo 2007 was excluded because the patients had suffered lung trauma.
- Fan 2012 was excluded because the mouthrinse ingredients were not listed and may have contained antibiotic, and in Li 2012 the mouthrinse did contain antibiotic.
- In Wang 2012 the target intervention was bed elevation and endotracheal suctioning.
- Bordenave 2011 was excluded because communication from the investigators revealed that this study, listed on clinicaltrials.gov website as ongoing, was not undertaken due to funding issues.

For further information see Characteristics of excluded studies.

## Risk of bias in included studies

### Allocation

#### Sequence generation

Twenty-six of the included studies described clearly a random method of sequence generation and were assessed at low risk of bias

for this domain. The remaining nine studies (Caruso 2009; Feng 2012; Fields 2008; Long 2012; Panchabhai 2009; Roca Biosca 2011; Xu 2007; Xu 2008; Zhao 2012) stated that allocation was random but provided no further details and were therefore assessed at unclear risk of bias for this domain.

#### Allocation concealment

Allocation concealment was clearly described in 19 of the included studies and they were assessed at low risk of bias for this domain. In 13 studies (Cabov 2010; Caruso 2009; Chen 2008; Feng 2012; Fourrier 2000; Grap 2011; Long 2012; Lorente 2012; McCartt 2010; Panchabhai 2009; Xu 2007; Yao 2011; Zhao 2012) allocation concealment was not described in sufficient detail to determine risk of bias and these studies were assessed at unclear risk of bias. The remaining three studies (Bopp 2006; Tantipong 2008; Xu 2008) were assessed at high risk of bias because the allocation was not concealed from the researchers.

The risk of selection bias based on combined assessment of these two domains was high in three studies (Bopp 2006; Tantipong 2008; Xu 2008), unclear in 15 studies (Cabov 2010; Caruso 2009; Chen 2008; Feng 2012; Fields 2008; Fourrier 2000; Grap 2011; Long 2012; Lorente 2012; McCartt 2010; Panchabhai 2009; Roca Biosca 2011; Xu 2007; Yao 2011; Zhao 2012) and low in the remaining 17 studies.

### Blinding

Ten studies (Bellissimo-Rodrigues 2009; Cabov 2010; DeRiso 1996; Fourrier 2005; Jacomo 2011; Koeman 2006; Kusahara 2012; Ozcaka 2012; Scannapieco 2009; Sebastian 2012) were described as double blind and were assessed at low risk of performance bias. In the remaining 25 studies blinding of the patients and their caregivers to the allocated treatment was not possible because the active and control treatments were so different, and no placebos were used. These studies were assessed at unclear risk of performance bias.

Blinding of outcome assessment was possible in all of the included studies and was described in 22 studies (Bellissimo-Rodrigues 2009; Berry 2011; Cabov 2010; Caruso 2009; DeRiso 1996; Fourrier 2000; Fourrier 2005; Grap 2004; Hu 2009; Jacomo 2011; Koeman 2006; Kusahara 2012; Lorente 2012; Needleman 2011; Ozcaka 2012; Panchabhai 2009; Pobo 2009; Prendergast 2012; Scannapieco 2009; Sebastian 2012; Tantipong 2008; Yao 2011) which were assessed as being at low risk of detection bias. Seven of the included studies (Bopp 2006; Grap 2011; McCartt 2010; Munro 2009; Seguin 2006; Xu 2007; Xu 2008) reported no blinding of outcome assessment and were assessed at high risk of detection bias. In the remaining six studies there was insufficient information provided and the risk of detection bias was assessed as unclear.

### Incomplete outcome data

In the studies included in this review loss of participants during the course of the study is to be expected as these critically ill people leave the intensive care unit either because they recover and no longer require mechanical ventilation, or because they die from their illness. In 20 of the included studies (Bellissimo-Rodrigues 2009; Bopp 2006; Cabov 2010; Caruso 2009; Chen 2008; Feng 2012; Fourrier 2005; Jacomo 2011; Koeman 2006; Kusahara 2012; Long 2012; Lorente 2012; Ozcaka 2012; Pobo 2009; Sebastian 2012; Seguin 2006; Xu 2007; Xu 2008; Yao 2011; Zhao 2012) either all the randomised participants were included in the outcome, or the number of losses/withdrawals and the reasons given were similar in both arms of the study, and these studies were assessed at low risk of attrition bias.

Eleven of the included studies were assessed at high risk of attrition bias because the numbers and reasons for withdrawal/exclusion were different in each arm of the study, or because the number of participants withdrawn or excluded from the outcomes evaluation were high and insufficient information was provided (Berry 2011; Fields 2008; Grap 2004; Grap 2011; Hu 2009; McCartt 2010; Munro 2009; Needleman 2011; Prendergast 2012; Roca Biosca 2011; Scannapieco 2009). In the remaining four studies there was insufficient information available to determine the risk of attrition bias.

### Selective reporting

Twenty-three of the included studies (Bellissimo-Rodrigues 2009; Berry 2011; Cabov 2010; Caruso 2009; DeRiso 1996; Feng 2012; Fourrier 2000; Fourrier 2005; Koeman 2006; Kusahara 2012; Long 2012; Lorente 2012; Needleman 2011; Ozcaka 2012; Panchabhai 2009; Pobo 2009; Prendergast 2012; Scannapieco 2009; Seguin 2006; Xu 2007; Xu 2008; Yao 2011; Zhao 2012) reported the outcomes specified in their methods section in full, or this information was supplied by trial authors, and these studies were assessed at low risk of reporting bias.

Four studies did not report all the outcomes specified in their methods sections (Grap 2004; Grap 2011; McCartt 2010; Roca Biosca 2011), one study reported outcomes as percentages, and the denominators for each arm were unclear (Hu 2009), and one study did not report the number of participants evaluated (Fields 2008). These six trials were assessed at high risk of reporting bias.

The remaining six trials (Bopp 2006; Chen 2008; Jacomo 2011; Munro 2009; Sebastian 2012; Tantipong 2008) were assessed at unclear risk of reporting bias because there was insufficient information reported to make a clear judgement.

### Other potential sources of bias

Four studies were assessed at high risk of other bias. The study by Berry 2011 was stopped early due to withdrawal of one of the investigational products by a regulatory authority, and the study by

Pobo 2009 was stopped after 37% of the planned 400 patients had been recruited because there appeared to be no difference between the study arms in the outcome of VAP. Grap 2011 did not report baseline data for each randomised treatment group but the trial report noted that there was a "statistically significant difference in gender and CPIS score between groups at baseline", and we considered that this difference was likely to have biased the results. In the study by Scannapieco 2009 the imputations used for the missing data were unclear and the pre-study exposure to systemic antibiotics was greater in the control group, so this study was assessed at high risk of other bias.

In nine studies (Chen 2008; Fields 2008; Kusahara 2012; Long 2012; Panchabhai 2009; Roca Biosca 2011; Tantipong 2008; Yao 2011; Zhao 2012) the risk of other bias was assessed as unclear. The reasons for this are as follows. The participants in the treatment group in the study by Chen 2008 received a co-intervention that was not given to the control group, and in both Fields 2008 and Roca Biosca 2011 the study reports contained insufficient information for us to be confident that study methodology was robust. In the study by Kusahara 2012, there was a statistically significant difference in the age of the children in each arm of the study and we are unclear whether this is associated with potential bias. Panchabhai 2009 reported baseline characteristics only for those participants completing the study, Tantipong 2008 included participants treated in different units of the hospital where care and co-interventions are likely to have been different, and in Yao 2011 there is no information as to how the edentulous participants in each arm were treated. Long 2012 and Zhao 2012 reported the criteria for VAP diagnosis as being positive culture of lower respiratory tract secretions, with no other criteria and it is unclear if this would have introduced a bias in these unblinded studies.

The remaining 22 studies were assessed at low risk of other bias.

### Overall risk of bias

Overall just five of the included studies (14%) were assessed at low risk of bias (Bellissimo-Rodrigues 2009; Fourrier 2005; Koeman 2006; Ozcaka 2012; Sebastian 2012) for all domains and 13 studies (37%) were at unclear risk of bias for at least one domain. Nearly half of the included studies (17 studies, 49%) were at high risk of bias in at least one domain (Figure 1; Figure 2).

## Effects of interventions

See: **Summary of findings for the main comparison** Chlorhexidine (mouthrinse or gel) versus placebo/usual care for critically ill patients to prevent ventilator-associated pneumonia; **Summary of findings 2** Toothbrushing (± chlorhexidine) versus no toothbrushing (± chlorhexidine) for critically ill patients to prevent ventilator-associated pneumonia

### Comparison 1: Chlorhexidine versus placebo/usual care (with or without toothbrushing)

Chlorhexidine antiseptic was evaluated in a total of 20 studies included in this review, but only 17 studies could be included in meta-analysis for VAP. One study was a very small pilot study (Bopp 2006, n = 5) and no usable outcome data could be extracted, another study (McCartt 2010) did not report outcome data in a form that could be used in a meta-analysis. The study by Scannapieco 2009 reported data in a graph only and stated that there was no difference between the two chlorhexidine groups and the control group in the outcome of VAP. Available data from these studies are recorded in Additional Table 1.

Five of the 20 studies were assessed at high risk of bias (Bopp 2006; Grap 2004; Grap 2011; McCartt 2010; Munro 2009), four studies were at low risk of bias (Bellissimo-Rodrigues 2009; Fourrier 2005; Koeman 2006; Ozcaka 2012) and the remaining 11 studies were at unclear risk of bias.

These studies have been subgrouped according to whether chlorhexidine was administered as a liquid mouthrinse or a gel, and whether chlorhexidine was used in conjunction with toothbrushing or not.

#### Incidence of VAP

Overall the combined meta-analysis of 17 studies (two at high risk of bias, 11 at unclear risk of bias and four at low risk of bias) showed a reduction in VAP with use of chlorhexidine odds ratio (OR) 0.60, 95% confidence interval (CI) 0.47 to 0.77, P < 0.001, $I^2$ = 21%) (Analysis 1.1). The statistical heterogeneity observed in this estimate is not likely to be important.

Seven studies (with a total of 1037 participants) compared chlorhexidine solution (0.12% or 0.2%) with either placebo (six studies) or 'usual care' (Grap 2011) without toothbrushing. However, six studies report the use of a swab to either clean the mouth prior to chlorhexidine application, or to ensure that the chlorhexidine solution was applied to all oral surfaces. (In the study by Chen 2008 the mode of application is unclear.)

The meta-analysis showed a reduction in VAP in the chlorhexidine group (OR 0.60, 95% CI 0.38 to 0.94, P = 0.03, $I^2$ = 41%) (Analysis 1.1, Subgroup 1.1.1). This equates to a number needed to treat (NNT) of 15 (95% CI 10 to 34).

A further five studies (669 participants) compared chlorhexidine gel (0.2% or 2%) with placebo (no toothbrushing in either group) and the meta-analysis showed a similar reduction in VAP associated with chlorhexidine gel (OR 0.57, 95% CI 0.31 to 1.06, P = 0.08, $I^2$ = 45%) (Analysis 1.1, Subgroup 1.1.2).

Three studies (total 408 participants) compared chlorhexidine solution (2%, 0.12% or 0.2%) with placebo (with toothbrushing in both groups). The meta-analysis showed a reduction in VAP in the chlorhexidine group (OR 0.44, 95% CI 0.23 to 0.85, P = 0.01, $I^2$ = 0%) (Analysis 1.1, Subgroup 1.1.3).

A further study (Kusahara 2012, including 96 children) at unclear risk of bias compared chlorhexidine gel (0.12%) with placebo (with toothbrushing in both groups) and found no difference in the incidence of VAP (Analysis 1.1, Subgroup 1.1.4).

Munro 2009 reported the results from some of the patients randomised into a study with a factorial design. This study showed a reduction in VAP which did not attain statistical significance (P = 0.06) associated with the use of chlorhexidine, where exposure to toothbrushing was equal in both groups (Analysis 1.1, Subgroup 1.1.5).

The pilot study by Bopp 2006 also showed a reduction in VAP associated with chlorhexidine. McCartt 2010 did not report VAP as an outcome, but instead reported mean CPIS scores. While CPIS > 6 may generally be considered to indicate VAP, this study did not dichotomise the outcome data. Mean CPIS score showed no evidence of a difference between chlorhexidine alone, chlorhexidine + toothbrushing and usual care, perhaps because mean CPIS lacks sensitivity as an outcome measure (Additional Table 1).

#### Mortality

The outcome of mortality was reported in 15 studies and overall the meta-analysis showed no evidence of a difference between chlorhexidine and placebo/usual care with minimal heterogeneity (OR 1.10, 95% CI 0.87 to 1.38, P = 0.44, $I^2$ = 2%) (Analysis 1.2).

Likewise there was no evidence of a difference in mortality in all of the subgroups (chlorhexidine mouthrinse with or without toothbrushing).

- Chlorhexidine mouthrinse (no toothbrushing) compared to placebo/usual care (OR 1.16, 95% CI 0.72 to 1.88, P = 0.54, $I^2$ = 36% (Analysis 1.2, Subgroup 1.2.1).
- Chlorhexidine gel (no toothbrushing) compared to placebo/usual care (OR 0.89, 95% CI 0.45 to 1.76, P = 0.73, $I^2$ = 43%) (Analysis 1.2, Subgroup 1.2.2).
- Chlorhexidine mouthrinse plus toothbrushing versus toothbrushing alone (OR 1.09, 95% CI 0.72 to 1.64, P = 0.69, $I^2$ = 0%) (Analysis 1.2, Subgroup 1.2.3).
- The single study (Kusahara 2012) of children receiving chlorhexidine gel + toothbrushing versus usual care (including toothbrushing) also showed no difference in the outcome of mortality (Analysis 1.2, Subgroup 1.2.4).
- Koeman 2006 comparing chlorhexidine gel with placebo showed no difference in mortality (Additional Table 1).

#### Duration of ventilation

From the six studies which reported this outcome there is no evidence of a difference in the duration of ventilation between the groups receiving chlorhexidine solution compared to those receiving placebo/usual care (mean difference (MD) 0.09, 95% CI -0.84 to 1.01 days, P = 0.85, $I^2$ = 24%) (Analysis 1.3).

There was no evidence of a difference in duration of ventilation in any of the subgroups.

#### Duration of ICU stay

Likewise there was no evidence of a difference between the group receiving chlorhexidine rinse solution compared to placebo/usual care in the outcome of duration of ICU stay (six RCTs, MD 0.21 days, 95% CI -1.48 to 1.89, P = 0.81, $I^2$ = 9%) and similarly there was no evidence of a difference in two subgroups (Analysis 1.4, Subgroup 1.4.1; Analysis 1.4, Subgroup 1.4.2) and insufficient evidence to determine whether or not there was a difference in Analysis 1.4, Subgroup 1.4.3.

#### Duration of systemic antibiotic therapy

Two trials (total of 374 participants) reported this outcome and there was insufficient evidence to determine whether or not there is a difference in duration of use of systemic antibiotics between the chlorhexidine and control groups (MD 0.23 days, 95% CI -0.85 to 1.30, P = 0.68, $I^2$ = 50%) with moderate heterogeneity probably due to the differences between the two studies in the mode of chlorhexidine used (Analysis 1.5).

#### Microbial colonisation

There was also insufficient evidence to determine whether there is a difference between chlorhexidine and control groups in the outcome of positive microbiological cultures (three studies, OR 0.69, 95% CI 0.35 to 1.33, P = 0.26, $I^2$ = 70%) (Analysis 1.6). We combined the two chlorhexidine groups in the Grap 2004 study for the meta-analysis and the raw data are recorded in Additional Table 1. Two studies of adults (Cabov 2010; Grap 2004) reported cultures from the mouth, and trachea respectively and the third study (Kusahara 2012) of children, reported oropharyngeal culture results. The clinical differences between these studies may explain some of the heterogeneity in the meta-analysis.

Another study (Berry 2011) where the data could not be incorporated into the meta-analysis showed no difference in positive cultures between the interventions compared (Additional Table 1).

#### Oral health indices: plaque index

Two of the studies in this group (Ozcaka 2012; Scannapieco 2009) reported the outcome of plaque index but only Ozcaka 2012 reported numerical data. Neither study found a difference in plaque indices between the chlorhexidine and control groups (Analysis 1.7, Additional Table 1).

### Adverse effects

Three studies in this group reported adverse effects. Bellissimo-Rodrigues 2009 reported that three patients in the chlorhexidine group and five in the placebo group found the taste unpleasant and Tantipong 2008 found mild reversible irritation of the oral mucosa in 10% of the chlorhexidine patients compared to 1% of the control group patients (Analysis 1.8). Berry 2011 stated that there were no adverse effects in either group.

Adverse effects were not mentioned in the other studies in this group.

The outcomes of caregivers' preferences and cost were not reported.

### Heterogeneity

There is moderate heterogeneity in two of the subgroups (Analysis 1.1, Subgroups 1.1.1 and 1.1.2) which is likely to be due to clinical differences between these studies, due to variability in the frequency, application method, volume and concentration of chlorhexidine solution. In Subgroup 1.1.1, six of the seven studies used a placebo control and the volume of chlorhexidine (either 0.12% or 0.2%) used varied between 10 and 50 ml administered either two, three or four times daily. One study (Grap 2011) used a single application by swab of a very small volume of chlorhexidine pre-operatively. One of the seven studies was on children aged from birth to 14 years (Jacomo 2011) and the others recruited adults. In Subgroup 1.1.2, there is also moderate heterogeneity which may be due to variations in the way the intervention was delivered. Three of the five studies in this subgroup (Cabov 2010; Fourrier 2000; Fourrier 2005) administered 0.2% chlorhexidine gel three times daily following rinsing of the mouth and aspiration of rinse. The other two studies (Koeman 2006; Sebastian 2012) used a gel with higher chlorhexidine concentration (2% and 1% respectively) and applied the gel using a swab.

### Sensitivity analysis

For the primary outcome of VAP we conducted a sensitivity analysis excluding the studies at high risk of bias. The estimate remained very similar (OR 0.61, 95% CI 0.49 to 0.78, P < 0.001, $I^2$ = 29%).

However a meta-analysis of the three studies of children (Jacomo 2011; Kusahara 2012; Sebastian 2012) (342 participants, aged from 3 months to 15 years) provided no evidence that chlorhexidine compared to placebo showed a difference in the outcomes of VAP (OR 1.07, 95% CI 0.65 to 1.77, P = 0.79, $I^2$ = 0%) or mortality (OR 0.73, 95% CI 0.41 to 1.30, P = 0.28, $I^2$ = 0%) (Analyses not shown).

### Publication bias

Each of the subgroups in this comparison contained a small number of studies and therefore it was not appropriate to produce a funnel plot to investigate possible publication bias.

## Comparison 2: Toothbrushing versus no toothbrushing

The eight studies included in this comparison (Bopp 2006; Fields 2008; Lorente 2012; Munro 2009; Needleman 2011; Pobo 2009; Roca Biosca 2011; Yao 2011) all had toothbrushing as part of the intervention, versus no toothbrushing in the control group. Six of these studies were at high risk of bias and two studies (Lorente 2012; Yao 2011) had an unclear risk of bias. Three studies used a powered toothbrush (Pobo 2009; Roca Biosca 2011; Yao 2011 ) and five used a manual toothbrush. One study (Bopp 2006) was a very small pilot study (n = 5) and the data from this study are recorded in Additional Table 1, and the study by Fields 2008 reported no numerical data at all. The study by Roca Biosca 2011 did not report data for each arm of the study and we were not able to obtain these data from the authors. Available data from this study are recorded in Additional Table 1.

### Incidence of VAP

One small study (Yao 2011, 53 participants), at high risk of bias, compared usual care plus the addition of twice daily toothbrushing with a powered toothbrush, to usual care alone, and found a reduction in VAP. The usual care intervention comprised patient's bed being elevated 30 to 45 degrees, hypopharyngeal suctioning, lips moistened with 'toothette' swab and water, then further hypopharyngeal suctioning. A second study with 147 participants, also assessed at high risk of bias (Pobo 2009), compared powered toothbrushing plus usual care including chlorhexidine , with usual care alone and found no difference in the outcome of VAP. The combined estimate from these studies showed no difference in the incidence of VAP (OR 0.35, 95% CI 0.06 to 1.97, P = 0.23, $I^2$ = 81%) (Analysis 2.1, Subgroup 2.1.1) with the heterogeneity likely due to the additional exposure to chlorhexidine in both groups of only one of the studies.

In Lorente 2012 where the intervention group received toothbrushing with a manual toothbrush as well as chlorhexidine, compared to chlorhexidine alone in the control group, there was no evidence of a difference in the incidence of VAP between the intervention and control groups.

A study with a factorial design (Munro 2009) compared toothbrushing with no toothbrushing (equal exposure to chlorhexidine in both arms), and reported no difference in the development of VAP (Analysis 2.1, Subgroup 2.1.3).

Bopp 2006 was a very small pilot study (n = 5) of toothbrushing versus none, and the data are reported in Additional Table 1. There were no numerical outcome data in the study by Fields 2008; the report makes the statement that "the VAP rate dropped to

zero within a week of beginning the every 8 hours toothbrushing regimen in the intervention group." This rate of zero incidence of VAP was reportedly sustained for 6 months. Roca Biosca 2011 recruited 117 participants and reported a summary estimate for the outcome of VAP and found no difference between powered toothbrushing and no toothbrushing (Additional Table 1).
The combined meta-analysis of four studies (Lorente 2012; Munro 2009; Pobo 2009; Yao 2011) shows no evidence of a difference in the incidence of VAP due to toothbrushing (OR 0.69, 95% CI 0.36 to 1.29, P = 0.24 , $I^2$ = 64%) with substantial statistical heterogeneity likely to be explained by the differences in exposure to chlorhexidine between the studies (Analysis 2.1).

#### Mortality

Four studies (Lorente 2012; Munro 2009; Pobo 2009; Yao 2011) evaluated the effect of toothbrushing as an addition to oral care, on the outcome of mortality. The comparisons were slightly different in each trial but the overall meta-analysis found no evidence of a difference between intervention and control groups without heterogeneity (OR 0.85, 95% CI 0.62 to 1.16, P = 0.31, $I^2$ = 0%) (Analysis 2.2).

#### Duration of ventilation

Meta-analysis of two trials (total 583 participants) reported the outcome of mean duration of mechanical ventilation, and showed no difference associated with toothbrushing (MD -0.85 days, 95% CI -2.43 to 0.73 days, P = 0.29, $I^2$ = 0%) (Analysis 2.3).
The data from Bopp 2006 are reported in Additional Table 1.

#### Duration of ICU stay

Meta-analysis of two trials (total 583 participants) which reported the outcome of mean duration of ICU stay found no evidence of a difference between the groups (MD -1.82, 95%CI -3.95 to 0.32, P = 0.10, $I^2$ = 0%, Analysis 2.4). The data from Bopp 2006 are reported in Additional Table 1.

#### Duration of systemic antibiotic therapy

This outcome was not reported by any of the studies in this group.

#### Microbial colonisation

One small study (Needleman 2011, n = 28) reported the number of patients per group with colonisation of plaque by VAP-associated pathogens and found no difference between the intervention and control groups (Analysis 2.5).

#### Oral health indices: plaque score

Two studies (Needleman 2011; Yao 2011) also reported the outcome of plaque score in each group after 5 days or 7-8 days respectively. Each study used a different scale so these data were combined for meta-analysis using standardised mean difference (SMD) and showed evidence of reduced plaque in the toothbrushing group (SMD -1.20, 95% CI -1.70 to -0.70, P < 0.001, $I^2$ = 0%) (Analysis 2.6).
Roca Biosca 2011 reported plaque scores, without any estimates of variance. The trial report also stated that there was no difference between the groups (Additional Table 1).

#### Adverse effects

Pobo 2009 reported that there were no adverse effects reported in either arm of the study and none of the other studies in this comparison mentioned adverse effects.
The outcomes of caregivers' preferences and cost were not reported.

### Comparison 3: Powered toothbrushing versus manual toothbrushing

One small study of 78 participants (Prendergast 2012), assessed at high risk of bias, compared the use of a powered toothbrush as a component of 'comprehensive oral care' with a control group receiving manual toothbrushing and standard oral care.
In this study there was no difference between the intervention and control groups with regard to the outcomes of incidence of VAP, mortality or mean duration of ventilation or ICU stay (Analysis 3.1; Analysis 3.2; Analysis 3.3; Analysis 3.4). There were no adverse effects mentioned in this study. The outcomes of oral health indices, microbiological cultures, systemic antibiotic therapy, caregivers' preferences for oral hygiene care or cost were not reported in the study.

### Comparison 4: Other oral care solutions

Nine studies (Berry 2011; Caruso 2009; Feng 2012; Hu 2009; Long 2012; Seguin 2006; Xu 2007; Xu 2008; Zhao 2012) with a combined total of 1457 participants randomised to treatments, and all at high risk of bias, evaluated the effects of other solutions with a potential antiseptic effect on the outcomes of VAP, mortality and duration of ventilation.

#### Incidence of VAP

Two studies (Feng 2012; Seguin 2006) compared povidone iodine rinse with a saline rinse and showed evidence of a reduction in VAP (OR 0.35, 95% CI 0.19 to 0.65, P < 0.001, $I^2$ = 53%).

The heterogeneity in this estimate could be due to the additional intervention of toothbrushing in both groups in Feng 2012.

Seguin 2006 also compared povidone iodine rinse with usual care (suction alone with no rinse) and found a reduction in VAP. The result of this study has not been replicated so should be interpreted with caution.

Long 2012 compared povidone iodine rinse plus toothbrushing with povidone iodine rinse alone and found a reduction in VAP. The result of this study has not been replicated so should be interpreted with caution.

Two small studies with a total of 83 participants (Xu 2007; Xu 2008), both at high risk of bias, which compared a saline rinse with a saline soaked swab found no difference in incidence of VAP (OR 0.65, 95% CI 0.37 to 1.14, P = 0.13, $I^2$ = 41%).

The studies by Hu 2009 and Xu 2007, both at high risk of bias, compared both saline rinse plus swab, with a saline soaked swab alone (usual care) and found some very weak evidence (from total of 40 participants) that the combined rinse plus swab reduced the incidence of VAP (OR 0.30, 95% CI 0.14 to 0.63, P = 0.002, $I^2$ = 0%).

Two studies (Caruso 2009; Seguin 2006), both at high risk of bias, compared a saline rinse with usual care (no rinse) and found a reduction in VAP (OR 0.50, 95% CI 0.29 to 0.88, P = 0.02, $I^2$ = 39%). While this result should be interpreted cautiously due to the high risk of bias, there appears to be some evidence that the use of a saline rinse prior to aspiration of secretions was associated with reduction of ventilator-associated pneumonia.

A single study (Berry 2011), at high risk of bias, compared bicarbonate rinse plus toothbrushing with a water rinse plus toothbrushing and found no difference in the incidence of VAP.

Another single study (Zhao 2012) compared triclosan rinse with saline rinse and found no difference in the outcome of VAP over the duration of the study (Analysis 4.1, Subgroup 4.1.8). The results of this study have not been replicated so should be interpreted with caution.

A single 3-arm study compared povidone iodine, furacilin and usual care (Feng 2012) and found both antiseptics combined with toothbrushing were more effective than usual care (Analysis 4.1, Subgroup 4.1.1 and Analysis 4.1, Subgroup 4.1.10) with little difference between the two antiseptic solutions (Analysis 4.1, Subgroup 4.1.9).

#### Mortality

There was only a single study at high risk of bias in each of five subgroups reporting mortality (Analysis 4.2, Subgroups 4.2.1, 4.2.2, 4.2.3, 4.2.4 and 4.2.6), providing insufficient evidence to determine whether or not there is a difference in mortality. Two studies comparing saline rinse with usual care with no rinse (Caruso 2009; Seguin 2006) showed no difference in mortality (OR 1.20, 95% CI 0.77 to 1.87, P = 0.43, $I^2$ = 0%) (Analysis 4.2, Subgroup 4.2.5). There is no evidence of a difference in mortality for any of the comparisons reported.

#### Duration of ventilation and duration of ICU stay

These outcomes were evaluated by single studies within each subgroup, providing insufficient evidence to determine whether or not there is a difference between the various interventions and controls.

Saline rinse versus usual care (with no rinse) was evaluated by two studies (Caruso 2009; Seguin 2006) and there was no evidence of a difference in either duration of ventilation (MD -0.40 days, 95% CI -2.55 to 1.75, P = 0.72, $I^2$ = 0%) or duration of ICU stay (MD -1.17 days, 95% CI -3.95 to 1.60, P = 0.41, $I^2$ = 32%).

#### Microbial colonisation

One study (Feng 2012) reported a reduction in positive cultures in the povidone iodine group but the results of this study have not been replicated so should be interpreted with caution.

None of these nine studies reported the outcomes of duration of systemic antibiotic therapy, adverse effects, caregivers' preferences for oral hygiene care or cost.

## ADDITIONAL SUMMARY OF FINDINGS [*Explanation*]

**Toothbrushing (± chlorhexidine) versus no toothbrushing (± chlorhexidine) for critically ill patients to prevent ventilator-associated pneumonia (VAP)**

**Patient or population:** Critically ill patients to prevent ventilator-associated pneumonia
**Settings:** Intensive care units (ICUs)
**Intervention:** Toothbrushing (± chlorhexidine)
**Comparison:** No toothbrushing (± chlorhexidine)

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | No toothbrushing | Toothbrushing | | | | |
| **Incidence of VAP**<br>Follow-up: mean 1 month | **245 per 1000** [1] | **183 per 1000**<br>(105 to 295) | **OR 0.69**<br>(0.36 to 1.29) | 828<br>(4 studies)[2] | ⊕⊕◯◯<br>**low**[3,4] | [5] |
| **Mortality**<br>Follow-up: mean 1 month | **277 per 1000** [1] | **245 per 1000**<br>(192 to 307) | **OR 0.85**<br>(0.62 to 1.16) | 828<br>(4 studies) | ⊕⊕⊕◯<br>**moderate**[2] | |
| **Duration of ventilation**<br>Follow-up: mean 1 month | The mean duration of ventilation in the control groups ranged from 9.8 to 10 days | The mean duration of ventilation in the intervention groups was<br>**0.85 lower**<br>(2.43 lower to 0.73 higher) | | 583<br>(2 studies) | ⊕⊕⊕◯<br>**moderate** [6] | |
| **Duration of ICU stay**<br>Follow-up: mean 1 month | The mean duration of ICU stay in the control groups ranged from 13 to 15 days | The mean duration of ICU stay in the intervention groups was<br>**1.82 lower**<br>(3.95 lower to 0.32 higher) | | 583<br>(2 studies) | ⊕⊕⊕◯<br>**moderate**[6] | |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)
**CI:** confidence interval; **OR:** odds ratio

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
**Very low quality:** We are very uncertain about the estimate

[1] Assumed risk is based on the outcomes in the control groups of the included studies
[2] 3 studies compared toothbrushing + chlorhexidine with chlorhexidine alone and the fourth study compared toothbrushing with no toothbrushing (no chlorhexidine in either group)
[3]2 studies at high risk of bias and 2 studies at unclear risk of bias
[4]Substantial heterogeneity ($I^2 = 64\%$). Meta-analysis of 3 studies with chlorhexidine in both groups shows no heterogeneity ($I^2 = 0\%$)
[5]A fifth study, which randomised 117 participants showed no difference between toothbrushing + chlorhexidine and chlorhexidine alone (OR 0.78, 95% CI 0.36 to 1.68, P = 0.56). This study was at high risk of bias, and there was insufficient information to include data from this study in the meta-analysis
[6] 1 study at high risk of bias and 1 study at unclear risk of bias

# DISCUSSION

## Summary of main results

Thirty-five randomised controlled trials are included in this review and these studies evaluate four main groups of interventions, in the oral hygiene care of critically ill patients receiving mechanical ventilation in intensive care units.

- Chlorhexidine antiseptic versus placebo/usual care (with or without toothbrushing)

There is moderate quality evidence from 17 RCTs that the use of chlorhexidine (either as a mouthrinse or a gel) reduces the odds of developing VAP (OR 0.60, 95% CI 0.47 to 0.77, P < 0.001, $I^2$ = 21%) (Summary of findings for the main comparison), with an NNT of 15 (95% CI 10 to 34). There is no evidence that use of chlorhexidine is associated with a difference in mortality (15 studies), duration of mechanical ventilation (six studies) or duration of ICU stay (six studies) (moderate quality evidence). There is insufficient evidence to determine the effect of chlorhexidine on the other secondary outcomes of this review.
From the three studies of children there was no evidence of a difference between chlorhexidine and placebo for the outcomes of VAP and mortality (moderate quality evidence).

- Toothbrushing versus no toothbrushing (with or without chlorhexidine)

Based on four RCTs (low quality evidence) we found no evidence of a difference between oral care with chlorhexidine plus toothbrushing and oral care with chlorhexidine alone with regard to the outcome of VAP (OR 0.69, 95% CI 0.36 to 1.29, P = 0.24 , $I^2$ = 64%). There is no evidence of a difference between toothbrushing or no toothbrushing for the outcomes of mortality (OR 0.85, 95% CI 0.62 to 1.16, P = 0.31, $I^2$ = 0%), duration of ventilation (MD -0.85 days, 95% CI -2.43 to 0.73, P = 0.29, $I^2$ = 0%) or duration of ICU stay (MD -1.82 days, 95% CI -3.95 to 0.32 days, P = 0.10, $I^2$ = 0%) (moderate quality evidence).

- Oral care with powered toothbrush versus oral care with manual toothbrush

From the single study in this comparison there is insufficient evidence to determine the effects of powered versus manual toothbrushing on the outcomes of VAP, mortality, duration of mechanical ventilation or duration of ICU stay.

- Oral care with other solutions

The studies in this comparison were at high overall risk of bias and made different comparisons. There is some weak evidence that povidone iodine rinse is more effective than saline in reducing VAP (OR 0.35, 95% CI 0.19 to 0.65, P = 0.0009, $I^2$ = 53%) (two studies, 206 participants, high risk of bias). We found no evidence of a difference between a saline swab and a saline rinse with regard to the reduction of VAP (OR 0.65, 95% CI 0.37 to 1.14, P = 0.13, $I^2$ = 41%) (two studies, 83 participants, high risk of bias), and very weak evidence that use of both a saline swab and a saline rinse may be more effective than a saline swab alone (OR 0.30, 95% CI 0.14 to 0.63, P = 0.002, $I^2$ = 0%) (two studies, 40 participants, high risk of bias). There is insufficient evidence to clearly determine the effectiveness of any of the oral care solutions for any of the outcomes evaluated.

## Overall completeness and applicability of evidence

In this review we have included studies which compared active oral hygiene care interventions with either placebo or usual care. We recognise that the use of a placebo is a better control comparison in research studies because it enables the masking of caregivers as to which patients are in the active or control group, thus eliminating some possible performance bias. However, we chose to include pragmatic studies where 'usual care' was the control comparator, despite recognising that in many instances 'usual care' was not specified and may have varied between patients and between individual caregivers. Likewise in some of the included studies, the precise details of what was involved in the oral hygiene care intervention were poorly described making it difficult to determine the similarity in oral hygiene care practices between studies.
We also recognise that participation in a research study is likely to have a positive effect on the performance of 'usual care' improving both the quality of care and compliance with routine practice - a Hawthorne effect (McCarney 2007). The combination of a 'usual care' control group, the absence of caregiver blinding in most cases, and the Hawthorne effect of being part of a study may have reduced the observed difference in effect between the active and control interventions in these studies. Two of the studies noted that care was recorded in patient notes but none of the studies included in this review reported compliance with oral hygiene care protocols.
Another area of variability between the studies (and possibly also between studies and usual practice) is the diagnosis of VAP, which is at least partly subjective and may be made based on variable diagnostic criteria. Most studies (26/35) stated the criteria used to diagnose VAP, and the two most common were some version of the clinical pulmonary infection score (CPIS) based on Pugin's criteria (Cook 1998; Pugin 1991) (16 studies) and Centers for Disease Control (CDC) criteria as described in Horan 2008 (six studies). Four studies conducted in China (Chen 2008; Feng 2012; Xu 2007; Xu 2008) used Chinese Society of Respiratory Diseases (CSRD) criteria for diagnosis of VAP. In two studies some of the study participants had pneumonia at baseline (Munro 2009; Sebastian 2012).
Although this review found evidence that the use of chlorhexidine as part of oral care reduces the incidence of VAP, there was no evidence of a reduction in mortality. There is some debate in the literature about the attributable mortality of VAP, but a recent survival analysis of nearly 4500 patients found that ICU mortality

attributable to VAP was about 1% on day 30 (Bekaert 2011), which might explain our findings.

This review has not found evidence that oral care including both toothbrushing and chlorhexidine is different from oral care with chlorhexidine alone in reducing VAP. Only one of the trials of toothbrushing which reported the outcome of VAP also reported plaque levels as an indicator of the effectiveness of the toothbrushing carried out in this trial (Yao 2011). This small trial (53 participants), which was assessed at high risk of bias, did not use chlorhexidine in either group, and found a reduction in both plaque and VAP in the powered toothbrushing group compared to the no toothbrushing group. Three other trials of toothbrushing in our meta-analysis (Lorente 2012 (manual), Munro 2009 (manual), Pobo 2009 (powered toothbrush)), with a combined total of 775 participants included exposure to chlorhexidine in both intervention and control groups. Assessed at unclear, high and high risk of bias respectively, meta-analysis of these three trials showed no evidence of a difference in the outcome of VAP. A further study (Roca Biosca 2011), included in this review and also at high risk of bias, was not able to be included in the meta-analysis, but also found no difference between oral care with chlorhexidine and toothbrushing and oral care with chlorhexidine alone. All five of these studies describe the toothbrushing intervention in detail, and note that nurses delivering the intervention received specific training. While the presence of ventilator tubes in the mouths of trial participants makes effective toothbrushing difficult, despite this, it seems likely that the toothbrushing intervention was carried out thoroughly within these trials.

Earlier cohort studies noted that patients in ICU who developed VAP were likely to have increased length of stay in the ICU (Apostolopoulou 2003; Cook 1998). However, this Cochrane review has not evaluated duration of ICU stay in patients who develop VAP. The studies in this review report mean length of ICU stay and the standard deviation for each arm of the study. These are combined in meta-analysis based on an assumption the duration of ICU stay in each arm of each trial follows an approximately normal distribution. In fact the distribution of duration of stay in ICU is likely to be skewed and the means are likely to be a poor indicator of the effect of oral hygiene care on duration of ICU stay.

This systematic review has not looked at the outcome of cost of interventions. However, it is likely that the additional cost of using an antiseptic mouthrinse or gel is low in comparison with the cost of the antibiotics used to treat VAP. One study (Jacomo 2011) reported the cost of the chlorhexidine gluconate solution per patient was USD 3.15. Reducing the incidence of VAP using relatively inexpensive additions to usual care is likely to be a cost effective, as well as avoiding additional morbidity for the patient.

It is interesting that only mild adverse reactions of chlorhexidine were reported in three of the 20 studies which evaluated chlorhexidine. In over 2000 participants included in these studies there was no report of hypersensitivity to chlorhexidine.

Three of the included studies evaluated chlorhexidine in children aged from a few months to 15 years. These studies found no evidence of a difference in VAP associated with including chlorhexidine in oral hygiene care. The reason(s) for this are unclear.

## Quality of the evidence

All the included studies were prospective, randomised controlled trials but only five of the included studies (14%) were assessed at low risk of bias (Bellissimo-Rodrigues 2009; Fourrier 2005; Koeman 2006; Ozcaka 2012; Sebastian 2012) for all domains, 13 studies (37%) were at unclear risk of bias for at least one domain. Nearly half of the included studies (17 studies, 49%) were at high risk of bias in at least one domain.

## Potential biases in the review process

In order to reduce the risk of publication bias we conducted a broad search, for both published and unpublished studies, and there were no restrictions on language. We searched the reference lists of included studies and contacted many of the authors of the included studies in order to obtain information that was not included in the published reports. We also searched the reference lists of other published reviews of oral hygiene care for critically ill patients.

We have made a number of changes to the methods of this review since the publication of the protocol (see Differences between protocol and review). Some of these changes were clarifications, and some were to take account of other Cochrane reviews published or in preparation, to avoid unnecessary duplication of effort. We acknowledge that post hoc changes to the review methods may introduce a risk of bias into this review.

## Agreements and disagreements with other studies or reviews

A recent meta-analysis by Pineda 2006 found that the use of chlorhexidine for oral decontamination did not reduce the incidence of nosocomial pneumonia. However this meta-analysis included only four studies and the outcome was nosocomial pneumonia rather than VAP. A recent review by Labeau 2011 included 14 studies of either chlorhexidine or povidone iodine antiseptics and found that the use of antiseptics as part of oral hygiene care reduced the incidence of VAP by approximately one third. Our review confirmed these findings.

Two published meta-analyses (Alhazzani 2013; Gu 2012) of toothbrushing to reduce VAP included four trials and found no evidence of a difference in incidence of VAP, again possibly due to low statistical power. Our review has similar conclusions.

## AUTHORS' CONCLUSIONS

### Implications for practice

Effective oral hygiene care is important for ventilated patients in intensive care to reduce ventilator-associated pneumonia. There is evidence from this review that oral hygiene care incorporating chlorhexidine mouthrinse or gel, is effective in reducing the development of ventilator-associated pneumonia in adult patients in intensive care. The definition of oral hygiene care varied among the studies included in this review but common elements include cleaning of the teeth and gums with a swab or gauze, removing secretions using suction and rinsing the mouth.

### Implications for research

Although the included studies provided some evidence of the benefits of oral hygiene care for critically ill patients to prevent ventilator-associated pneumonia, incomplete reporting of studies is a major limitation. More consistent use of the CONSORT statement for reporting of randomised controlled clinical trials would increase the value of research.

1. Detailed reporting of methods, such as generation of allocation sequence, allocation concealment, and numbers and reasons for withdrawals and exclusions.

2. Use of a placebo where possible to enable blinding.

3. Full reporting of methods used to diagnose ventilator-associated pneumonia.

4. Reporting of adverse effects of interventions.

Further trials of oral hygiene care (including use of manual or powered toothbrushes, or swabs) should report both measures of effectiveness of plaque removal and prevention of ventilator-associated pneumonia.

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**Whittaker 1996**
Whittaker CJ, Lier CM, Kolenbrander PE. Mechanisms of adhesion by oral bacteria. *Annual Review of Microbiology* 1996;**50**:513–52.

**Zanatta 2011**
Zanatta FB, Bergoli AD, Werle SB, Antoniazzi RP. Biofilm removal and gingival abrasion with medium and soft toothbrushes. *Oral Health and Preventive Dentistry* 2011;**9** (2):177–83.

* *Indicates the major publication for the study*

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies *[ordered by study ID]*

**Bellissimo-Rodrigues 2009**

| | |
|---|---|
| Methods | Study design: RCT, 2 parallel groups<br>Location: Sao Paulo, Brazil<br>Number of centres: 1<br>Study period: March 2006 to February 2008<br>Funding source: Not stated |
| Participants | Setting: ICU in tertiary care hospital<br>Inclusion criteria: All patients admitted to ICU with expected stay > 48 hours. Not all participants received mechanical ventilation<br>Exclusion criteria: Previous chlorhexidine sensitivity, pregnancy, formal indication for chlorhexidine use, prescription of another oral topical medication<br>Number randomised: 200 (only 133 on ventilators)<br>Number evaluated: 194<br>Baseline characteristics:<br>-Intervention group: Age: median 62.5 (17-89) M/F: 47/51; APACHEII Score: median 17 (5-35)<br>-Control group: Age: median 54.0 (15-85) M/F: 51/45; APACHEII Score: median 19 (5-41) |
| Interventions | **Comparison: 0.12% chlorhexidine solution versus placebo**<br>Experimental group (n = 64 on vent): 0.12% chlorhexidine solution applied orally 3 times daily. Oral hygiene was conducted by nurses specially trained in the protocol. 3 times daily after mechanical cleaning of the mouth by a nurse, 15 ml of study solution was applied and attempts made to distribute solution over all oral surfaces<br>Control group (n = 69 on vent): The same protocol was conducted with the placebo solution, which was identical in colour consistency smell and taste |
| Outcomes | 1. Respiratory tract infections (VAP for those on ventilators)<br>2. Respiratory tract infection-free survival time<br>3. Time from ICU admission to first RTI<br>4. Duration of mechanical ventilation<br>5. Length of ICU stay<br>6. Total mortality<br>7. Mortality due to RTI<br>8. Antibiotic use<br>9. Microbiological culture of endotracheal secretions<br>10. Adverse effects |
| Notes | Sample size calculation: "to have sufficient power to detect a 69% difference in incidence of VAP with $\alpha$ = 5% and $\beta$ = 20% it was estimated that 96 patients per group were required"<br>Only 133/194 of patients evaluated received mechanical ventilation<br>Email sent 3 September 2012. Reply received |

**Bellissimo-Rodrigues 2009** (*Continued*)

| *Risk of bias* | | |
|---|---|---|
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | "randomised" Method of sequence generation not described but undertaken by pharmacy |
| Allocation concealment (selection bias) | Low risk | "only the pharmacist knew which code numbers corresponded to which type of solution" |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Double blind |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Double blind |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 6/200 patients were excluded from the analysis. 1 control patient needed to receive chlorhexidine treatment, and further 3 in control group and 2 in experimental group were excluded due to protocol violation. Unlikely to have introduced a bias |
| Selective reporting (reporting bias) | Low risk | All planned outcomes reported |
| Other bias | Low risk | No other sources of bias identified |

**Berry 2011**

| | |
|---|---|
| Methods | Study design: Feasibility study - single blind parallel group RCT with 3 groups<br>Location: Australia<br>Number of centres: 1<br>Study period:<br>Funding source: Hospital |
| Participants | Setting: A 20-bed adult intensive care unit in a university hospital<br>Inclusion criteria: All intubated patients admitted to the unit were considered for inclusion in the study provided they met the following criteria: able to be randomised within 12 hours of intubation, aged over 15 years and next of kin able to give informed consent<br>Exclusion criteria: Patients were ineligible for study participation if they: required specific oral hygiene procedures in relation to maxillofacial trauma or dental trauma/surgery; had been in the ICU previously during the current period of hospitalisation; received irradiation or chemotherapy on admission to the ICU or in the preceding 6 weeks; or suffered an autoimmune disease. Informed consent was obtained for all subjects and |

| | |
|---|---|
| | agreement to participate could be withdrawn at any time<br>Number randomised: 225 (71, 76, 78 in Groups 1, 2, 3)<br>Number evaluated: 109 (33, 33, 43 in Groups 1, 2, 3)<br>Group 1 (chlorhexidine 0.2% aqueous) group: Age: 58.2±19.4; M/F: 35/36; APACHEII Score: 22.8±7.8<br>Group 2 (sodium bicarbonate mouthwash rinsed 2 hourly): Age: 60.4±17.5; M/F: 42/24; APACHEII Score: 22.0±7.5<br>Group 3 (sterile water rinsed 2 hourly): Age: 59.1±18.1; M/F: 44/34; APACHEII Score: 21.6±7.8 |
| Interventions | **Comparison: Chlorhexidine 0.2% versus water versus sodium bicarbonate**<br>Group 1: Twice daily irrigation with chlorhexidine 0.2% aqueous oral rinse with 2 hourly irrigation with sterile water<br>Group 2: Sodium bicarbonate mouthwash rinsed 2 hourly<br>Group 3: sterile water rinsed 2 hourly (used as the control in this review)<br>"All treatment options included a comprehensive cleaning of the mouth using a soft, pediatric toothbrush 3 times a day" |
| Outcomes | 3 outcome variables were reported:<br>1. Microbial colonisation of dental plaque (or gums in edentulous patients)<br>2. Incidence of VAP<br>3. Adverse events |
| Notes | Sample size calculation: Feasibility study to inform sample size calculation for main study |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "...randomisation into one of three groups according to a balanced randomisation table prepared by biostatistician" |
| Allocation concealment (selection bias) | Low risk | Study packs were identical in outward appearance and allocation remained blinded until study pack opened by attending nurse |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Participants: Blinding not possible, but non-blinding of carers may have introduced a risk of bias |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Microbiologist and radiologists who assessed outcomes were blinded to allocated treatment |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 102/225 participants evaluated. High rate of attrition and reasons varied in each group. Death rate higher in Group B, breach of inclusion criteria more likely in |

**Berry 2011** (*Continued*)

| | | |
|---|---|---|
| | | Groups B &C |
| Selective reporting (reporting bias) | Low risk | Planned outcomes reported |
| Other bias | High risk | Study stopped early due to withdrawal of investigational product by regulator |

**Bopp 2006**

| | |
|---|---|
| Methods | Study design: Pilot study, 2-arm RCT<br>Location: USA<br>Number of centres: 1<br>Study period: February to August 2002<br>Funding source: Grant from American Dental Hygienists' Association's Institute for Oral Health |
| Participants | Setting: Critical care unit<br>Inclusion criteria: Orally and nasally intubated patients entering critical care unit<br>Exclusion criteria: Taking metronidazole, history of allergy to chlorhexidine, sensitive to alcohol, risk for endocarditis, history of other serious illness (specified), those with pneumonia<br>Number randomised: 5<br>Number evaluated: 5<br>Baseline characteristics:<br>-Intervention group: Age: 40, range 28-52; M/F: 0/2<br>-Control group: Age: 73.7, range 62-81; M/F: 2/1 |
| Interventions | **Comparison: 0.12% chlorhexidine + suction toothbrush versus suction swab + hydrogen peroxide**<br>Experimental group (n = 2): Twice daily oral hygiene care with 0.12% chlorhexidine gluconate during intubation period plus oral cleaning with PlaqVac suction toothbrush<br>Control group (n = 3): Standard oral care 6 times daily using a suctioning soft foam swab and half strength hydrogen peroxide, plus oral lubricant |
| Outcomes | Microbial colonisation VAP, mortality |
| Notes | Sample size calculation: This was a pilot study. Data were not used in meta-analysis on advice of statistician<br>Email sent to contact author 14 November 2012, reply received 19 November 2012 |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "...randomly assigned to either control or experimental treatment by the flip of a coin" |

**Bopp 2006** (*Continued*)

| | | |
|---|---|---|
| Allocation concealment (selection bias) | High risk | Coin toss was undertaken by researcher. No allocation concealment |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Blinding not possible. Reply from contact author "they were not blinded" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Reply from contact author "they were not blinded" |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | All randomised patients included in outcome evaluation |
| Selective reporting (reporting bias) | Unclear risk | VAP planned and reported in this pilot study. Microbial culture data not reported per person, and mortality is also reported |
| Other bias | Low risk | No other sources of bias detected |

**Cabov 2010**

| | |
|---|---|
| Methods | Study design: 2-parallel arm RCT<br>Location: Croatia<br>Number of centres: 1<br>Study period: March to December 2008<br>Funding source: Supported by Croatian Ministry of Science Education and Sports Grant number 065-1080057-0429 |
| Participants | Setting: Surgical ICU in university hospital<br>Inclusion criteria: Aged > 18 years, medical condition suggesting hospitalisation in ICU > 3 days, eventual requirement for mechanical ventilation by oro or nasotracheal ventilation<br>Exclusion criteria:<br>Number randomised: 60. 40 of the 60 participants (17 and 23 in each group) were on mechanical ventilation<br>Number evaluated: 60<br>Baseline characteristics:<br>-Intervention group: Age: 57±16; M/F: 19/11<br>-Control group: Age: 52±19; M/F: 20/10 |
| Interventions | **Comparison: Chlorhexidine gel versus placebo**<br>Experimental group (n = 17): 3 times daily, following standard oral care comprising rinsing mouth with bicarbonate isotonic serum, followed by gently oropharyngeal sterile aspiration, patients received application of 0.2% chlorhexidine gel applied by nurses to dental gingival and oral surfaces using a sterile gloved finger<br>Control group (n = 23): Standard oral care, 3 times daily as above followed by administration of placebo gel<br>In both groups gel was left in place and oral cavity was not rinsed |

**Cabov 2010** (*Continued*)

| | | |
|---|---|---|
| Outcomes | Simplified acute physiological score (SAPS), dental status, dental plaque, plaque culture, nosocomial infections, mortality | |
| Notes | Sample size calculation: Not reported | |
| ***Risk of bias*** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | "...randomized into two groups using a computer-generated balanced randomization table" |
| Allocation concealment (selection bias) | Unclear risk | Unclear who conducted the allocation and whether it was concealed from the investigators |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Double blind |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Double blind |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | All randomised participants included in outcome evaluations |
| Selective reporting (reporting bias) | Low risk | All planned outcomes reported |
| Other bias | Low risk | No other sources of bias identified |

**Caruso 2009**

| | |
|---|---|
| Methods | Study design: 2-arm RCT<br>Location: Brazil<br>Number of centres: 1<br>Study period: August 2001 to December 2004<br>Funding source: Not stated |
| Participants | Setting: Closed medical surgical ICU unit in oncologic hospital<br>Inclusion criteria: Patients aged > 18 years expected to need mechanical ventilation for > 72 hours through orotracheal or tracheotomy tube<br>Exclusion criteria: Previous mechanical ventilation within past month, mechanical ventilation for > 6 hours prior to study enrolment, contraindication to bronchoscopy and expected to die or stop treatment within 48 hours<br>Number randomised: 262<br>Number evaluated: 262 |

**Caruso 2009** (*Continued*)

| | |
|---|---|
| | Baseline characteristics:<br>-Intervention group: Age: 65±14 years; M/F: 66/64<br>-Control group: Age: 63±6 years; M/F: 70/62 |
| Interventions | **Comparison: Saline rinse versus usual care**<br>Experimental group (n = 130): Instillation of 8 ml of isotonic saline prior to tracheal suctioning, which was conducted by respiratory therapists<br>Control group (n = 132): Tracheal suction alone with no saline instillation<br>Aspirations were carried out when 1 of the following occurred: visible airway secretion into endotracheal tube, discomfort or patient asynchrony, noisy breathing, increased peak expiratory pressures, or decreased tidal volume during ventilation attributed to airway secretion |
| Outcomes | 1. Incidence of VAP<br>2. Duration of ventilation in ICU<br>3. Length of stay in ICU<br>4. ICU mortality<br>5. Tracheal colonisation<br>6. Suctions per day, chest radiographs |
| Notes | Sample size calculation: Estimated that 130 patients per group required to give 80% power with alpha 5% to detect a decrease in VAP from 30% to 15% |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | "randomised" No details of method of sequence generation provided in report |
| Allocation concealment (selection bias) | Unclear risk | Not described |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Attending physicians and nurses blinded to study group. Intervention carried out by respiratory therapists available on ICU 24/7 |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Outcome assessment conducted by physicians and nurses blinded to allocated treatment |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | All randomised patients included in outcome evaluation |
| Selective reporting (reporting bias) | Low risk | All planned outcomes reported in full |
| Other bias | Low risk | No other sources of bias identified |

**Chen 2008**

| | |
|---|---|
| Methods | Study design: A single centre RCT with 2 parallel groups<br>Location: China<br>Number of centres: 1 surgical ICU in provincial hospital<br>Study period: Not stated<br>Funding source: External |
| Participants | Inclusion criteria: Admission into the ICU, orally intubated, receiving mechanical ventilation $\geq$ 7 days, without oral and lung disease<br>Exclusion criteria: Using hormone therapy, with diabetes<br>Number randomised: 120<br>Number evaluated: 120<br>Intervention group: n = 60; mean age: 42.0±9.0; M/F: 39/21<br>Control group: n = 60; mean age: 40.0±8.0; M/F: 45/15<br>Baseline characteristics were comparable |
| Interventions | **Comparison: Oral care + chlorhexidine rinse versus saline rinse**<br>Intervention group: Oral cavity irrigated with 50 ml GSE rinse (chlorhexidine + extracts of grapefruit + FE enzyme) then aspirated off, 4 times a day, and routine oral nursing care was given once a day after the first irrigation<br>Control group: Oral irrigation with 50 ml saline, 4 times a day, without the combination of routine oral care |
| Outcomes | 3 outcome variables were reported:<br>1. Incidence of VAP after 7 days of mechanical ventilation<br>2. Incidence of oral inflammation (ulceration and herpes)<br>3. Change in bacteria colonisation: the throat swab cultures at baseline and after treatment |
| Notes | GSE rinse: We are advised by reviewers from China that GSE rinse should be treated as chlorhexidine + 2 potentially active other antiseptics<br>Diagnosis of VAP was according to Chinese Society of Respiratory Diseases criteria<br>Information translated from Chinese paper by Shi Zongdao and colleagues |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Patients were randomised into different groups according to a randomised number table |
| Allocation concealment (selection bias) | Unclear risk | Not mentioned |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Blinding not described and not possible. Difference between intervention and control means carers would be aware of who was in each group |
| Blinding of outcome assessment (detection bias) | Unclear risk | Blinding not described |

**Chen 2008** (*Continued*)

| | | |
|---|---|---|
| All outcomes | | |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | No withdrawals |
| Selective reporting (reporting bias) | Unclear risk | Insufficient information on throat swab culture result (baseline and after treatment) |
| Other bias | Unclear risk | The treatment group received co-intervention of routine oral nursing care once daily, but this was not done in the control group |

**DeRiso 1996**

| | |
|---|---|
| Methods | Study design: Parallel group RCT<br>Location: Indiana USA<br>Number of centres: 1<br>Study period: Not stated<br>Funding source: The study was supported by a grant from the August Tomusk Foundation |
| Participants | Setting: Surgical ICU for post-operative cardiac surgery<br>Inclusion criteria: Patients undergoing cardiac surgery which required cardiopulmonary bypass<br>Exclusion criteria: Intra-operative death, pre-operative infection or intubation, pregnancy, heart and lung transplant recipients, known hypersensitivity to chlorhexidine<br>Number randomised: Unclear<br>Number evaluated: 353 (173 in chlorhexidine group and 180 in control)<br>Baseline characteristics:<br>-Intervention group: Age: 64.1±0.86; M/F: 119/54<br>-Control group: Age: 63.5±0.84; M/F: 123/57 |
| Interventions | **Comparison: Chlorhexidine oral rinse versus placebo**<br>Experimental group: 0.5 fl ounce (approx 15 ml) of 0.12% chlorhexidine (+ 11.6% ethanol (Proctor & Gamble)) mouthrinse used as oropharyngeal rinse and "rigorously applied" to buccal, pharyngeal, gingival tongue and tooth surfaces for 30 seconds twice daily<br>Control group: Placebo mouthrinse identical in appearance containing base solution and 3.2% ethanol (1/3 of concentration of active solution)<br>All patients also received the standard oral care of the ICU (systemic antibiotics, pressor agents and nutritional support as deemed necessary |
| Outcomes | 5 outcome variables were reported:<br>1. Nosocomial infection rates (upper & lower RTI, UTI, fungemias, line sepsis, wound & blood infection, other infection)<br>2. Non-prophylactic antibiotic use<br>3. Length of stay in hospital<br>4. Duration of intubation<br>5. Mortality |

**DeRiso 1996** (*Continued*)

| | |
|---|---|
| Notes | Sample size calculation: Not reported<br>Unclear duration of mechanical ventilation. Unable to contact author |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "..the pharmacy randomised the patients to either experimental or control group by means of computer driven random number generator" |
| Allocation concealment (selection bias) | Low risk | Allocation was performed in pharmacy and solutions wit identical appearance were dispensed for use in ICU |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Double blind. Quote: "…matching placebo…Both were packaged in 120-mL brown bottles and labelled 'Oral Rinse Solution: Peridex/Placebo Trial Solution' with a 1-week expiration date" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Double blind |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Number of patients originally randomised to treatment or control groups not stated |
| Selective reporting (reporting bias) | Low risk | Planned outcomes reported (no data for length of stays, duration of ventilation) |
| Other bias | Low risk | No other sources of bias identified |

**Feng 2012**

| | |
|---|---|
| Methods | Study design: A single centre RCT with 3 parallel groups (2 groups included in this review)<br>Location: China<br>Number of centres: 1 ICU in a city hospital<br>Study period: February 2009 to January 2011<br>Funding source: Not stated |
| Participants | Inclusion criteria: Entry ICU, with orotracheal intubation and ventilation<br>Exclusion criteria: Pulmonary infection, stomatitis or oral tumours before intubation, accompanied with ulcer of the digestive tract, malignant tumours of the body, taking steroids > 3 days, diabetes<br>Number randomised: 204 |

| | |
|---|---|
| | Number evaluated: 204<br>Intervention group: 0.05% povidone iodine: n = 71; mean age: 43.7±8.1 years<br>Intervention group: 1/5000 furacilin: n = 65; mean age: 38.5±11.6 years<br>Control group: Saline n = 68; mean age: 40.3±8.5 years<br>Baseline characteristics: Not specified |
| Interventions | **Comparison: Povidone iodine + toothbrushing versus saline + toothbrushing**<br>Group A (n = 71): Toothbrushing along the slits between the teeth with 0.05% povidone iodine by nurses, then the oropharyngeal cavity was rinsed with 50 ml of the solution and it was suctioned out completely. This procedure was repeated 4 times a day<br>Group B: Toothbrushing along the slits between the teeth with 1/5000 furacilin (antibiotic) by nurses. Excluded from this review<br>Control group (n = 68): Toothbrushing along the slits between the teeth with 0.9% saline by nurses, then the oropharyngeal cavity was rinsed with 50 ml of the saline and it was suctioned out completely. This procedure was repeated 4 times a day |
| Outcomes | 4 outcome variables were reported:<br>1. Incidence of VAP<br>2. Rates of oral ulcer and/or herpes<br>3. Oral cleaness - no odour, no foreign bodies and visually clean surfaces of tube and equipment<br>4. Throat swab culture |
| Notes | Diagnosis of VAP was according to Chinese Society of Respiratory Diseases criteria |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | "Patients were divided into three groups according to randomisation principle" |
| Allocation concealment (selection bias) | Unclear risk | Not specified |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Blinding not described and not possible for the carers who would be aware of who was in each group |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not specified |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | All randomised participants included in the outcome evaluation |
| Selective reporting (reporting bias) | Low risk | The results were fully reported |
| Other bias | Low risk | No other sources of bias identified |

**Fields 2008**

| | |
|---|---|
| Methods | Study design: Parallel group RCT<br>Location: Akron Ohio, USA<br>Number of centres: 1<br>Study period: October 2005 to March 2006<br>Funding source: Internal hospital funding |
| Participants | Setting: 24-bed stroke, neurological and medical ICU<br>Inclusion criteria: Any mechanically ventilated patient on the stroke/medical ICU intubated in the hospital for < 24 hours , no previous diagnosis of pneumonia<br>Exclusion criteria: Patients with prior tracheotomies, younger than 18 years, AIDS secondary to immunocompromised systems, edentulous patients<br>Number randomised: Not stated<br>Number evaluated: Not stated<br>Baseline characteristics: Not reported |
| Interventions | **Comparison: Toothbrushing 8 hourly versus usual care**<br>Experimental group: Nurse brushed patient's teeth, tongue and hard palate for > 1 minute, then used toothette swab to swab patient's teeth tongue and hard palate for > 1 minute, then apply moisturiser to lips. Mouth and pharynx were suctioned as needed using catheter which was replaced every 24 hours. Oral assessment every 12 hours. Oral care kit #2 provided for each participant, with worksheet #2<br>Control group: Usual care (unspecified) which could include up to 2 toothbrushings daily and toothette mouthcare as needed. Nurses used oral care kit #1 and worksheet #1 |
| Outcomes | 1. Incidence of VAP |
| Notes | Sample size calculation: "Desired sample size was 200 ventilator dependent patients or 2000 ventilator days"<br>Email sent to authors 3 September 2012 requesting numbers of patients treated. No reply received. Trial included in text as narrative only |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | "..a plastic bin labelled 1-350, containing sealed envelopes which each had either worksheet #1 or #2, plus information about the trial to give to families". No mention of whether envelopes were sequentially numbered. Method of sequence generation not described |
| Allocation concealment (selection bias) | Low risk | Allocation contained in sealed envelopes |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Not possible, both nurses and patients would have known allocated treatment |

**Fields 2008** (*Continued*)

| | | |
|---|---|---|
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Outcome of VAP assessed by infection control nurse. Unclear whether this person was blinded to allocated treatment |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Comment: The study neither reports the number of patients randomised nor the number analysed |
| Selective reporting (reporting bias) | High risk | Comment: No numerical data were reported in this paper. VAP incidence was not reported by treatment group or with any measure of variance |
| Other bias | Unclear risk | Insufficient information in the trial report to produce confidence in the methodology of this trial |

**Fourrier 2000**

| | |
|---|---|
| Methods | Study design: Single blind RCT<br>Location: Lille, France<br>Number of centres: 1<br>Study period: June 1997 to July 1998<br>Funding source: Not stated |
| Participants | Setting: Adult ICU<br>Inclusion criteria: Patients admitted to ICU aged > 18 years, medical condition likely to require ICU stay of 5 days, requiring mechanical ventilation by oro or nasopharyngeal intubation or tracheostomy<br>Exclusion criteria: Edentulous patients<br>Number randomised: 60<br>Number evaluated: 58<br>Baseline characteristics:<br>-Intervention group: Age: 51.2±15.2; M/F: 19/11; SAPS II Score: 37±15<br>-Control group: Age: 50.4±15.5; M/F: 19/11; SAPS II Score: 33±13 |
| Interventions | **Comparison: Rinse + chlorhexidine gel versus rinse alone**<br>Experimental group: After mouthrinsing and oropharyngeal aspiration, 0.2% chlorhexidine gel was applied to dental and gingival surfaces of the patient using glove protected finger. Intervention 3 times daily<br>Control group: Mouthrinsing with bicarbonate isotonic serum followed by gentle oropharyngeal aspiration 4 times daily during ICU stay<br>Patients were allowed to eat and drink freely |
| Outcomes | 1. Incidence of nosocomial infections<br>2. Dental status (DMFT/CAO)<br>3. Amount of dental plaque (Loe & Silness Index)<br>4. Plaque bacterial culture |

**Fourrier 2000** (*Continued*)

| | |
|---|---|
| Notes | Sample size calculation: Not reported<br>Investigators verified antibacterial activity of chlorhexidine gel in vitro prior to study<br>Unclear numbers on mechanical ventilation developing VAP. Email sent 14 November 2012 |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "...patients were randomized into two groups according to a computer-generated balanced randomization table" |
| Allocation concealment (selection bias) | Unclear risk | Insufficient information was reported to determine whether or not the allocation of the sequence was concealed |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Not possible as no placebo used |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Bacteriologist blinded to randomisation code, and evaluation of nosocomial infections done by hygienist nurse and physician not aware of the treatment given |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Unclear how many patients are included in the evaluation of the outcomes |
| Selective reporting (reporting bias) | Low risk | Planned outcome of nosocomial infection, dental plaque, and colonisation reported |
| Other bias | Low risk | Groups appear similar at baseline. No other sources of bias identified |

**Fourrier 2005**

| | |
|---|---|
| Methods | Study design: A multicentre double-blind placebo-controlled study with 2 parallel groups<br>Location: France<br>Number of centres: 6 ICUs (3 in university hospitals & 3 in general hospitals)<br>Study period: January 2001 to September 2002<br>Funding source: Partial funding from Programme Hospitalier de Recherche Clinique PHRC (French Ministry of Health) |
| Participants | Inclusion criteria: Age > 18 years and a medical condition suggesting an ICU stay at least 5 days and the requirement of mechanical ventilation by orotracheal or nasotracheal intubation. Only patients hospitalised for 48 hours before admission in the ICU could be included |

| | |
|---|---|
| | Exclusion criteria: Patients with a tracheostomy tube at recruitment; completely edentulous; suffering from facial trauma; post-surgical and requiring specific oropharyngeal care; known allergy to chlorhexidine<br>Age group: Mean 61.0 SD 14.7, 61.1 years SD 14.9 in each group<br>Number randomised: 228<br>Number evaluated: 228 (ITT)<br>Intervention group: Age: 61.1±14.9; M/F: 73/41; SAPS II Score: 45.0±17.5<br>Control group: Age: 61.0±14.7; M/F: 83/31; SAPS II Score: 45.2±17.5 |
| Interventions | **Comparison: Chlorhexidine gel versus placebo**<br>Intervention (n = 114): After mouthrinsing and aspiration, plaque antiseptic decontamination of gingival and dental plaque with a 0.2% chlorhexidine gel provided by nurses at least 3 times a day during the entire ICU stay<br>Control (n = 114): A placebo gel, same usage as that of plaque antiseptic decontamination<br>"Toothbrushing was not allowed in the protocol" |
| Outcomes | The following variables were reported and compared:<br>1. Incidence of VAP<br>2. Incidence of VAP (%) per 1000 days of mechanical ventilation<br>3. Incidence of VAP (%) per 1000 days of intubation<br>5. Mortality from day 0 to day 28<br>6. ICU days (mean±SD)<br>7. Days of intubation (mean±SD)<br>8. Antibiotic days (mean±SD) |
| Notes | Sample size calculation: Calculation provided based on expected incidence of nosocomial infections of 30% in placebo group and 15% in treatment group. Planned interim analysis to determine effects of interventions, and study stopped based on pre-planned stopping rule after this interim analysis<br>Email sent to author 14 November 2012 |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "...randomly assigned … block randomization stratified by site" |
| Allocation concealment (selection bias) | Low risk | "all randomization lists were held in sealed envelopes in the pharmacy departments of the 6 centres" |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | The placebo gel was undistinguishable by colour, taste or odour with the tested agent. The investigators were unaware of patients assignments |

**Fourrier 2005** (*Continued*)

| | | |
|---|---|---|
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Double blind |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Only 1 patient in intervention group was excluded and the reason was clearly explained. ITT analysis |
| Selective reporting (reporting bias) | Low risk | All planned outcomes clearly defined and reported |
| Other bias | Low risk | No other sources of bias identified. Although this study was stopped early interim analysis was planned in protocol and carried out appropriately |

**Grap 2004**

| | |
|---|---|
| Methods | Study design: Multicentre RCT with 3 parallel groups<br>Location: USA<br>Number of centres: 1<br>Study period: Not stated<br>Funding source: AD Williams Foundation of Virginia Commonwealth University |
| Participants | Inclusion criteria: ≥18 years, admitted to the ED, surgical trauma ICU or neuroscience ICU who required endotracheal intubation and were mechanically ventilated<br>Exclusion criteria: Edentulous persons<br>Age group: Mean 50.3 SD 16.0 range 20-87<br>Number randomised: 34<br>Number evaluated: Variable<br>Spray group: n = 11; swab group: n = 12; control group: n = 11. M/F: 24/10; mean APACHE III Score: 63.1±23.8 |
| Interventions | **Comparison: Chlorhexidine spray versus chlorhexidine swab versus usual care**<br>Spray group (n = 11): At early post-intubation a single oral application of 0.12% chlorhexidine gluconate was given in 20 sprays for about 2 ml of the agent<br>Swab group (n = 12): At early post-intubation a single oral application of 0.12% chlorhexidine gluconate was given by swabbing for about 2 ml of the agent<br>Control (n = 11): Usual care method but not described |
| Outcomes | 1. Change of mean CPIS from admission to the time of 48 hours<br>2. Number of the cases with positive cultures in the study period |
| Notes | Sample size calculation: Not reported but study was a pilot |

***Risk of bias***

**Grap 2004** (*Continued*)

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "Randomized …. using a block randomization scheme" |
| Allocation concealment (selection bias) | Low risk | "The block size varied so that the research assistants were not able to predict the next group assignment" |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Not possible as no placebos used |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Data collectors and culture evaluators were blinded |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Only 12/34 participants had complete data at admission and at 48 hours for evaluation of VAP. Attrition mainly due to endotracheal extubation but numbers greater in both chlorhexidine groups compared to control |
| Selective reporting (reporting bias) | High risk | Planned outcomes of negative oral cultures and CPIS (no variance estimates) reported in minority of participants. Unclear number of VAP, and no mortality data reported |
| Other bias | Low risk | No other sources of bias identified |

**Grap 2011**

| | |
|---|---|
| Methods | Study design: RCT<br>Location: Virginia USA<br>Number of centres: 2 units in same hospital, Level 1 trauma centre<br>Study period: Not stated<br>Funding source: Triservice Nursing research program grant TSNRP MDA-905-03-TS02 |
| Participants | Setting: Surgical trauma ICU & neuroscience ICU<br>Inclusion criteria: Patients intubated within 12 hours of admission to trauma centre (intubation may have occurred in emergency department, in the field or in pre-hospital setting)<br>Exclusion criteria: Previous endotracheal tube placed in 48 hours prior to admission, clinical diagnosis of pneumonia on admission, burn injuries, edentulous persons<br>Number randomised: 152, 7 lost, enrolled sample 145 (71/74) (only 75 were still intubated after 48 hours)<br>Number evaluated: At 48 or 72 hours = 60 (36/24) (for VAP) 39 (21/18) |

**Grap 2011** (*Continued*)

| | |
|---|---|
| | Baseline characteristics: Not reported for each randomised group in total<br>Those with 48/72 hour data:<br>-Experimental group: n = 36, M/F 27/9, APACHE II 70.69±30.14<br>-Control group: n = 24, M/F 11/13, APACHE II 60.46±23.45 |
| Interventions | **Comparison: Chlorhexidine applied by swab versus usual care**<br>Experimental group: 1 5 ml dose of chlorhexidine 0.12% applied to all areas of oral cavity by swab within 12 hours prior to intubation. All patients received usual oral comfort care (details not reported)<br>Control group: Usual oral comfort care as per usual practice |
| Outcomes | 1. Incidence of VAP<br>2. CPIS score<br>3. APACHE III<br>4. TRISS<br>5. Oral Health (DMFT) |
| Notes | Sample size calculation: Not reported (but pilot study published in 2004)<br>Email sent and reply received to clarify the data |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "The subjects were randomised to a treatment group or control group using a block randomisation scheme" |
| Allocation concealment (selection bias) | Unclear risk | Not described |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Not possible because no placebo used |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Not mentioned and probably not done as researchers were nurses and likely to be involved in both delivery of interventions and assessment of outcomes |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Huge attrition, and reasons for losses not described for each group. Conclusions based on 39/152 (26%) of those originally randomised to treatment or control |
| Selective reporting (reporting bias) | High risk | Primary outcome planned was development of VAP but inclusion criteria used in this study meant that less than half those randomised were at risk of developing VAP |

**Grap 2011** (*Continued*)

| | | |
|---|---|---|
| Other bias | High risk | Study report notes statistically significant difference in gender and CPIS score between groups at baseline. No baseline characteristics data reported for each randomised group, and likely that important prognostic factors e.g. place of intubation, surgery, may have been different in each group |

**Hu 2009**

| | |
|---|---|
| Methods | Study design: RCT<br>Location: Beijing, China<br>Number of centres: 1<br>Study period:<br>Funding source: No external funding |
| Participants | Setting: ICU in second affiliated hospital of PLA General Hospital<br>Inclusion criteria: Patients in ICU receiving mechanical ventilation<br>Exclusion criteria: Unclear<br>Number randomised: 47<br>Number evaluated: Unclear<br>Baseline characteristics: Not reported for each randomised group in total<br>Those with 48/72 hour data:<br>-Experimenal group: n = 25, M/F 16/9, age range 19-68<br>-Control group: n = 22, M/F 13/9, age range 22-60 |
| Interventions | **Comparison: Saline swab + rinse versus saline swab**<br>Experimental group: Lips, teeth, tongue and palate were swabbed with a saline saturated cotton ball and the oral cavity was rinsed with saline twice daily<br>Control group: Lips, teeth, tongue and palate were swabbed with saline saturated cotton ball twice daily |
| Outcomes | VAP, mortality, days on ventilator, days in hospital, halitosis, ulceration |
| Notes | Information translated from Chinese paper by Shi Zongdao and colleagues. Unable to confirm outcome data with trial authors |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Email from author "the sequence was generated by using a random number table" |
| Allocation concealment (selection bias) | Low risk | Email from author "allocation was concealed using opaque envelopes numbered with inclusion sequence" |

**Hu 2009** (*Continued*)

| | | |
|---|---|---|
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Patients and carers were not blinded to interventions received |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Email from author "the outcome assessors were are group of nurses not involved with the interventions". Probably blinded to allocated treatment group |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | The number of participants included in the outcome assessments at each time point is unclear. VAP reported as percentages only? |
| Selective reporting (reporting bias) | High risk | All planned outcomes reported but as percentages only? |
| Other bias | Low risk | No other sources of bias identified |

**Jacomo 2011**

| | |
|---|---|
| Methods | Study design: Double-blind placebo-controlled RCT (NCT00829842)<br>Location: Sao Paulo, Brazil<br>Number of centres: 1<br>Study period: February 2006 to February 2008<br>Funding source: Not stated |
| Participants | Setting: Tertiary care hospital paediatric ICU<br>Inclusion criteria: Children with congenital heart disease undergoing cardiac surgery with or without cardiopulmonary bypass, admitted to paediatric ICU for post-operative care<br>Exclusion criteria: Pre-operative pneumonia, hypersensitivity to chlorhexidine, congenital or acquired immunodeficiency, refusal to participate<br>Number randomised: 164<br>Number evaluated: 160 (4 intra-operative deaths)<br>Baseline characteristics:<br>-Intervention group: Age: median12.2 (0-176 months); M/F: 42/45<br>-Control group: Age: median 10.8 (0-204 months); M/F: 35/38 |
| Interventions | **Comparison: Chlorhexidine (gargle or swab) versus placebo**<br>Experimental group: Oral hygiene with 0.12% chlorhexidine gluconate solution, administered pre-operatively and twice daily post-operatively. 0.3 ml/kg of body weight were used in children aged > 6 years, who gargled for 30 seconds avoiding ingestion. In younger children and intubated post-operative patients solution was applied to oral mucosa, gingival, tongue and tooth surfaces for 30 seconds with a spatula wrapped in gauze<br>Control group: Received the same treatment with placebo solution that looked and tasted the same |

| | |
|---|---|
| | All patients received orotracheal intubation and prophylactic systemic antibiotics intravenously for 48 hours |
| Outcomes | 1. Incidence of nosocomial pneumonia<br>2. Incidence of VAP<br>3. Duration of intubation<br>4. Need for reintubation<br>5. Time to development of pneumonia<br>6. Length of paediatric ICU/hospital stay<br>7. 28-day mortality |
| Notes | Sample size calculation: Estimated that 160 participants would detect a reduction in 50% in incidence of nosocomial pneumonia (31% to 15.5%) with $\alpha$ = 0.05 & $\beta$ = 0.20<br>NCT 00829842 at ClinicalTrials.gov |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "..randomized to the experimental or control groups by means of a list generated by a computerized system that uses a random number generator to produce customized sets of random numbers" |
| Allocation concealment (selection bias) | Low risk | "The randomisation list was held in the hospital pharmacy and all investigators were unaware of patients assignments" |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Double blind. Texture, colour, and flavour of placebo similar to active solution, placed in similar containers and labelled A or B |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Double blind. "..the diagnosis of nosocomial pneumonia was made independently by the PICU physicians and an infection control practitioner blinded to the patient's group" |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 2 participants in each group died and were therefore excluded from pneumonia outcomes |
| Selective reporting (reporting bias) | Unclear risk | Planned outcomes clearly reported but unclear how many trial participants were ventilated for at least 48 hours |
| Other bias | Low risk | No other sources of bias identified |

**Koeman 2006**

| | |
|---|---|
| Methods | Study design: A multicentre randomised double-blind placebo-controlled trial with 3 parallel groups<br>Location: 2 university hospitals and 3 general hospitals in the Netherlands<br>Number of centres: 5 hospitals (2 surgical and 5 mixed ICUs)<br>Study period: February 2001 to March 2003<br>Funding source: ZONMw Netherlands Organization for Health Research and Development (project number 2200.0046) |
| Participants | Inclusion criteria: Consecutive adult patients (> 18 years of age) needing mechanical ventilation for at least 48 hours were included within 24 hours after intubation and start of mechanical ventilation<br>Exclusion criteria: A pre-admission immunocompromised status, pregnancy, and if the physical condition did not allow oral application of study medication<br>Age group:<br>Number randomised: 385<br>Number evaluated: 379<br>Group A: Chlorhexidine group: n = 127; mean age: 60.9±15.3; M/F: 71/57; APACHEII: 22.2±7.02<br>Group B: Chlorhexidine/COL group: n = 128; mean age: 62.4±19.1; M/F: 66/61; APACHEII: 23.7±7.38<br>Group C: Control group: n = 130; mean age: 62.1±15.9; M/F: 93/37; APACHEII: 21.8±7.43 |
| Interventions | **Comparison: Chlorhexidine (in petroleum jelly) versus petroleum jelly alone**<br>Group A: Chlorhexidine group (n = 127): Oral decontamination with chlorhexidine (2%) in Vaseline petroleum jelly<br>Group B: Chlorhexidine/COL group (n = 128): Oral decontamination with chlorhexidine plus colistin antibiotic chlorhexidine/colistin (CHX/COL 2%/2%) in Vaseline petroleum jelly<br>Group C: Control (n = 130): Oral decontamination with Vaseline petroleum jelly<br>Trial medication was administered 4 times daily, after removing remnants of the previous dose with a gauze moistened with saline. Approximately 2 cm of paste, approximately 0.5 g was put on a gloved fingertip and administered to each side of the buccal cavity |
| Outcomes | The following outcome variables were reported for each group:<br>1. Incidence of VAP<br>2. Incidence of early onset VAP<br>3. Days ventilated (mean±SD)<br>4. ICU stay (mean±SD)<br>5. Days in hospital after ICU discharge (mean±SD)<br>6. Changes of endotracheal colonisation through cultures in 3 time windows after ventilation, 1-3 days, 5-8 days and 9-12 days respectively |
| Notes | Sample size calculation: Reported in paper together with planned sequential analysis<br>Only Group A and Group C included in this review |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|

**Koeman 2006** (*Continued*)

| | | |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "...randomly assigned to one of three study groups by computerised randomisation schedule. Randomization was stratified by hospital" |
| Allocation concealment (selection bias) | Low risk | Trial medication (chlorhexidine 2% in petroleum jelly (Vaseline) FNA, chlorhexidine 2% with COL 2% in Vaseline FNA, and Vaseline FNA) was produced and labelled by the Department of Clinical Pharmacy of the University Hospital Maastricht. Experimental and placebo pastes were tasteless and of comparable smell and consistency |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Double blind, placebo controlled |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Double blind, placebo controlled |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | The study was discontinued in 6 patients, 5 participants withdrew consent, 1 due to adverse event. Intention-to-treat analysis included all participants for primary outcome |
| Selective reporting (reporting bias) | Low risk | All planned outcomes reported |
| Other bias | Low risk | Unlikely |

**Kusahara 2012**

| | |
|---|---|
| Methods | Study design: Double-blind placebo-controlled RCT<br>Location: Sao Paulo Brazil<br>Number of centres: 1, tertiary care hospital affiliated with Federal University of Sao Paulo Brazil<br>Study period: 36 months dates not stated<br>Funding source: Funded by a grant from Fundacao de Amparo a Pesquisa do Estado de Sao Paulo (04-13361-2) |
| Participants | Setting: PICU<br>Inclusion criteria: Children admitted to PICU likely to require ventilation within 24 hours of admission<br>Exclusion criteria: Newborn, confirmed diagnosis of pneumonia at admission, known hypersensitivity to chlorhexidine, tracheostomy, duration of ventilation less than 48 hours, intubated for more than 24 hours prior to PICU admission |

| | |
|---|---|
| | Number randomised: 96 (46/50)<br>Number evaluated: 96, at day 2 (44/45), at day 4 23/23<br>Baseline characteristics:<br>-Intervention group: Age: 12±49.75 months; M/F: 28/18<br>-Control group: Age: 34.5±58.8 months; M/F: 32/18 |
| Interventions | **Toothbrushing + 0.12% chlorhexidine gel versus toothbrushing + placebo**<br>Experimental group: Oral care with toothbrushing and oral gel containing chlorhexidine twice daily (08:00 & 20:00 hours). Mouth was divided into 4 quadrants and each brushed in a defined pattern. With child in lateral position, gel was applied directly to toothbrush, and all tooth surfaces (vestibular, lingual, occlusal and incisal) were cleaned and ventral surface of tongue was brushed posterior to anterior. Each quadrant was rinsed with water and excess fluid and debris was removed with continuous suction. Finally oral foam applicator was immersed in the gel and applied all over the gingival surfaces of the patient<br>Control group: Oral care with toothbrushing and placebo oral gel twice daily. With child in lateral position, gel was applied directly to toothbrush, and all tooth surfaces (vestibular, lingual, occlusal and incisal) were cleaned and ventral surface of tongue was brushed posterior to anterior. Each quadrant was rinsed with water and excess fluid and debris was removed with continual suction. Finally oral foam applicator was immersed in the gel and applied all over the gingival surfaces of the patient |
| Outcomes | 1. Incidence of VAP<br>2. Duration of ventilation in PICU<br>3. Length of stay in PICU<br>4. Hospital mortality<br>5. Tracheal colonisation with Gram +ve & -ve organisms |
| Notes | Sample size calculation: Reported that this was not done "due to the absence of previous research on this population"<br>Email correspondence with Prof Pedreira confirmed that Pedreira 2009 and Kusuhara 2012 both refer to the same study. NCT 01083407 & NCT0410682 at ClinicalTrials.gov |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "..randomised into two groups using a balanced randomisation table generated by True Epistat Program" |
| Allocation concealment (selection bias) | Low risk | Both chlorhexidine and identical placebo gels were supplied by pharmacy in identical containers and only the pharmacist was aware of the gel type for each patient |

**Kusahara 2012** (*Continued*)

| | | |
|---|---|---|
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Double blind. Identical placebo used so that neither participants nor clinical staff were aware of allocated treatment |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Double blind. Only the pharmacist was aware of the gel type for each patient |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | All randomised participants included in the outcome evaluation |
| Selective reporting (reporting bias) | Low risk | One primary and 4 secondary outcomes reported in full |
| Other bias | Unclear risk | Statistically significant difference in mean age of children in each group. This may have introduced a bias |

**Long 2012**

| | |
|---|---|
| Methods | Study design: A single centre RCT with 2 parallel groups<br>Location: China<br>Number of centres: 1 ICU in the university hospital<br>Study period: February 2010 to March 2012<br>Funding source: Program for masters degree |
| Participants | Inclusion criteria: Patients admitted to ICU, with oral intubation, receiving mechanical ventilation $\geq$ 48 hours, age $\geq$ 18 years, patients or their relatives agreed to participate in the study<br>Exclusion criteria: Intubated in emergency e.g. after cardiac arrest, operations upon the oral cavity, trauma of the respiratory tract, with severe bleeding or coagulation disorders<br>Number randomised: 70<br>Number evaluated: 61 (the other 9 were death or ventilation < 48 hours)<br>Intervention group: Mean age: 60.06±10.71 years, M/F 20/11, APACHE 17.94±1.24<br>Control group: Mean age: 63.67±10.02 years, M/F 18/12, APACHE 18.23±0.57 |
| Interventions | **Comparison: Povidone iodine + toothbrushing versus povidone iodine alone**<br>Experimental group (n = 31): Modified oral nursing method: swab with 0.1% povidone iodine immediately before intubation, then toothbrushing and rinsing with 0.1 povidone iodine, 3 times a day<br>Control group (n = 30): Usual oral nursing method: swab with cotton balls soaked with 0.1% povidone iodine |
| Outcomes | 3 outcome variables were available:<br>1. Incidence of VAP<br>2. Mortality<br>3. Ventilation days |

**Long 2012** (*Continued*)

| | |
|---|---|
| Notes | Microbial examinations for the aspirate secretions obtained from inferior respiratory tract every day after intubation were referred for diagnosis of VAP |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | "...patients were randomly assigned into 2 groups, observing group and control group with 35 cases in each group" |
| Allocation concealment (selection bias) | Unclear risk | Not specified |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Blinding not described and not possible for the carers who would be aware of who was in each group |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not specified |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 9 randomised patients were excluded from analysis, numbers and reasons similar for each group |
| Selective reporting (reporting bias) | Low risk | Planned outcomes reported |
| Other bias | Unclear risk | Only the results of microbial examination of the aspirate secretions from the inferior respiratory tract as tool of VAP diagnosis may not be enough |

**Lorente 2012**

| | |
|---|---|
| Methods | Study design: Parallel group RCT<br>Location: Tenerife, Spain<br>Number of centres: 1<br>Study period: August 2010 to August 2011<br>Funding source: Hospital funding |
| Participants | Setting: Medical/surgical ICU<br>Inclusion criteria: Consecutive patients undergoing invasive mechanical ventilation for at least 24 hours<br>Exclusion criteria: Edentulous, aged < 18 years, pregnant, HIV positive, white blood cells < 1000 cells/$mm^3$, solid or haematological tumour, immunosuppressive therapy, mechanical ventilation duration less than 24 hours<br>Number randomised: 436 (217/219) |

| | |
|---|---|
| | Number evaluated: 436<br>Baseline characteristics:<br>-Intervention group: Age: 61.0±15.6 years; M/F: 146/71<br>-Control group: Age: 60.4±16.6 years; M/F: 145/74 |
| Interventions | **Toothbrushing + 0.12% chlorhexidine gel versus chlorhexidine alone**<br>Experimental group (n = 217): Oral cleansing performed with 0.12% chlorhexidine impregnated gauze, and oral cavity injection, followed by manual brushing of the teeth with a brush impregnated with 0.12% chlorhexidine (tooth by tooth on the anterior and posterior surfaces, the gum line and the tongue for a period of 90 seconds)<br>Control group (n = 219): Oral cleansing performed with 0.12% chlorhexidine impregnated gauze, and oral cavity injection only<br>In both groups nurse performed oral care every 8 hours. First endotracheal cuff pressure was tested, oropharyngeal secretions were aspirated, then chlorhexidine impregnated gauze was used to cleanse the teeth tongue and mucosal surfaces, followed by injection of 10 ml 0.12% of chlorhexidine digluconate into oral cavity, and finally after 30 seconds the OParea was suctioned |
| Outcomes | 1. Incidence of VAP<br>2. Duration of ventilation<br>3. ICU mortality<br>4. Tracheal colonisation with Gram +ve & -ve organisms<br>5. Antibiotic exposure |
| Notes | Sample size calculation: Estimated that 218 patients per group required to give 80% power and alpha error of 5%, to show a reduction in VAP from 15% to 7.5% |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "..a list of random numbers generated with Excel software (Microsoft, Seattle, WA)" |
| Allocation concealment (selection bias) | Unclear risk | No information about allocation concealment |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Not possible |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | "The diagnosis of VAP was made by an expert panel, blinded to group assignment" |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | All randomised patients are included in the outcome evaluations |
| Selective reporting (reporting bias) | Low risk | Planned outcomes reported in full |

| | | |
|---|---|---|
| Other bias | Low risk | No other sources of bias identified |

**McCartt 2010**

| | |
|---|---|
| Methods | Study design: 3-arm "quasi experimental" RCT<br>Location: Florida, USA<br>Number of centres: 1<br>Study period: Not stated<br>Funding source: Nursing dissertation |
| Participants | Setting: Medical/surgical ICU<br>Inclusion criteria: Patients aged > 18 years, anticipated to be orally intubated for at least 72 hours<br>Exclusion criteria: Admitting diagnosis of pneumonia, nasally intubated, expected to be extubated within 24 hours<br>Number randomised: 85<br>Number evaluated: Variable (70-80)<br>Baseline characteristics:<br>-Experimental group A: Age: 63 years; M/F: 11/18<br>-Experimental group B: Age: 60 years; M/F:16/15<br>-Control group: Age: 57 years; M/F: 11/14 |
| Interventions | **Comparison: Toothbrushing + 0.12% chlorhexidine gel versus chlorhexidine alone**<br>Experimental group (n = 29): Chlorhexidine gluconate spray 0.12% twice daily at 12-hour intervals<br>Experimental group (n = 31): Chlorhexidine gluconate spray + toothbrushing twice daily at 12-hour intervals<br>Control group (n = 25): Standard hygiene care with toothette swabs |
| Outcomes | 1. Oral pH<br>2. Oral cultures<br>3. Clinical Pulmonary Infection score<br>4. Oral assessment |
| Notes | Sample size calculation: Reported to have been done but unclear numbers per group required<br>Email sent to author 24 January 2013 - no reply received |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "..randomly assigned" "utilizing random tables generated by the Office of Research and Development in the Department of Nursing at the University of Florida" |
| Allocation concealment (selection bias) | Unclear risk | Not described |

| | | |
|---|---|---|
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Not possible |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Not done |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Numbers evaluated at 72 hours appear to be 69 (5, 7, 4 lost from groups A, B & C respectively) reasons not stated |
| Selective reporting (reporting bias) | High risk | Stated purpose of the study was to determine whether there was a difference in VAP but this outcome was not reported |
| Other bias | Low risk | No other sources of bias identified |

**Munro 2009**

| | |
|---|---|
| Methods | Study design: A single centre RCT with 4 parallel groups<br>Location: 3 ICUs in large urban University Medical Centre, Virginia, USA<br>Number of centres: 3 (ICUs)<br>Study period: Not stated<br>Funding source: Grant NIH R01 NR07652 |
| Participants | Inclusion criteria: Critically ill adults (over 18) in 3 intensive care units were enrolled within 24 hours of intubation. All patients older than 18 years (n = 10913) in medical, surgical/trauma, and neuroscience ICUs were screened for inclusion<br>Exclusion criteria: Clinical diagnosis of pneumonia at the time of intubation, edentulous patients, patients who had a previous endotracheal intubation during the current hospital admission<br>Group 1: 26/18 M/F, age mean 46.1 (18.2)<br>Group 2: 28/21 M/F, age mean 47.1 (15.7)<br>Group 3: 28/20 M/F, age mean 47.3 (18.8)<br>Group 4: 37/14 M/F, age mean 46.8 (16.4)<br>Number randomised: 547 (but 355 subsequently excluded due to pneumonia at baseline)<br>Number evaluated: 192 |
| Interventions | **Comparison: Chlorhexidine swab versus toothbrushing versus both versus usual care**<br>Group 1: (n = 44) a 0.12% solution of chlorhexidine gluconate (chlorhexidine) 5 mL by oral swab twice daily (at 10 AM and 10 PM)<br>Group 2: (n = 49) toothbrushing (manual toothbrush) 3 times a day (at 9 AM, 2 PM, and 8 PM), detailed toothbrushing protocol followed quadrant by quadrant<br>Group 3: (n = 48) combination care (toothbrushing 3 times a day and chlorhexidine every 12 hours)<br>Group 4: (n = 51) control (usual care) |

| | | |
|---|---|---|
| Outcomes | VAP measured by CPIS score, also dichotomised at day 1, 3, 5, 7<br>Mortality (died during hospitalisation) | |
| Notes | Median length of stay and stay in ICU were presented | |
| ***Risk of bias*** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | "A randomized controlled 2 × 2 factorial experimental design was used...Patients were randomly assigned to 1 of 4 treatments". "Patients were randomized to treatment within each ICU according to a permuted block design developed by the biostatistician (D.K.M.) before the start of the study" |
| Allocation concealment (selection bias) | Low risk | Not mentioned but probably done as allocation was made by statistician |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Not possible |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Not described, and probably not done |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 355/547 (65%) of those originally randomised were excluded from the analysis at day 3 because they were found to have pneumonia at baseline |
| Selective reporting (reporting bias) | Unclear risk | VAP reported as percentages only and denominator unclear |
| Other bias | Low risk | No other sources of bias identified |

**Needleman 2011**

| | |
|---|---|
| Methods | Study design: Parallel group RCT<br>Location: London UK<br>Number of centres: 1<br>Study period: March 2007 to May 2009<br>Funding source: Partially funded by UK Department of Health NIHR Biomedical Research Centres funding scheme |
| Participants | Setting: Neurocritical care unit<br>Inclusion criteria: Admitted to hospital < 48 hours prior to neurocritical care unit admission, expected to survive > 48 hours, and expected to require endotracheal intubation for > 48 hours<br>Exclusion criteria: Edentulous, known adverse reaction to chlorhexidine, recent history of chest infection, received antibiotics within 3 months prior to study start<br>Number randomised: 46<br>Number evaluated: 44 - 28 (attrition over time)<br>Baseline characteristics:<br>-Intervention group: Age: 53.0±12.5; M/F: 14/9<br>-Control group: Age: 42.7±12.8; M/F: 13/10 |
| Interventions | **Comparison: Chlorhexidine rinse + powered toothbrush versus chlorhexidine swab alone**<br>Experimental group (n = 23): Oral hygiene using a powered toothbrush (Colgate Actibrush) plus 20 ml of chlorhexidine solution 4 times daily for 2 minutes per session Oropharyngeal suction was used to remove excess fluid or debris<br>Control group (n = 23): Oral hygiene using a sponge toothette plus 20 ml of chlorhexidine solution 4 times daily for 2 minutes per session. Oropharyngeal suction was used to remove excess fluid or debris |
| Outcomes | 1. Oral plaque colonisation with VAP-associated bacteria<br>2. Amount of dental plaque<br>Outcomes measured on days 1 (pre-oral hygiene), 3 and 5 |
| Notes | Sample size calculation: Estimated that 16 patients per group would be required to detect a reduction from 63% to 10% in presence of VAP-associated pathogens, which would be clinically important |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "Randomization sequence was computer generated using SPSS statistical software" |
| Allocation concealment (selection bias) | Low risk | Randomisation was "concealed from those recruiting patients in sequentially numbered sealed opaque envelopes", which were prepared by the statistician |

**Needleman 2011** (*Continued*)

| | | |
|---|---|---|
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Not possible because experimental and control interventions were so different |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | "..oral hygiene assessment, microbial sampling, microbial assessment and data analysis were masked with regard to experimental group status" |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Losses to follow-up were high, due to early tracheal extubation, death or transfer to another facility. Numbers for each cause not given and total numbers were high and different in each group (13/23 (57%) control and 5/23 (22%) experimental participants at day 5) |
| Selective reporting (reporting bias) | Low risk | Planned outcomes reported in full |
| Other bias | Low risk | No other sources of bias identified |

**Ozcaka 2012**

| | |
|---|---|
| Methods | Study design: Double-blind placebo-controlled RCT<br>Location: Izmir, Turkey<br>Number of centres: 1<br>Study period: November 2007 to November 2009<br>Funding source: "The study was funded solely by the institutions of the authors" |
| Participants | Setting: Respiratory ICU<br>Inclusion criteria: Patients aged 18 or over, admitted to respiratory ICU expecting to require ventilation for > 48 hours<br>Exclusion criteria: Witnessed episode of aspiration, confirmed diagnosis of post-obstructive pneumonia, known hypersensitivity to chlorhexidine, diagnosed thrombocytopenia, pregnancy, oral mucositis, readmission to same ICU, expected survival < 1 week, edentulism<br>Number randomised: 66<br>Number evaluated: 61<br>Baseline characteristics:<br>-Intervention group: Age: 60.5±14.7 years<br>-Control group: Age: 56.0±18.2 years |
| Interventions | **Comparison: Chlorhexidine solution versus saline**<br>Experimental group (n = 32): Oral mucosa was swabbed with 0.2% chlorhexidine on sponge pellets, 4 times daily. Excess rinse was suctioned from patient's mouth after 1 minute<br>Control group (n = 34): Oral mucosa was swabbed with saline on sponge pellets, 4 times daily. Excess rinse was suctioned from patient's mouth after 1 minute |

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|---|---|
| | Deep suctioning was performed in both groups every 6 hours and following position changes to remove pooled secretions from around the cuff of the endotracheal tube |
| Outcomes | 1. Incidence of VAP<br>2. Mortality<br>3. Duration of ventilation in ICU<br>4. Length of stay in ICU<br>5. Presence of potential respiratory pathogens in minibronchoalveolar lavage |
| Notes | Sample size calculation: Estimated that 28 participants per group would be required to give 81% power with alpha of 5%, to show a reduction in VAP from 70% to 30%<br>Email sent 22 January 2013 and reply received 29 January 2013 |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "The randomisation prepared a set of subject identification (SID) numbers which had assigned treatment"<br>Comment: Description unclear, but involvement of statistician suggests this was well done |
| Allocation concealment (selection bias) | Low risk | "Study nurse obtained the SID number when the patient was enrolled"<br>Comment: Allocation was probably concealed and not able to be anticipated by investigators |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | "Assignment of treatment was blinded to patients and to all investigators, including periodontist, .... respiratory ICU physicians and outcome statisticians" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | "Assignment of treatment was blinded to patients and to all investigators, including periodontist, .... respiratory ICU physicians and outcome statisticians" |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 66 patients randomised, 1 secondary exclusion from each group, and 2 and1 early deaths in chlorhexidine and control groups, respectively<br>Comment: Unlikely to have introduced a bias |
| Selective reporting (reporting bias) | Low risk | Planned outcomes reported |

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|---|---|---|
| Other bias | Low risk | No other sources of bias identified |

**Panchabhai 2009**

| | |
|---|---|
| Methods | Study design: Open-label RCT<br>Location: Mumbai India<br>Number of centres: 1<br>Study period: 8 months - dates not stated<br>Funding source: Not stated |
| Participants | Setting: ICU (mixed medical and surgical), tertiary care hospital<br>Inclusion criteria: All patients admitted to ICU during study period who signed consent<br>Exclusion criteria: Pregnant women, those with pneumonia at baseline, those for whom oral care was contraindicated, those with allergy to chlorhexidine<br>Number randomised: 512<br>Number evaluated: 471 (only 88/83 = 171 on mechanical ventilation)<br>Baseline characteristics (given for 471 who completed the trial only):<br>-Intervention group: Age: 35.2±15.9; M/F: 136/88; APACHEII Score: 12(9-17)<br>-Control group: Age: 36.9±16.2; M/F: 171/76; APACHEII Score: 14±(9-19) |
| Interventions | **Comparison: Chlorhexidine versus potassium permanganate**<br>Experimental group (n = 250): Oral and pharyngeal suction of pooled secretions followed by swabbing of the oral cavity, teeth, palate, buccal spaces, posterior pharyngeal wall, and hypopharynx with normal saline.Then oropharyngeal cleansing, following the same procedure, twice daily with 0.2% chlorhexidine solution<br>Control group (n = 262): Oral and pharyngeal suction of pooled secretions followed by swabbing of the oral cavity, teeth, palate, buccal spaces, posterior pharyngeal wall, and hypopharynx with normal saline.Then oropharyngeal cleansing twice daily, following the same procedure, with 0.01% potassium permanganate solution<br>Non-intubated patients, rinsed with water, then rinsed and gargled with 10 ml of study solution. No eating/drinking for 1 hour post-intervention |
| Outcomes | 1. Incidence of nosocomial pneumonia<br>2. Day of development of pneumonia<br>3. Mortality (hospital)<br>4. Duration of ICU stay |
| Notes | Sample size calculation: "This study had a statistical power of 75% to detect a 50% reduction in the incidence of nosocomial pneumonia in the study group with 95% level of confidence. Assuming the incidence of pneumonia in the control group was 16%, 506 subjects were required"<br>Email sent to author 14 November 2012 |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|

**Panchabhai 2009** (*Continued*)

| | | |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | "..randomly assigned to treatment .... by concealed simple random sampling"<br>Comment: No details of sequence generation provided |
| Allocation concealment (selection bias) | Unclear risk | "..concealed simple randomisation"<br>Comment: Unclear whether allocation was concealed from researchers |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Open-label RCT |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Open-label RCT but "two independent, blinded reviewers made the diagnosis of nosocomial pneumonia" |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | 26/250 (10%) and 15/262 (5.7%) were excluded from the analysis in the chlorhexidine and control groups respectively. Reasons given were ICU stay < 48 hours, 14/250 versus 6/262, and protocol violation 12/250 and 9/262 respectively |
| Selective reporting (reporting bias) | Low risk | All planned outcomes reported in full |
| Other bias | Unclear risk | Baseline parameters only reported for those who completed the study |

**Pobo 2009**

| | |
|---|---|
| Methods | Study design: Prospective, single blind, randomised trial with parallel groups<br>Location: Spain<br>Number of centres: 1 ICU at a hospital<br>Study period: Not stated<br>Funding source: This work was supported by Fondo de Investigaciones Sanitarias (FISS 06/060), Centro de Investigación Biomédica en Red Enfermedades Respiratorias (06/06/36), and the Agency for the Administration of University and Research Grants (2005/SGR/920) |
| Participants | Inclusion criteria: Intubated adults without evidence of pulmonary infection, expected to remain ventilated for longer than 48 hours. Randomised within 12 hours of intubation<br>Exclusion criteria: Edentulous, suspicion of pneumonia at time of intubation or evidence of massive aspiration during intubation, tracheostomy (or expected within 48 hours), recent enrolment in other trials, pregnancy, and chlorhexidine allergy<br>Age group: Adults<br>Intervention group: n = 74; age: 55.3±17.9; M/F: 49/25; mean APACHEII Score: 18.8±7.1 |

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|---|---|
| | Control group: n = 73; age: 52.6±17.2; M/F: 46/27; mean APACHEII Score: 18.7±7.3<br>Number randomised: 147 (74 in toothbrush group and 73 in standard care group)<br>Number evaluated: 147 |
| Interventions | **Comparison: Powered toothbrush + standard oral care versus standard oral care alone**<br>Group 1 (n = 74): Standard oral care plus toothbrush group: besides the standard oral care, toothbrushing was performed tooth by tooth, on anterior and posterior surfaces, and along the gumline, the tongue was also brushed. A powered toothbrush was used (Braun Oral B AdvancePower 450 TX, Braun GmbH). This procedure was repeated once every 8 hours<br>Group 2 (n = 73): Standard oral care: maintaining head elevation at 30 degrees. After aspiration of oropharyngeal secretions and adjustment of endotracheal cuff pressure, a gauze containing 20 ml of 0.12% chlorhexidine digluconate was applied to all the oral surfaces including tongue and mucosal surface, and 10 ml of 0.12% chlorhexidine digluconate was injected into oral cavity, being aspirated after 30 seconds, repeated every 8 hours |
| Outcomes | The following outcome variables were reported for each group:<br>1. Incidence of VAP<br>2. Incidence of suspected VAP per 1000 days of mechanical ventilation<br>3. Mean days of mechanical ventilation (mean±SD)<br>4. ICU length of stay (mean±SD)<br>5. Mortality |
| Notes | In the review, the standard oral care group was viewed as intervention with chlorhexidine and the other group was viewed as control with toothbrushing<br>Sample size calculation: Estimated that 200 patients per group would be required to show a 50% reduction in VAP with 80% power and alpha error of 5%. After 147 of planned 400 patients were randomised the study was stopped by the steering committee due to no difference in VAP between the groups<br>NCT 00842478 at ClinicalTrials.gov |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Randomisation by means of a computer generated list, stratified for antibiotic use at admission |
| Allocation concealment (selection bias) | Low risk | The list was concealed in opaque sealed envelopes opened by the nurse within 12 hours of intubation |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Blinding not possible. Participants unlikely to be aware of treatment, but carers were aware |

**Pobo 2009** (*Continued*)

| | | |
|---|---|---|
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Investigators and attending physicians were blinded to assigned groups |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | No withdrawals. All randomised participants included in the analysis |
| Selective reporting (reporting bias) | Low risk | Expected outcomes reported including adverse events |
| Other bias | High risk | Study stopped early after recruitment of 147 of planned 400 patients because no differences between groups were found and revised estimates indicated that 1500 patients would need to be recruited to show a difference. Numbers not feasible in this centre |

**Prendergast 2012**

| | |
|---|---|
| Methods | Study design: Prospective, randomised trial with 2 parallel groups. NCT 00518752<br>Location: USA<br>Number of centres: 1 neuroscience ICU at a tertiary medical centre<br>Study period: August 2007 to August 2009<br>Funding source: Not stated |
| Participants | Inclusion criteria: All patients aged at least 18 years admitted to neuroscience ICU, intubated within 24 hours of admission<br>Exclusion criteria: Pregnancy, edentulous, aged < 18 years, facial fractures or trauma affecting oral cavity, unstable cervical fractures, anticipated extubation within 24 hours, grim prognosis<br>Intervention group: n = 38; age: 54±17.8; M/F: 19/19<br>Control group: n = 40; age: 51±18.4; M/F: 23/17<br>Number randomised: 78 (38 in comprehensive group and 40 in standard care group)<br>Number evaluated: Variable (less than 11 patients/group) |
| Interventions | **Comparison: Powered toothbrush + comprehensive oral care versus manual toothbrush + standard oral care**<br>Group 1 (n = 38): Tongue scraping using a low profile tongue scraper with posterior to anterior sweeping motion across the dorsal surface of the tongue. Then toothbrushing with Oral B vitality powered toothbrush + Biotene (non-foaming) toothpaste for 2 minutes, then a liberal application or Oral Balance gel. Care performed twice daily<br>Group 2 (n = 40): Standard oral care: using manual paediatric toothbrush, toothpaste with 1000 ppm fluoride with SLS and water-based inert lubricant (KY jelly). Care performed twice daily |

**Prendergast 2012** (*Continued*)

| | |
|---|---|
| Outcomes | The following outcome variables were reported for each group:<br>1. Oral and sputum cultures every 48 hours<br>2. Incidence of suspected VAP (day 2-6)<br>3. ICU length of stay (mean±SD)<br>4. Mortality |
| Notes | Sample size calculation: Not reported<br>NCT 00518752 at ClinicalTrials.gov |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "..randomized ... using a computer generated list maintained in a separate locked cabinet" |
| Allocation concealment (selection bias) | Low risk | "..list was maintained in a separate locked cabinet from enrolment forms to prevent manipulation of eligibility judgements" |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Not possible |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Diagnosis of VAP by examination of chest radiographs, by physicians blinded to allocated treatment (information in Prendergast dissertation) |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Unclear how many were assessed at each time point but paper states that "less than 11 patients in each group at each time point" |
| Selective reporting (reporting bias) | Low risk | All planned outcomes reported |
| Other bias | Low risk | No other sources of bias identified |

**Roca Biosca 2011**

| | |
|---|---|
| Methods | Study design: Single blind RCT<br>Location: Tarragona, Spain<br>Number of centres: 1<br>Study period: June 2006 to May 2009<br>Funding source: Grant from Health Investigation Fund (FISS 06/060) |
| Participants | Setting: ICU (14-bed)<br>Inclusion criteria: Adults aged > 18 years, requiring mechanical ventilation for at least 48 hours, no pneumonia at baseline, at least 2 premolars and 1 incisor, consenting to take part<br>Exclusion criteria: Edentulous, suspected pneumonia < 18 years, requiring < 48 mechanical ventilation, tracheotomy, moribund (death expected within 72 hours) allergic to chlorhexidine<br>Number randomised: 147<br>Number evaluated:<br>Baseline characteristics: Report states that there were no differences in gender, age, diagnosis, APACHE scores between the groups at baseline. No supporting data reported |
| Interventions | **Comparison: Powered toothbrush + standard oral care versus standard oral care alone**<br>Experimental group: RASPALL - Standard oral hygiene protocol + powered toothbrush. Patient was elevated to 35 degrees, oropharyngeal secretions were aspirated, intubation cuff pressure checked, then teeth, tongue and oral cavity cleaned with swab soaked in 10 ml 0.12% chlorhexidine digluconate. Solution left for 30 seconds then excess was aspirated. All tooth surfaces then brushed using a powered toothbrush<br>Control group: Standard oral hygiene protocol alone as described for treatment group |
| Outcomes | 4 outcome variables planned:<br>1. Plaque index (Loe & Silness) days 1, 5 and 10<br>2. Plaque cultures<br>3. VAP (reported as NAV)<br>4. Halitosis |
| Notes | Sample size calculation: Not reported<br>Translated from Portuguese by Luisa Fernandez-Mauleffinch<br>Email to authors sent 14 November 2012 |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | "Group assignment was done randomly by sealed envelope"<br>Method of sequence generation not described |
| Allocation concealment (selection bias) | Low risk | "Group assignment was done randomly by sealed envelope" |

**Roca Biosca 2011** (*Continued*)

| | | |
|---|---|---|
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Not possible to blind patients or personnel |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Study described as single blind but unclear who was blinded. Microbiologist? |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Numbers of patients included in outcome of plaque index were 74 and 73 at day 0, 60 and 57, at day 5 and 29 and 32 at day 10 for toothbrush and control groups respectively. Reasons for missing outcome data are extubation, need for tracheotomy, VAP, death or intubation for total of 28 days. No information as to numbers per group missing for each reason |
| Selective reporting (reporting bias) | High risk | Planned outcomes of plaque index and microbiological culture reported but data for VAP and halitosis in each group not reported |
| Other bias | Unclear risk | Insufficient information in trial report to be clear about potential for other bias |

**Scannapieco 2009**

| | |
|---|---|
| Methods | Study design: A randomised, double-blind, placebo-controlled clinical trial<br>Location: USA<br>Number of centres: 1 18-bed trauma ICU<br>Study period: March 2004 until November 2007<br>Funding source: USPH grant R01DE-14685 from the National Institute of Dental and Craniofacial Research |
| Participants | Inclusion criteria: Those admitted to the ICU who were expected to be intubated and mechanically ventilated within 48 hours of admission<br>Exclusion criteria: A witnessed aspiration suspected with chemical pneumonitis; a confirmed diagnosis of post-obstructive pneumonia e.g. advanced lung cancer; a known hypersensitivity to chlorhexidine; absence of consent; a diagnosed thrombocytopenia (platelet count less than 40 and/or a INR above 2, or other coagulopathy); a do not intubate order; children under the age of 18 years; pregnant women; legal incarceration; transfer from another ICU; oral mucositis; immunosuppression either-HIV or drug-induced e.g. organ transplant patients or those on long term steroid therapy; and readmission to the ICU<br>Number randomised: 175<br>Number evaluated: 146<br>Intervention group (chlorhexidine 1): n = 47; mean age: 44.8±19.9; M/F: 43/15; mean |

| | |
|---|---|
| | APACHEII Score: 18.5±4.1<br>Intervention group (chlorhexidine 2): n = 50; mean age: 47.6±19.1; M/F: 44/14; mean APACHEII Score: 19.7±6.1<br>Control group: n = 49; mean age: 50.0±22.5; M/F: 36/23; mean APACHEII Score: 19.1±6.1 |
| Interventions | **Comparison: Chlorhexidine twice per day + toothbrush versus chlorhexidine once per day + toothbrush versus placebo + toothbrush**<br>Intervention group: Chlorhexidine (0.12% CHX gluconate) was applied using a rinse-saturated oral foam applicator (Sage Products, Cary, IL, USA) once a day (placebo at other time)<br>Intervention group: Chlorhexidine (0.12% CHX gluconate) was applied using a rinse-saturated oral foam applicator (Sage Products, Cary, IL, USA) twice a day (in the morning at about 8 AM and in the evening at about 8 PM)<br>Control group: Placebo was applied using a rinse-saturated oral foam applicator twice per day<br>All groups had routine oral care using a suction toothbrush (Sage Products, Cary, IL, USA) twice a day and as needed to brush teeth and the surface of the tongue or approximately 1 to 2 minutes, and applying suction at completion and as needed during the brushing |
| Outcomes | 1. Incidence of VAP (diagnosed as the presence of more than $10^4$ CFU of pathogen/ml of bqBAL fluid)<br>2. Death<br>3. Days ventilated<br>4. Days in hospital<br>5. Antibiotic use |
| Notes | Sample size calculation: Estimated that 53 patients per arm would give 90% power to detect a 505 decrease in colonisation. For outcomes 2 to 5, the P values were for 3 group comparisons<br>NCT00123123 at ClinicalTrials.gov |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | A web-based subject enrolment system which allocated randomised subject identification numbers |
| Allocation concealment (selection bias) | Low risk | The oral topical treatment for each box was formulated and prepared by the hospital pharmacy. Sealed envelopes containing a random number were generated in blocks of 6 to provide concealment of patient assignment from the investigators |

**Scannapieco 2009** (*Continued*)

| | | |
|---|---|---|
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | "Assignment of treatment was blinded to patients and all investigators including outcome assessors, statisticians and care providers" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | "Assignment of treatment was blinded to patients and all investigators including outcome assessors, statisticians and care providers" |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 175 subjects were randomised, microbiological baseline data were available for 146 subjects, 115 had full data at 48 hours. Greater than 20% drop-outs in all groups. ITT analysis used for 175 patients but unclear what imputation was used to account for losses |
| Selective reporting (reporting bias) | Unclear risk | Planned microbiological outcomes were reported only in graphs with no data presented |
| Other bias | High risk | Problems with data analysis due to unclear denominator and imputations. Pre-study antibiotic exposure higher in control group |

**Sebastian 2012**

| | |
|---|---|
| Methods | Study design: Double-blind stratified placebo-controlled RCT<br>Location: New Delhi, India<br>Number of centres: 1<br>Study period: November 2007 to April 2009<br>Funding source: Indian Council of Medical Research Grant. Chlorhexidine gel and placebo supplied by ICPA Health Products Limited |
| Participants | Setting: Paediatric ICU (6 beds)<br>Inclusion criteria: Patients aged 3 months to 15 years who required orotracheal or nasotracheal intubation and mechanical ventilation. Patients with pneumonia at baseline were also included as these made up 66% of patient population<br>Exclusion criteria: Patients mechanically ventilated for > 48 hours prior to paediatric ICU admission, those with tracheostomies, with inaccessible oral cavities, or with known hypersensitivity to chlorhexidine<br>Number randomised: 86 (41/45)<br>Number evaluated: 86<br>Baseline characteristics:<br>-Intervention group: Age: 13/41, 3-12 months; 28/41, 1 year to 15 years; M/F: 23/18<br>-Control group: Age: 15/45, 3-12 months; 30/45, 1 year to 15 years; M/F: 27/18 |

| | |
|---|---|
| Interventions | **Comparison: Chlorhexidine gel versus placebo**<br>Experimental group (n = 41): Oral cavity was suctioned to remove secretions then mucosal surfaces were cleaned with saline soaked gauze. Then 0.75 cm 1% chlorhexidine gel was applied to each side of the mouth using a standardised disposable applicator<br>Control group (n = 45): Oral cavity was suctioned to remove secretions then mucosal surfaces were cleaned with saline soaked gauze. Then 0.75 cm placebo gel was applied to each side of the mouth using a standardised disposable applicator<br>Care was repeated every 8 hours |
| Outcomes | 1. Incidence of VAP<br>2. Length of stay in ICU<br>3. Duration of hospital stay<br>4. Hospital mortality<br>5. Type and antibiotic sensitivity of organisms cultured |
| Notes | Sample size calculation: Estimated that 91 patients per group were required to give 80% power with alpha 5% to detect a reduction in VAP from 40% to 20%<br>NCT00597688 at ClinicalTrials.gov<br>This study included patients with pneumonia at baseline and used age appropriate CDC criteria to diagnose VAP |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Eligible participants were stratified into 1 of 4 groups based on age group and presence or pneumonia at baseline. Within each stratum patients were randomised to receive either chlorhexidine or placebo gel. "..the random sequence was generated for each stratum using STATA 9.0 in blocks of 6" |
| Allocation concealment (selection bias) | Low risk | No details about how the allocation was communicated to the researchers, but allocation likely to have been concealed |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Double blind |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Double blind |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | All randomised participants included in the ITT analysis |

**Sebastian 2012** (*Continued*)

| | | |
|---|---|---|
| Selective reporting (reporting bias) | Low risk | All planned outcomes reported. Medians and IQRs (as reported) are the correct statistic for a skewed distribution but cannot be combined in meta-analysis |
| Other bias | Low risk | Paper states that "the funding agency did not have any role in the study design, data collection and analysis, decision to publish or preparation of the manuscript" |

**Seguin 2006**

| | |
|---|---|
| Methods | Study design: 3-arm parallel RCT<br>Location: Rennes, France<br>Number of centres: 1<br>Study period: August 2001 to January 2003<br>Funding source: Not stated |
| Participants | Setting: Surgical ICU<br>Inclusion criteria: Adult patients (> 18 years) with closed head trauma admitted to ICU and expected to need mechanical ventilation for at least 2 days<br>Exclusion criteria: Admitted more than 12 hours after initial trauma, those with facial, thoracic, abdominal or spinal injuries, known history of reaction to iodine or of respiratory disease, chest infiltrates at admission or need for curative antibiotics<br>Number randomised: 110 (38/36/36)<br>Number evaluated: 98 (36/31/31)<br>Baseline characteristics:<br>-Iodine group: Age: 38±17 years; M/F: 28/10<br>-Saline group: Age: 38±16 years; M/F: 24/12<br>-Control group: Age: 41±18 years; M/F: 23/13 |
| Interventions | **Comparison: Povidone Iodine versus saline versus usual care (no rinse)**<br>Iodine group (n = 38): Nasopharynx and oropharynx rinsed 4 hourly with 20 ml of 10% povidone iodine aqueous solution (Betadine oral rinse solution) reconstituted in a 60 ml solution with sterile water, followed by aspiration of oropharyngeal secretions<br>Saline group (n = 36): Nasopharynx and oropharynx rinsed 4 hourly with 60 ml saline, followed by aspiration of oropharyngeal secretions<br>Control group (n = 36): Standard regimen without any installation but with aspiration of oropharyngeal secretions<br>For all patients the suction catheters were inserted as distally as possible. Procedures were reported on patients chart |
| Outcomes | 1. Incidence of VAP - early and late onset<br>2. Duration of ventilation in surgical ICU<br>3. Length of stay in surgical ICU<br>4. Surgical ICU mortality |

**Seguin 2006** (*Continued*)

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|---|---|
| Notes | Sample size calculation: Estimated that 30 patients in each group would provide 80% power with alpha error 5% to detect a reduction in VAP from 50% to 20% |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "Patients were randomly assigned to received one of three regimens according to computer-generated random number codes kept in sealed envelopes" |
| Allocation concealment (selection bias) | Low risk | "Patients were randomly assigned to received one of three regimens according to computer-generated random number codes kept in sealed envelopes" |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Not possible |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Outcome assessors not blinded. Attempts were made to make the diagnosis of VAP as objective as possible using a clear set of criteria and VAP diagnosis was confirmed by positive bronchoalveolar lavage culture. However risk of detection bias remains |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 12 randomised patients (11%) excluded from analysis. 6 patients (1/3/2 in each group) were withdrawn because unexpected recovery meant that they were not on mechanical ventilation for 48 hours and a further 6 patients (1/2/3) died. Unlikely to have introduced a bias |
| Selective reporting (reporting bias) | Low risk | Planned outcomes reported in full |
| Other bias | Low risk | No other sources of bias identified |

**Tantipong 2008**

| | |
|---|---|
| Methods | Study design: A single centre RCT with 2 parallel groups<br>Location: Thailand<br>Number of centres: 1 tertiary care university hospital<br>Study period: January 2006 through March 2007<br>Funding source: Thailand Research Fund and Faculty of Medicine Siriraj Hospital |
| Participants | Inclusion criteria: Eligible patients were adults aged ≧ 18 years who were hospitalised in intensive care units (a total of 36 beds) or general medical wards (a total of 240 beds) at Siriraj Hospital and who received mechanical ventilation<br>Exclusion criteria: Patients who had pneumonia at enrolment or who had a chlorhexidine allergy<br>Number randomised: 207<br>Number evaluated: 207 (110 patients received mechanical ventilation for > 48 hours)<br>Experimental group: n = 102; age: 56.5±20.1; M/F: 50/52; mean APACHEII Score: 16.7±7.9<br>Control group: n = 105; age: 60.3±19.1; M/F: 51/54; mean APACHEII Score: 18.2±8.1<br>Patients' demographic characteristics between groups did not differ significantly |
| Interventions | **Comparison: Toothbrush + chlorhexidine versus toothbrush + placebo**<br>Experimental group (n = 102): Received oral care 4 times per day with brushing the teeth, suctioning any oral secretions, and rubbing the oropharyngeal mucosa with 15 ml of a 2% chlorhexidine solution, until their endotracheal tubes were removed<br>Control group (n = 105): Underwent the same oral care procedure with normal saline solution |
| Outcomes | The following outcome variables were reported for each group:<br>1. Incidence of VAP<br>2. Number of cases of VAP per 1000 ventilator-days<br>3. Incidence of VAP for patients who received mechanical ventilation for more than 2 days<br>4. Overall mortality<br>5. Mean days of mechanical ventilation (mean±SD)<br>6. Rate of irritation of oral mucosa |
| Notes | Sample size calculation: Estimated that 108 patient per group required to give 80% power to detect a 50% decrease in VAP with 5% Type 1 error |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "..randomized..... by stratified randomization according to sex and hospital location of eligible patient" |
| Allocation concealment (selection bias) | High risk | Not mentioned and probably not done |

**Tantipong 2008** (*Continued*)

| | | |
|---|---|---|
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Not blinded as chlorhexidine solution had different odour and taste from saline |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | The assessors who determined whether a patient developed pneumonia were unaware of the patient's study group assignment |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | All randomised participants included in outcome evaluation but only 53% of participants on ventilators for > 2 days and therefore at risk of VAP |
| Selective reporting (reporting bias) | Unclear risk | Planned outcome VAP but not all participants at risk and information unclear. Mortality reported |
| Other bias | Unclear risk | Only 60% of study participants received ventilation in ICU and only 53% of participants received mechanical ventilation for more than 48 hours. Likely that nursing care protocols were different in general medical wards compared to ICUs |

**Xu 2007**

| | |
|---|---|
| Methods | Study design: Parallel group RCT<br>Location: Nanjing, China<br>Number of centres: 1<br>Study period: December 2004 to June 2006<br>Funding source: No external funding |
| Participants | Setting: ICU in drum tower hospital of Nanjing University<br>Inclusion criteria: Critically ill adult patients in ICU receiving mechanical ventilation<br>Exclusion criteria: Participants with severe oral diseases, mechanical ventilation for more than 24 hours prior to study entry, those who refused oral care protocol<br>Number randomised: 164<br>Number evaluated: 164<br>Baseline characteristics: Not reported for each randomised group |
| Interventions | **Comparison: Saline swab versus saline rinse versus both**<br>Experimental group A (n = 58): Rinsing the oropharyngeal cavity with saline for 5-10 seconds, followed by suction aspiration, repeated 5-10 times twice daily for 7 days<br>Experimental group B (n = 62): Both wipe and rinse as above, twice daily for 7 days<br>Control group (n = 44): Usual care - wiping the oropharyngeal cavity with saline-soaked cotton ball twice daily for 7 days |

**Xu 2007** (*Continued*)

| | | |
|---|---|---|
| Outcomes | VAP, stomatitis, fungal infection | |
| Notes | Diagnosis of VAP was according to Chinese Society of Respiratory Diseases criteria<br>Information translated from Chinese paper by Shi Zongdao and colleagues | |
| ***Risk of bias*** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Unclear risk | "randomly allocated" but no details of sequence generation described |
| Allocation concealment (selection bias) | Unclear risk | Not described |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Not described, and probably not possible |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Not described and probably not done |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | All randomised participants included in outcome evaluation |
| Selective reporting (reporting bias) | Low risk | Planned outcomes reported |
| Other bias | Low risk | No other sources of bias identified |

**Xu 2008**

| | |
|---|---|
| Methods | Study design: Parallel group RCT<br>Location: Shandong, China<br>Number of centres: 1<br>Study period: No stated<br>Funding source: No external funding |
| Participants | Setting: ICU of the second hospital of Shandong University<br>Inclusion criteria: Adult patients entering ICU receiving mechanical ventilation expected to last > 48 hours<br>Exclusion criteria: Patients with pulmonary infections<br>Number randomised: 116<br>Number evaluated: 116<br>Baseline characteristics: Not reported for each randomised group |
| Interventions | **Comparison: Saline rinse versus saline swab**<br>Experimental group (n = 64): Rinse of the oropharyngeal cavity with saline for 5-10 seconds, followed by suction aspiration and repeated 5-10 times, twice daily |

**Xu 2008** (*Continued*)

| | |
|---|---|
| | Control group (n = 52): Standard oral care comprising scrubbing with a cotton ball soaked in saline, twice daily |
| Outcomes | VAP, duration of ventilation (days) |
| Notes | Diagnosis of VAP was according to Chinese Society of Respiratory Diseases criteria<br>Information translated from Chinese paper by Shi Zongdao and colleagues |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | "randomly allocated" Method of sequence generation not described |
| Allocation concealment (selection bias) | High risk | Not mentioned and probably not done |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Not mentioned and probably not possible |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Not mentioned and probably not done |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | All randomised participants included in the outcome evaluation |
| Selective reporting (reporting bias) | Low risk | Both outcomes listed in methods are reported in the results section |
| Other bias | Low risk | No other sources of bias identified |

**Yao 2011**

| | |
|---|---|
| Methods | Study design: Single blind pilot RCT (NCT 00604916)<br>Location: Taiwan<br>Number of centres: 1<br>Study period: March to November 2007<br>Funding source: Grants from Taiwan National Science Council and career development grant from National Health Research Institutes |
| Participants | Setting: Surgical ICU<br>Inclusion criteria: Intubated and ventilated post-operative patients expected to be in ICU > 48 hours and expected to require mechanical ventilation for 48-72 hours with nasal or endotracheal intubation<br>Exclusion criteria: Patients with pneumonia at baseline<br>Number randomised: 53 |

**Yao 2011** (*Continued*)

| | |
|---|---|
| | Number evaluated: 53 (VAP), day 3-4 50, day 7-8 42<br>Baseline characteristics:<br>-Intervention group: Age: 60.7±16.0; M/F: 17/11; APACHEII Score: 19.6± 5.2<br>-Control group: Age: 60.5±16.5; M/F: 17/8; APACHEII Score: 19.4± 4.4 |
| Interventions | **Comparison: Oral care + toothbrushing twice per day versus usual oral care**<br>Experimental group: Standardised oral care protocol twice daily for 15-20 minutes for 7 days from trained intervention nurse. Bed elevated 30 to 45 degrees, hypopharyngeal suctioning, mouth moistened with 5-10 ml purified water, buccal surfaces of teeth cleaned with powered toothbrush and lingual tooth surfaces and tongue, gums and mucosa massaged with soft paediatric toothbrush. Oral cavity then cleaned with toothette swab connected to a suction tube and rinsed with 50 ml water + hypopharyngeal suctioning<br>Control group: Received oral care protocol, twice daily for 10-15 minutes provided by same trained intervention nurse. Patients elevated, hypopharyngeal suctioning, lips moistened with toothette swab and water, then further hypopharyngeal suctioning |
| Outcomes | 1. Oral Assessment Guide (OAG Eilers et al 1988) score<br>2. Plaque score (Turesky-Gilmore-Glickman modification of Quigley-Hein plaque index with disclosing dye. Recorded 1 tooth from each quadrant (prioritising premolars and incisors) scores summed)<br>3. Duration of ventilation<br>4. Length of ICU stay<br>5. Incidence of VAP (defined as CPIS > 6)<br>4. Mortality (ICU) |
| Notes | Sample size calculation: Pilot study<br>NCT 00604916 at ClinicalTrials.gov<br>Email sent to author 14 November 2012. Reply received 12 December 2012 |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "...randomized using a computer generated randomization table" |
| Allocation concealment (selection bias) | Unclear risk | Not mentioned in trial report<br>Comment: Unclear whether allocation was concealed from researchers prior to assignment |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Experimental group received toothbrushing (both powered and manual) and control group did not, so blinding of participants and personnel not possible |

**Yao 2011** (*Continued*)

| | | |
|---|---|---|
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Outcomes assessed by 2 hygienists blinded to allocated treatment. VAP assessed by CPIS score |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | VAP outcome assessed in all randomised participants. For oral health and plaque outcomes 8/28 (experimental) and 7/25 (control) patients lost (transferred to ward) and 2/28 patients in experimental group died |
| Selective reporting (reporting bias) | Low risk | Planned outcomes reported, but denominators unclear for VAP and mortality. However this information was supplied by email from the authors |
| Other bias | Unclear risk | 3/28 (11%) and 1/25 (4%) patients in experimental and control groups were edentulous. Unclear how the intervention and outcomes were applied in these participants |

**Zhao 2012**

| | |
|---|---|
| Methods | Study design: A single centre RCT with 2 parallel groups<br>Location: China<br>Number of centres: 1 surgical ICU in city hospital<br>Study period: May 2010 to April 2011<br>Funding source: Not stated |
| Participants | Inclusion criteria: Admission into the ICU, orally intubated, receiving mechanical ventilation<br>Exclusion criteria: Not specified<br>Number randomised: 324 (162 per group)<br>Number evaluated: 324<br>Age group: Mean 66.25±15.28<br>Baseline characteristics were comparable |
| Interventions | **Comparison: Yikou (triclosan) rinse versus saline**<br>Experimental group: Oral cavity swab with 15 ml of Yikou gargle (triclosan is main ingredient), 4 times a day<br>Control group: Oral cavity swab with normal saline, 4 times a day<br>Secretions were aspirated using suction once daily and sent to lab for culture |
| Outcomes | 3 outcome variables were available:<br>1. Incidence of VAP in less than 4 days of ventilation and within 4 to 10 days of ventilation<br>2. Mechanical ventilation days<br>3. ICU stay days<br>4. Culture of the samples taking from oropharyngeal cavity and inferior respiratory tract |

| | |
|---|---|
| | (Table 3, detection rates of microbial pathogens before and after oral nursing care were listed) |
| Notes | Diagnosis of VAP was mainly determined by microbial examination of the aspirate secretions from the inferior respiratory tract, which was performed every day |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | "randomly divided into 2 groups" |
| Allocation concealment (selection bias) | Unclear risk | Not specified |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Blinding not described and not possible for the carers who would be aware of who was in each group |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not specified |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | The main results were all reported |
| Selective reporting (reporting bias) | Low risk | The results were fully reported |
| Other bias | Unclear risk | Only the results of microbial examination of the aspirate secretions from the inferior respiratory tract as tool of VAP diagnosis was mentioned and its diagnostic efficacy may not be enough |

APACHE II = Acute Physiology and Chronic Health Evaluation II; CAO = caries/absent/occluded; CDC = Centers for Disease Control; CHX = chlorhexidine; CPIS = Clinical Pulmonary Infection Score; DMFT = decayed/missing/filled teeth; ED = emergency department; ICU = intensive care unit; INR = international normalised ratio; IQRs = interquartile ranges; ITT = intention-to-treat; M/F = male/female; PICU = paediatric intensive care unit; ppm = parts per million; RCT = randomised controlled trial; RTI = respiratory tract infection; SAPS = Simplified Acute Physiologic Score; SD = standard deviation; SLS = sodium lauryl sulfate; TRISS = Trauma Injury Severity Score; UTI = urinary tract infection; VAP = ventilator-associated pneumonia

## Characteristics of excluded studies *[ordered by study ID]*

| Study | Reason for exclusion |
|---|---|
| Abusibeih 2010 | Quasi-randomised trial |
| Bordenave 2011 | Identified from ClinicalTrials.gov website as ongoing study but email from contact author on 8 November 2012 confirmed that this study did not proceed due to lack of funding |
| Chao 2009 | Not RCT |
| Epstein 1994 | The participants involved in the study were not critically ill |
| Fan 2012 | The ingredients of the mouthwash used in the trial were not reported, so we could not judge the mouthwash containing antibiotics or not |
| Ferozali 2007 | The target population was long term care residents, not critically ill patients in hospitals |
| Genuit 2001 | Not RCT |
| Guo 2007 | RCT, but patients had lung trauma (injury before receiving the oral nursing intervention) |
| Houston 2002 | Likely that less than 10% of study participants had mechanical ventilation for a minimum of 48 hours |
| Lai 1997 | RCT of critically ill patients, unclear how many were on mechanical ventilation, outcome candidiasis |
| Li 2011 | Participants allocated to groups by alternation (not RCT) |
| Li 2012 | The mouthwash Kouitai used in the trial contains both chlorhexidine and metronidazole, and the later is an antibiotic |
| Liang 2007 | The participants involved in the study did not use mechanical ventilation |
| Liwu 1990 | Clinical controlled trial, not an RCT |
| MacNaughton 2004 | Published as abstract only with interim analysis. Insufficient information in abstract to include this study in the systematic review and attempts to locate full publication or to contact the author unsuccessful |
| McCoy 2012 | Not RCT |
| Ogata 2004 | The target population was patients about to receive orotracheal intubation, they were not on mechanical ventilation. Study about gargling with povidone iodine before oral intubation to reduce the transport of bacteria into the trachea, not oral care intervention in critically ill patients to reduce VAP |
| Pawlak 2005 | Not RCT |
| Santos 2008 | Email reply from Dr Santos stated that "The nurse put the first admission on biotene and the second admission on cetylpyridium, the third admission on biotene and so on." Alternation as an allocation method is not truly random and therefore this study was excluded |

(*Continued*)

| | |
|---|---|
| Segers 2006 | The participants involved in the study did not use mechanical ventilation |
| Ueda 2004 | The target population was patients at nursing homes, not critically ill patients in hospitals |
| Wang 2006 | Quasi-randomised controlled trial |
| Wang 2012 | The interventions being tested in the experimental group includes elevation of the head of the bed, closed endotracheal suctioning in addition to oral nursing care, which is outside the scope of the review |
| Yin 2004 | RCT aiming to improve oral cleanliness. Unlikely that participants received mechanical ventilation |
| Zouka 2010 | Abstract only, insufficient information to include in review. Emailed contact author 6 November 2012 without response |

RCT = randomised controlled trial

## Characteristics of studies awaiting assessment *[ordered by study ID]*

**Anon 2012**

| | |
|---|---|
| Methods | |
| Participants | |
| Interventions | EB57 oral care-based programme for reducing VAP |
| Outcomes | |
| Notes | Full-text copy requested from library |

**Baradari 2012**

| | |
|---|---|
| Methods | Double-blind RCT |
| Participants | 60 ICU patients "divided into 2 equal groups". Seems unlikely that they are receiving mechanical ventilation |
| Interventions | Chlorhexidine versus herbal mouthrinse |
| Outcomes | |
| Notes | Language: Iranian - will require translation. Full-text copy requested from library |

**Seo 2011**

| | |
|---|---|
| Methods | |
| Participants | |
| Interventions | Oral hygiene |
| Outcomes | |
| Notes | Language: Korean - will require translation. Full-text copy requested from library |

**Yun 2011**

| | |
|---|---|
| Methods | |
| Participants | |
| Interventions | Toothbrushing |
| Outcomes | |
| Notes | Language: Korean - will require translation. Full-text copy requested from library |

ICU = intensive care unit; RCT = randomised controlled trial; VAP = ventilator-associated pneumonia

## Characteristics of ongoing studies *[ordered by study ID]*

**NCT 01657396**

| | |
|---|---|
| Trial name or title | Implementation and evaluation of revised protocols for oral hygiene for mechanically ventilated patients |
| Methods | RCT - 3-arm parallel group study |
| Participants | Adults in intensive care units in Alberta, Canada |
| Interventions | SAGE Q care (commercial package) versus SAGE Q care plus chlorhexidine versus standard oral hygiene care |
| Outcomes | VAP, frequency of oral care procedures, OA score, duration of ICU and hospital stay, ICU and hospital mortality, antimicrobial utilisation, acquisition of antimicrobial resistant organisms |
| Starting date | July 2012 (currently recruiting) |
| Contact information | Dr Dan Zuege (dan.zuege@albertahealthservices.ca ) |
| Notes | |

ICU = intensive care unit; OA = oral assessment; RCT = randomised controlled trial; VAP = ventilator-associated pneumonia

## DATA AND ANALYSES

### Comparison 1. Chlorhexidine versus placebo/usual care

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Incidence of VAP | 17 | 2402 | Odds Ratio (M-H, Random, 95% CI) | 0.60 [0.47, 0.77] |
| 1.1 Chlorhexidine solution versus placebo (no t'brushing in either group) | 7 | 1037 | Odds Ratio (M-H, Random, 95% CI) | 0.60 [0.38, 0.94] |
| 1.2 Chlorhexidine gel versus placebo (no t'brushing in either group) | 5 | 669 | Odds Ratio (M-H, Random, 95% CI) | 0.57 [0.31, 1.06] |
| 1.3 Chlorhexidine solution versus placebo (t'brushing both groups) | 3 | 408 | Odds Ratio (M-H, Random, 95% CI) | 0.44 [0.23, 0.85] |
| 1.4 Chlorhexidine gel versus placebo (t'brushing both groups) | 1 | 96 | Odds Ratio (M-H, Random, 95% CI) | 1.03 [0.44, 2.42] |
| 1.5 Chlorhexidine solution versus usual care (some t'brushing in each group) | 1 | 192 | Odds Ratio (M-H, Random, 95% CI) | 0.58 [0.32, 1.02] |
| 2 Mortality | 14 | 2111 | Odds Ratio (M-H, Random, 95% CI) | 1.10 [0.87, 1.38] |
| 2.1 Chlorhexidine solution versus placebo (no t'brushing in either group) | 6 | 973 | Odds Ratio (M-H, Random, 95% CI) | 1.16 [0.72, 1.88] |
| 2.2 Chlorhexidine gel versus placebo (no t'brushing in either group) | 4 | 414 | Odds Ratio (M-H, Random, 95% CI) | 0.89 [0.45, 1.76] |
| 2.3 Chlorhexidine solution versus placebo (t'brushing both groups) | 4 | 628 | Odds Ratio (M-H, Random, 95% CI) | 1.09 [0.72, 1.64] |
| 2.4 Chlorhexidine gel versus placebo (t'brushing both groups) | 1 | 96 | Odds Ratio (M-H, Random, 95% CI) | 0.67 [0.24, 1.81] |
| 3 Duration of ventilation | 6 | 933 | Mean Difference (IV, Random, 95% CI) | 0.09 [-0.84, 1.01] |
| 3.1 Chlorhexidine solution versus placebo (no t'brushing in either group) | 3 | 316 | Mean Difference (IV, Random, 95% CI) | -2.74 [-0.63, 0.63] |
| 3.2 Chlorhexidine gel versus placebo (no t'brushing in either group) | 3 | 543 | Mean Difference (IV, Random, 95% CI) | 1.26 [-0.78, 3.30] |
| 3.3 Chlorhexidine solution versus placebo (t'brushing both groups) | 1 | 74 | Mean Difference (IV, Random, 95% CI) | -1.30 [-4.20, 1.60] |
| 4 Duration of ICU stay | 6 | 833 | Mean Difference (IV, Random, 95% CI) | 0.21 [-1.48, 1.89] |
| 4.1 Chlorhexidine solution versus placebo (no t'brushing in either group) | 2 | 194 | Mean Difference (IV, Random, 95% CI) | -1.22 [-4.07, 1.62] |

| | | | | |
|---|---|---|---|---|
| 4.2 Chlorhexidine gel versus placebo (no t'brushing in either group) | 3 | 543 | Mean Difference (IV, Random, 95% CI) | 0.53 [-1.56, 2.61] |
| 4.3 Chlorhexidine gel versus placebo (t'brushing both groups) | 1 | 96 | Mean Difference (IV, Random, 95% CI) | 5.0 [-2.20, 12.20] |
| 5 Duration of systemic antibiotic therapy | 2 | 374 | Mean Difference (IV, Fixed, 95% CI) | 0.23 [-0.85, 1.30] |
| 5.1 Chlorhexidine gel versus placebo (no t'brushing in either group) | 1 | 228 | Mean Difference (IV, Fixed, 95% CI) | -1.18 [-3.41, 1.05] |
| 5.2 Chlorhexidine solution versus placebo (t'brushing both groups) | 1 | 146 | Mean Difference (IV, Fixed, 95% CI) | 0.65 [-0.58, 1.88] |
| 6 Positive cultures | 3 | 170 | Odds Ratio (M-H, Fixed, 95% CI) | 0.69 [0.35, 1.33] |
| 6.1 Chlorhexidine solution versus placebo (no t'brushing in either group) | 1 | 34 | Odds Ratio (M-H, Fixed, 95% CI) | 0.62 [0.13, 2.88] |
| 6.2 Chlorhexidine gel versus placebo (no t'brushing in either group) | 1 | 40 | Odds Ratio (M-H, Fixed, 95% CI) | 0.15 [0.03, 0.63] |
| 6.3 Chlorhexidine gel versus placebo (t'brushing both groups) | 1 | 96 | Odds Ratio (M-H, Fixed, 95% CI) | 1.40 [0.55, 3.53] |
| 7 Plaque index | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 8 Adverse effects | 2 | 401 | Odds Ratio (M-H, Fixed, 95% CI) | 2.22 [0.84, 5.90] |
| 8.1 Unpleasant taste | 1 | 194 | Odds Ratio (M-H, Fixed, 95% CI) | 0.57 [0.13, 2.47] |
| 8.2 Reversible mild irritation of oral mucosa | 1 | 207 | Odds Ratio (M-H, Fixed, 95% CI) | 11.30 [1.42, 90.01] |

**Comparison 2. Toothbrushing versus no toothbrushing**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Incidence of VAP | 4 | 828 | Odds Ratio (M-H, Random, 95% CI) | 0.69 [0.36, 1.29] |
| 1.1 Powered toothbrush + usual care (± CHX) versus usual care (± CHX) | 2 | 200 | Odds Ratio (M-H, Random, 95% CI) | 0.35 [0.06, 1.97] |
| 1.2 Toothbrush + CHX versus CHX alone | 1 | 436 | Odds Ratio (M-H, Random, 95% CI) | 0.87 [0.47, 1.62] |
| 1.3 Toothbrush (+some CHX) versus no toothbrush (+some CHX) | 1 | 192 | Odds Ratio (M-H, Random, 95% CI) | 1.09 [0.62, 1.92] |
| 2 Mortality | 4 | 828 | Odds Ratio (M-H, Random, 95% CI) | 0.85 [0.62, 1.16] |
| 2.1 Powered toothbrush+ usual care versus usual care | 2 | 200 | Odds Ratio (M-H, Random, 95% CI) | 1.32 [0.14, 12.90] |
| 2.2 Toothbrush + CHX versus CHX alone | 2 | 528 | Odds Ratio (M-H, Random, 95% CI) | 0.86 [0.59, 1.25] |

| | | | | |
|---|---|---|---|---|
| 2.3 Toothbrush alone versus no treatment | 1 | 100 | Odds Ratio (M-H, Random, 95% CI) | 1.20 [0.44, 3.25] |
| 3 Duration of ventilation | 2 | | Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| 3.1 Toothbrush + CHX versus CHX alone | 2 | 583 | Mean Difference (IV, Fixed, 95% CI) | -0.85 [-2.43, 0.73] |
| 4 Duration of ICU stay | 2 | | Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| 4.1 Toothbrush + CHX versus CHX alone | 2 | 583 | Mean Difference (IV, Fixed, 95% CI) | -1.82 [-3.95, 0.32] |
| 5 Colonisation with VAP associated organisms (Day 5) | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 5.1 versus CHX alone | 1 | 28 | Risk Ratio (M-H, Fixed, 95% CI) | 0.82 [0.40, 1.68] |
| 6 Plaque score | 2 | 76 | Std. Mean Difference (IV, Fixed, 95% CI) | -1.20 [-1.70, -0.70] |
| 6.1 Powered toothbrush versus usual care | 2 | 76 | Std. Mean Difference (IV, Fixed, 95% CI) | -1.20 [-1.70, -0.70] |

## Comparison 3. Powered toothbrush versus manual toothbrush

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Incidence of VAP | 1 | | Odds Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 1.1 Powered t'brush + comp oral care versus manual t'brush + std oral care | 1 | 78 | Odds Ratio (M-H, Fixed, 95% CI) | 0.8 [0.28, 2.31] |
| 2 Mortality | 1 | | Odds Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 2.1 Powered t'brush + comp oral care versus manual t'brush + std oral care | 1 | 78 | Odds Ratio (M-H, Fixed, 95% CI) | 1.06 [0.14, 7.90] |
| 3 Duration of ventilation | 1 | | Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| 3.1 Powered t'brush + comp oral care versus manual t'brush + std oral care | 1 | 78 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [-1.78, 1.78] |
| 4 Duration of ICU stay | 1 | | Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| 4.1 Powered t'brush + comp oral care versus manual t'brush + std oral care | 1 | 78 | Mean Difference (IV, Fixed, 95% CI) | -2.0 [-5.93, 1.93] |

## Comparison 4. Other oral care solutions

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Incidence of VAP | 9 | | Odds Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 1.1 Povidone iodine versus saline | 2 | 206 | Odds Ratio (M-H, Fixed, 95% CI) | 0.35 [0.19, 0.65] |
| 1.2 Povidone iodine versus usual care | 1 | 67 | Odds Ratio (M-H, Fixed, 95% CI) | 0.13 [0.03, 0.50] |

| | | | | |
|---|---|---|---|---|
| 1.3 Povidone iodine (+ t'brush) versus povidone iodine alone | 1 | 61 | Odds Ratio (M-H, Fixed, 95% CI) | 0.26 [0.07, 0.93] |
| 1.4 Saline rinse versus saline swab | 2 | 218 | Odds Ratio (M-H, Fixed, 95% CI) | 0.65 [0.37, 1.14] |
| 1.5 Saline rinse + swab versus saline swab (usual care) | 2 | 153 | Odds Ratio (M-H, Fixed, 95% CI) | 0.30 [0.14, 0.63] |
| 1.6 Saline rinse versus usual care | 2 | 324 | Odds Ratio (M-H, Fixed, 95% CI) | 0.50 [0.29, 0.88] |
| 1.7 Bicarbonate rinse versus water | 1 | 154 | Odds Ratio (M-H, Fixed, 95% CI) | 1.03 [0.25, 4.27] |
| 1.8 Triclosan rinse versus saline | 1 | 324 | Odds Ratio (M-H, Fixed, 95% CI) | 0.80 [0.52, 1.24] |
| 1.9 Furacilin versus povidone iodine | 1 | 136 | Odds Ratio (M-H, Fixed, 95% CI) | 0.41 [0.17, 1.03] |
| 1.10 Furacilin versus saline | 1 | 133 | Odds Ratio (M-H, Fixed, 95% CI) | 0.19 [0.08, 0.46] |
| 2 Mortality | 5 | | Odds Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 2.1 Povidone iodine versus saline | 1 | 67 | Odds Ratio (M-H, Fixed, 95% CI) | 0.42 [0.13, 1.33] |
| 2.2 Povidone iodine versus usual care | 1 | 67 | Odds Ratio (M-H, Fixed, 95% CI) | 0.83 [0.24, 2.91] |
| 2.3 Povidone iodine (+ t'brush) versus povidone iodine alone | 1 | 61 | Odds Ratio (M-H, Fixed, 95% CI) | 0.54 [0.12, 2.47] |
| 2.4 Saline rinse + swab versus saline swab (usual care) | 1 | 47 | Odds Ratio (M-H, Fixed, 95% CI) | 0.29 [0.06, 1.31] |
| 2.5 Saline rinse versus usual care | 2 | 324 | Odds Ratio (M-H, Fixed, 95% CI) | 1.20 [0.77, 1.87] |
| 2.6 Bicarbonate rinse versus water | 1 | 154 | Odds Ratio (M-H, Fixed, 95% CI) | 3.82 [1.18, 12.30] |
| 3 Duration of ventilation | 6 | | Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| 3.1 Povidone iodine versus saline | 1 | 67 | Mean Difference (IV, Fixed, 95% CI) | -1.0 [-4.36, 2.36] |
| 3.2 Povidone iodine versus usual care | 1 | 67 | Mean Difference (IV, Fixed, 95% CI) | -3.0 [-7.67, 1.67] |
| 3.3 Povidone iodine (+ t'brush) versus povidone iodine alone | 1 | 61 | Mean Difference (IV, Fixed, 95% CI) | 0.13 [-0.78, 1.04] |
| 3.4 Saline versus usual care | 2 | 324 | Mean Difference (IV, Fixed, 95% CI) | -0.40 [-2.55, 1.75] |
| 3.5 Saline rinse + swab versus saline swab | 1 | 47 | Mean Difference (IV, Fixed, 95% CI) | -3.91 [-5.85, -1.97] |
| 3.6 Saline rinse versus saline swab | 1 | 116 | Mean Difference (IV, Fixed, 95% CI) | -10.80 [-15.88, -5.72] |
| 3.7 Triclosan rinse versus saline | 1 | 324 | Mean Difference (IV, Fixed, 95% CI) | -5.24 [-5.64, -4.84] |
| 4 Duration of ICU stay | 3 | | Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| 4.1 Povidone iodine versus saline | 1 | 67 | Mean Difference (IV, Fixed, 95% CI) | 1.0 [-5.23, 7.23] |
| 4.2 Povidone iodine versus usual care | 1 | 67 | Mean Difference (IV, Fixed, 95% CI) | -4.0 [-10.99, 2.99] |
| 4.3 Saline versus usual care | 2 | 324 | Mean Difference (IV, Fixed, 95% CI) | -1.17 [-3.95, 1.60] |

| | | | | |
|---|---|---|---|---|
| 4.4 Triclosan rinse versus saline | 1 | 324 | Mean Difference (IV, Fixed, 95% CI) | -4.97 [-5.55, -4.39] |
| 5 Positive cultures | 1 | | Odds Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 5.1 Povidone iodine versus saline | 1 | 139 | Odds Ratio (M-H, Fixed, 95% CI) | 0.45 [0.21, 0.97] |

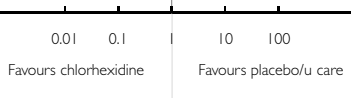
### Analysis 1.1. Comparison 1 Chlorhexidine versus placebo/usual care, Outcome 1 Incidence of VAP.

Review: Oral hygiene care for critically ill patients to prevent ventilator-associated pneumonia

Comparison: 1 Chlorhexidine versus placebo/usual care

Outcome: 1 Incidence of VAP

| Study or subgroup | Chlorhexidine n/N | Placebo/Usual care n/N | Odds Ratio M-H,Random,95% CI | Weight | Odds Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| 1 Chlorhexidine solution versus placebo (no t'brushing in either group) | | | | | |
| DeRiso 1996 | 5/173 | 17/180 | | 5.1 % | 0.29 [ 0.10, 0.79 ] |
| Chen 2008 (1) | 16/60 | 28/60 | | 7.9 % | 0.42 [ 0.19, 0.89 ] |
| Panchabhai 2009 | 14/88 | 15/83 | | 7.4 % | 0.86 [ 0.39, 1.91 ] |
| Bellissimo-Rodrigues 2009 | 16/64 | 17/69 | | 7.6 % | 1.02 [ 0.46, 2.24 ] |
| Grap 2011 (2) | 7/21 | 10/18 | | 3.3 % | 0.40 [ 0.11, 1.47 ] |
| Jacomo 2011 (3) | 16/87 | 11/73 | | 6.9 % | 1.27 [ 0.55, 2.94 ] |
| Ozcaka 2012 | 12/29 | 22/32 | | 4.8 % | 0.32 [ 0.11, 0.92 ] |
| **Subtotal (95% CI)** | **522** | **515** | | **43.1 %** | **0.60 [ 0.38, 0.94 ]** |
| Total events: 86 (Chlorhexidine), 120 (Placebo/Usual care) | | | | | |
| Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 10.19$, df = 6 (P = 0.12); $I^2 = 41\%$ | | | | | |
| Test for overall effect: Z = 2.24 (P = 0.025) | | | | | |
| 2 Chlorhexidine gel versus placebo (no t'brushing in either group) | | | | | |
| Fourrier 2000 | 5/30 | 14/28 | | 3.8 % | 0.20 [ 0.06, 0.67 ] |
| Fourrier 2005 | 13/114 | 12/114 | | 7.0 % | 1.09 [ 0.48, 2.51 ] |
| Koeman 2006 | 13/127 | 23/130 | | 8.5 % | 0.53 [ 0.26, 1.10 ] |
| Cabov 2010 | 1/17 | 6/23 | | 1.2 % | 0.18 [ 0.02, 1.64 ] |
| Sebastian 2012 (4) | 12/41 | 14/45 | | 6.0 % | 0.92 [ 0.36, 2.30 ] |
| **Subtotal (95% CI)** | **329** | **340** | | **26.5 %** | **0.57 [ 0.31, 1.06 ]** |
| Total events: 44 (Chlorhexidine), 69 (Placebo/Usual care) | | | | | |
| Heterogeneity: $Tau^2 = 0.21$; $Chi^2 = 7.23$, df = 4 (P = 0.12); $I^2 = 45\%$ | | | | | |
| Test for overall effect: Z = 1.78 (P = 0.075) | | | | | |
| 3 Chlorhexidine solution versus placebo (t'brushing both groups) | | | | | |

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| Study or subgroup | Chlorhexidine n/N | Placebo/Usual care n/N | Odds Ratio M-H,Random,95% CI | Weight | Odds Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| Tantipong 2008 | 5/58 | 10/52 | | 4.2 % | 0.40 [ 0.13, 1.25 ] |
| Scannapieco 2009 (5) | 14/100 | 12/49 | | 6.6 % | 0.50 [ 0.21, 1.19 ] |
| Berry 2011 | 1/71 | 4/78 | | 1.2 % | 0.26 [ 0.03, 2.42 ] |
| **Subtotal (95% CI)** | **229** | **179** | | **12.0 %** | **0.44 [ 0.23, 0.85 ]** |
| Total events: 20 (Chlorhexidine), 26 (Placebo/Usual care) | | | | | |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.33$, df = 2 (P = 0.85); $I^2 = 0.0\%$ | | | | | |
| Test for overall effect: Z = 2.45 (P = 0.014) | | | | | |
| 4 Chlorhexidine gel versus placebo (t'brushing both groups) | | | | | |
| Kusahara 2012 (6) | 15/46 | 16/50 | | 6.7 % | 1.03 [ 0.44, 2.42 ] |
| **Subtotal (95% CI)** | **46** | **50** | | **6.7 %** | **1.03 [ 0.44, 2.42 ]** |
| Total events: 15 (Chlorhexidine), 16 (Placebo/Usual care) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.06 (P = 0.95) | | | | | |
| 5 Chlorhexidine solution versus usual care (some t'brushing in each group) | | | | | |
| Munro 2009 (7) | 38/92 | 55/100 | | 11.7 % | 0.58 [ 0.32, 1.02 ] |
| **Subtotal (95% CI)** | **92** | **100** | | **11.7 %** | **0.58 [ 0.32, 1.02 ]** |
| Total events: 38 (Chlorhexidine), 55 (Placebo/Usual care) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 1.89 (P = 0.059) | | | | | |
| **Total (95% CI)** | **1218** | **1184** | | **100.0 %** | **0.60 [ 0.47, 0.77 ]** |
| Total events: 203 (Chlorhexidine), 286 (Placebo/Usual care) | | | | | |
| Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 20.19$, df = 16 (P = 0.21); $I^2 = 21\%$ | | | | | |
| Test for overall effect: Z = 3.96 (P = 0.000074) | | | | | |
| Test for subgroup differences: $Chi^2 = 2.42$, df = 4 (P = 0.66), $I^2 = 0.0\%$ | | | | | |


(1) CHX active ingredient in GSE rinse

(2) Single pre-operative CHX rinse, no placebo

(3) Children

(4) Children

(5) 50 patients treated 1x/day % 50 2x/day

(6) Children

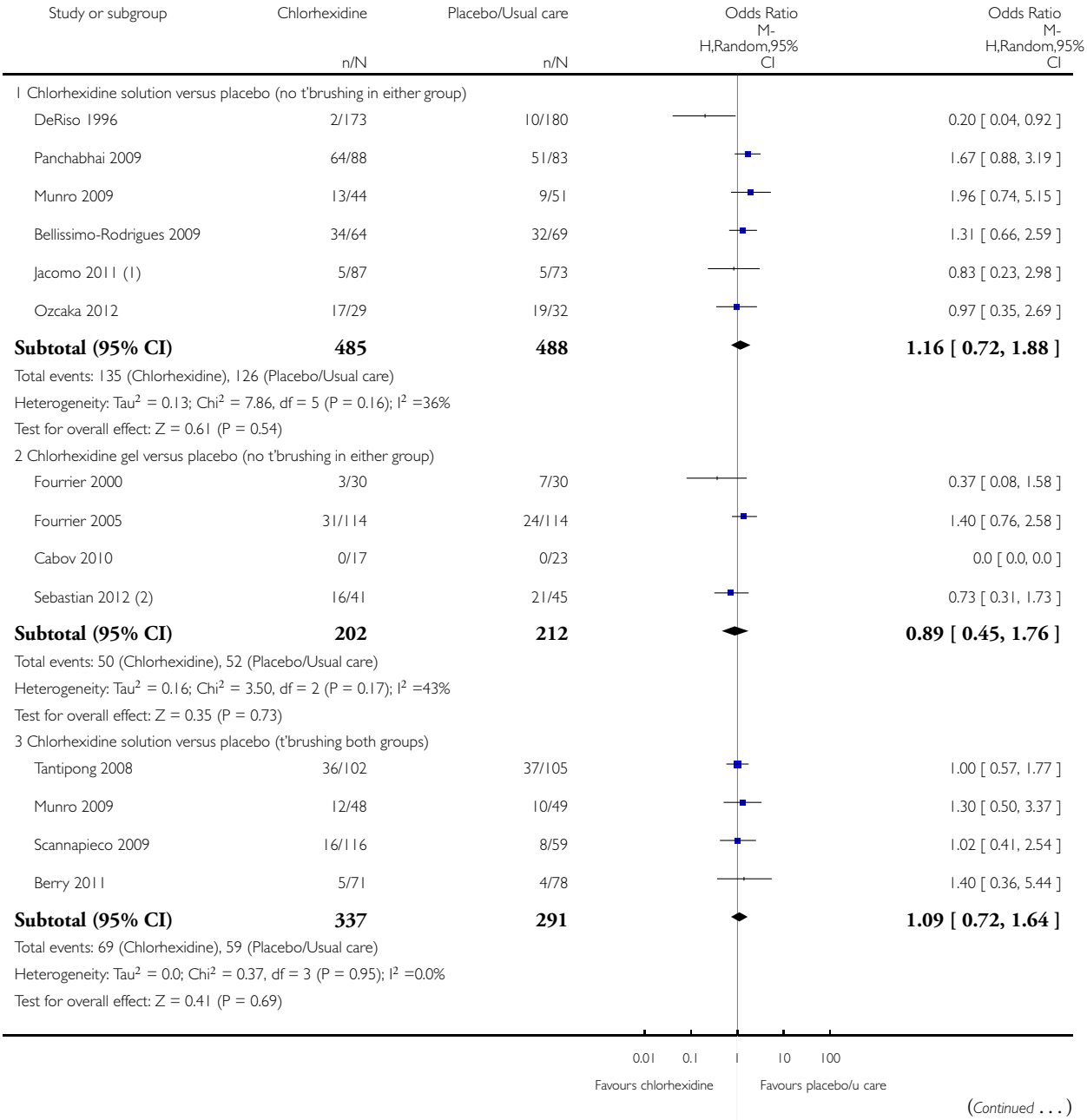
(7) Study with factorial design and equal exposure to toothbrushing in both groups

## Analysis 1.2. Comparison 1 Chlorhexidine versus placebo/usual care, Outcome 2 Mortality.

Review: Oral hygiene care for critically ill patients to prevent ventilator-associated pneumonia

Comparison: 1 Chlorhexidine versus placebo/usual care

Outcome: 2 Mortality

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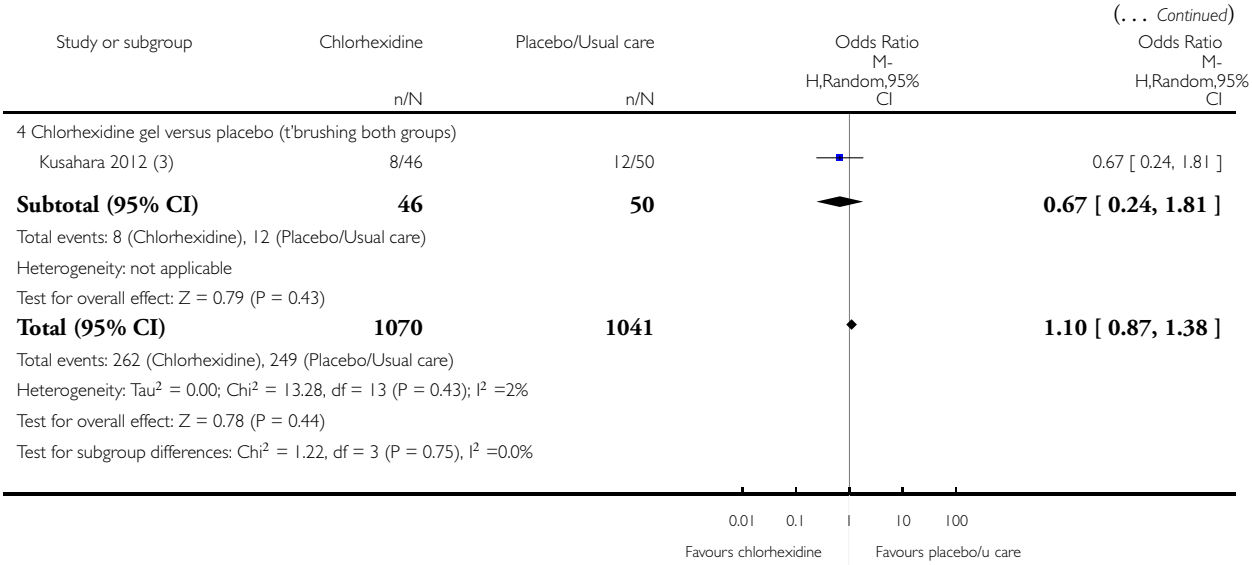



(1) Children

(2) Children

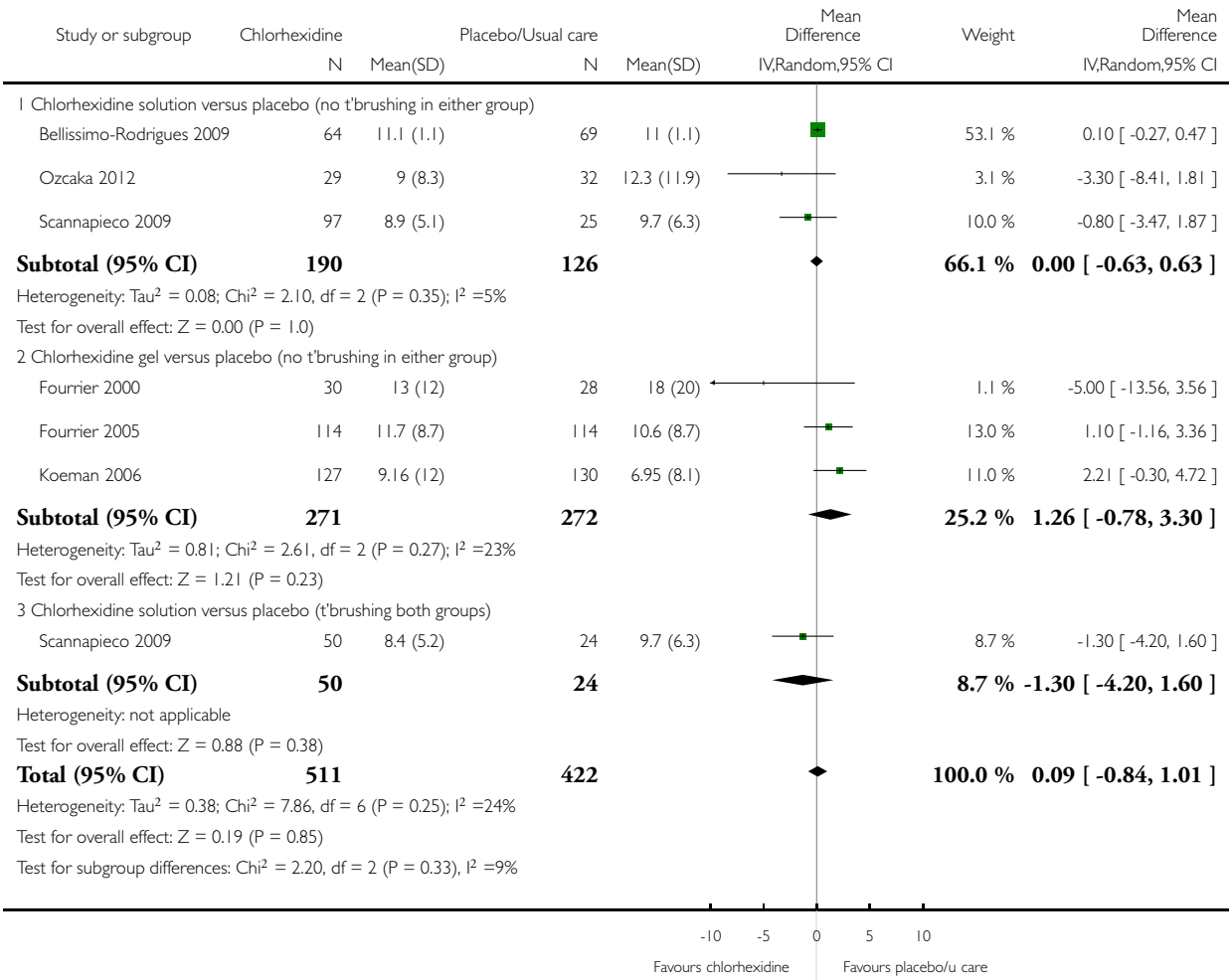
(3) Children

### Analysis 1.3. Comparison 1 Chlorhexidine versus placebo/usual care, Outcome 3 Duration of ventilation.

Review: Oral hygiene care for critically ill patients to prevent ventilator-associated pneumonia

Comparison: 1 Chlorhexidine versus placebo/usual care

Outcome: 3 Duration of ventilation

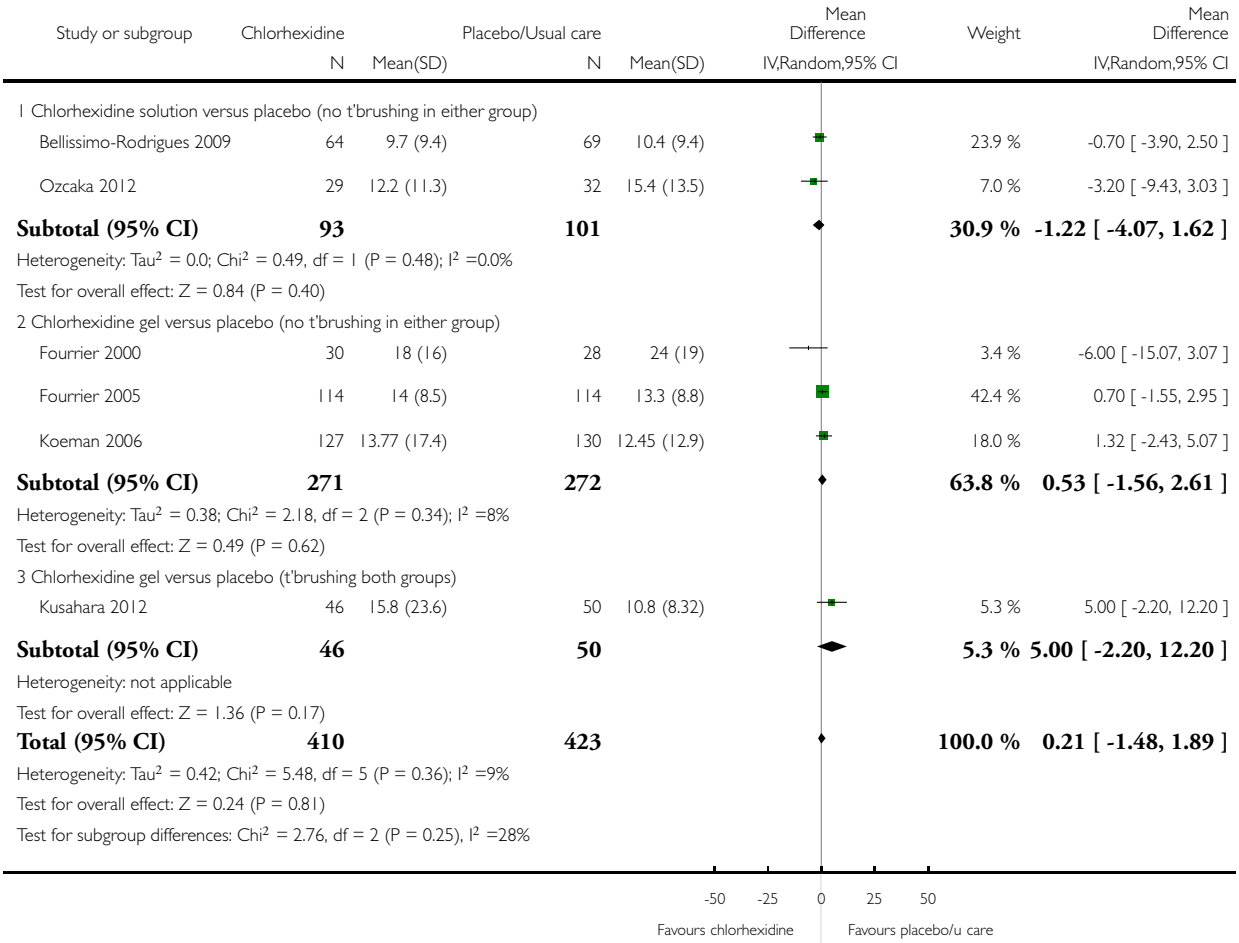


### Analysis 1.4. Comparison 1 Chlorhexidine versus placebo/usual care, Outcome 4 Duration of ICU stay.

Review: Oral hygiene care for critically ill patients to prevent ventilator-associated pneumonia

Comparison: 1 Chlorhexidine versus placebo/usual care

Outcome: 4 Duration of ICU stay



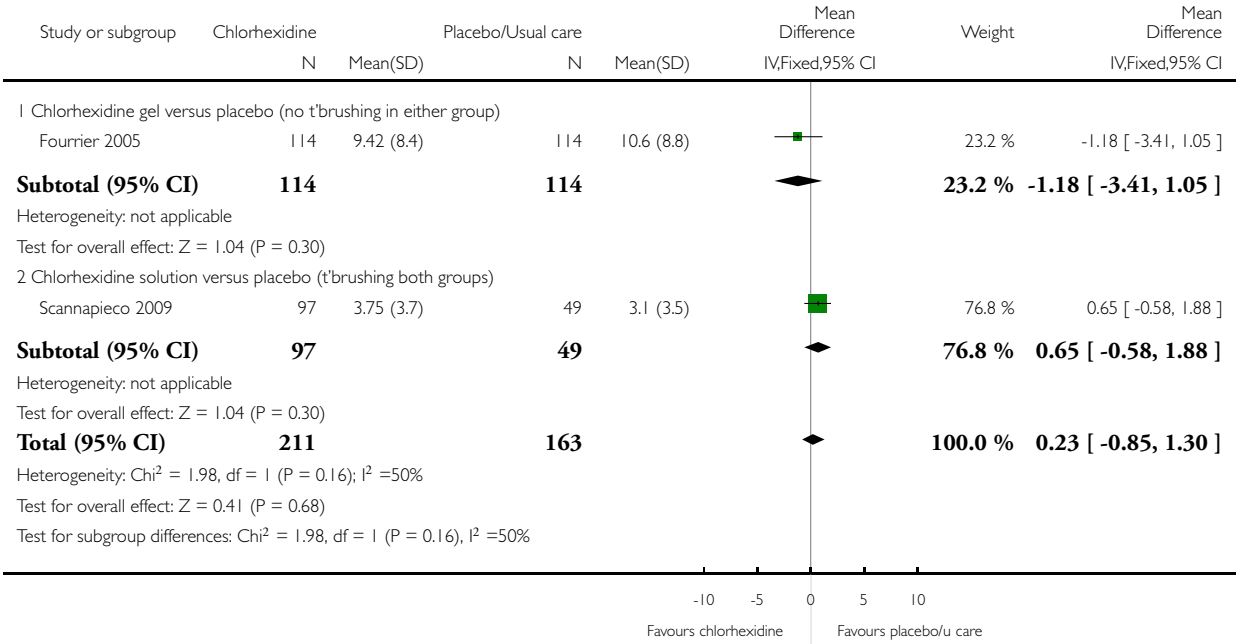
## Analysis 1.5. Comparison 1 Chlorhexidine versus placebo/usual care, Outcome 5 Duration of systemic antibiotic therapy.

Review: Oral hygiene care for critically ill patients to prevent ventilator-associated pneumonia

Comparison: 1 Chlorhexidine versus placebo/usual care

Outcome: 5 Duration of systemic antibiotic therapy

| Study or subgroup | Chlorhexidine N | Mean(SD) | Placebo/Usual care N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 Chlorhexidine gel versus placebo (no t'brushing in either group) | | | | | | | |
| Fourrier 2005 | 114 | 9.42 (8.4) | 114 | 10.6 (8.8) | | 23.2 % | -1.18 [ -3.41, 1.05 ] |
| **Subtotal (95% CI)** | **114** | | **114** | | | **23.2 %** | **-1.18 [ -3.41, 1.05 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 1.04 (P = 0.30) | | | | | | | |
| 2 Chlorhexidine solution versus placebo (t'brushing both groups) | | | | | | | |
| Scannapieco 2009 | 97 | 3.75 (3.7) | 49 | 3.1 (3.5) | | 76.8 % | 0.65 [ -0.58, 1.88 ] |
| **Subtotal (95% CI)** | **97** | | **49** | | | **76.8 %** | **0.65 [ -0.58, 1.88 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 1.04 (P = 0.30) | | | | | | | |
| **Total (95% CI)** | **211** | | **163** | | | **100.0 %** | **0.23 [ -0.85, 1.30 ]** |
| Heterogeneity: $Chi^2$ = 1.98, df = 1 (P = 0.16); $I^2$ =50% | | | | | | | |
| Test for overall effect: Z = 0.41 (P = 0.68) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 1.98, df = 1 (P = 0.16), $I^2$ =50% | | | | | | | |

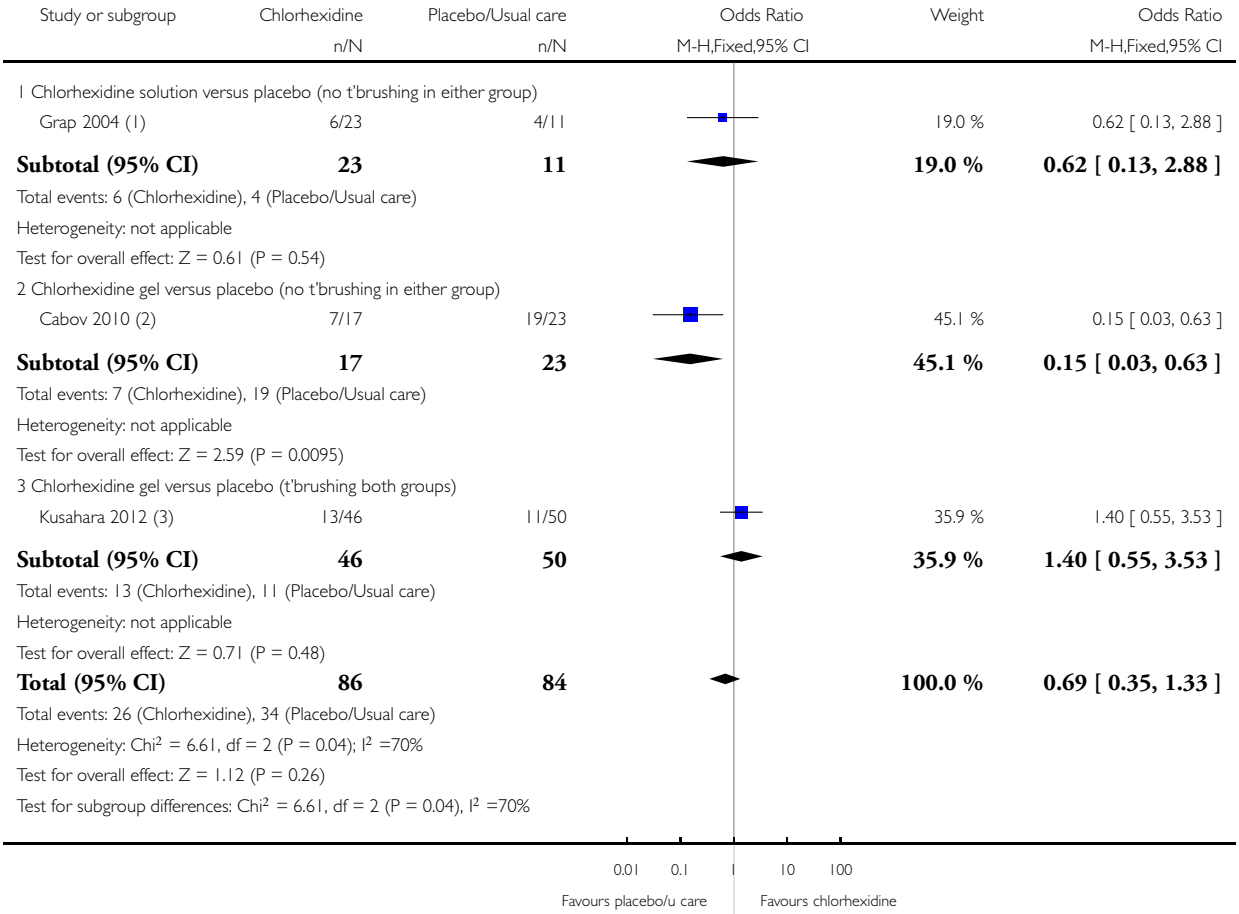


## Analysis 1.6. Comparison 1 Chlorhexidine versus placebo/usual care, Outcome 6 Positive cultures.

Review: Oral hygiene care for critically ill patients to prevent ventilator-associated pneumonia

Comparison: 1 Chlorhexidine versus placebo/usual care

Outcome: 6 Positive cultures




(1) Oral culture

(2) Tracheal culture

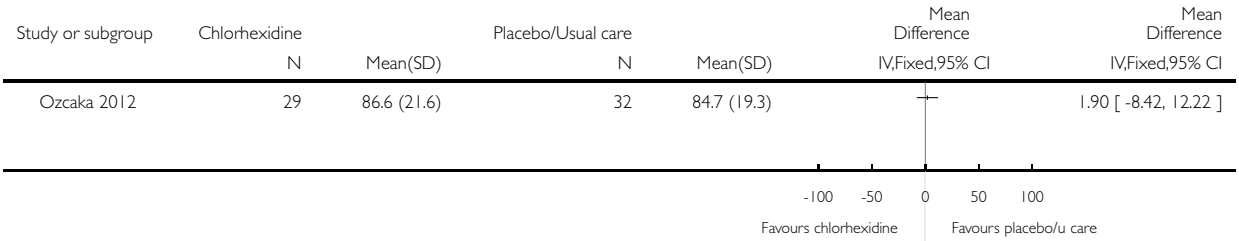
(3) Children

### Analysis 1.7. Comparison 1 Chlorhexidine versus placebo/usual care, Outcome 7 Plaque index.

Review: Oral hygiene care for critically ill patients to prevent ventilator-associated pneumonia

Comparison: 1 Chlorhexidine versus placebo/usual care

Outcome: 7 Plaque index

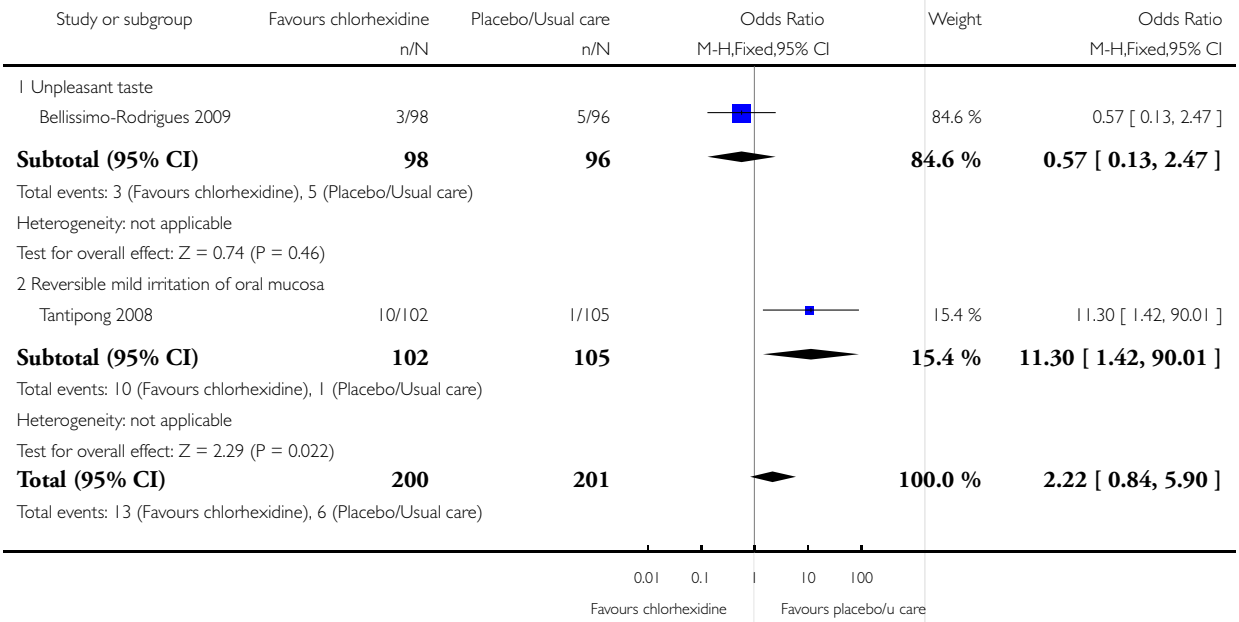



### Analysis 1.8. Comparison 1 Chlorhexidine versus placebo/usual care, Outcome 8 Adverse effects.

Review: Oral hygiene care for critically ill patients to prevent ventilator-associated pneumonia

Comparison: 1 Chlorhexidine versus placebo/usual care

Outcome: 8 Adverse effects

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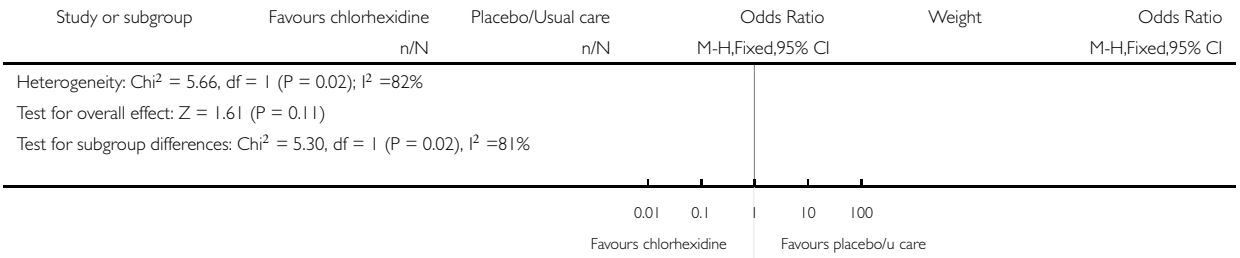
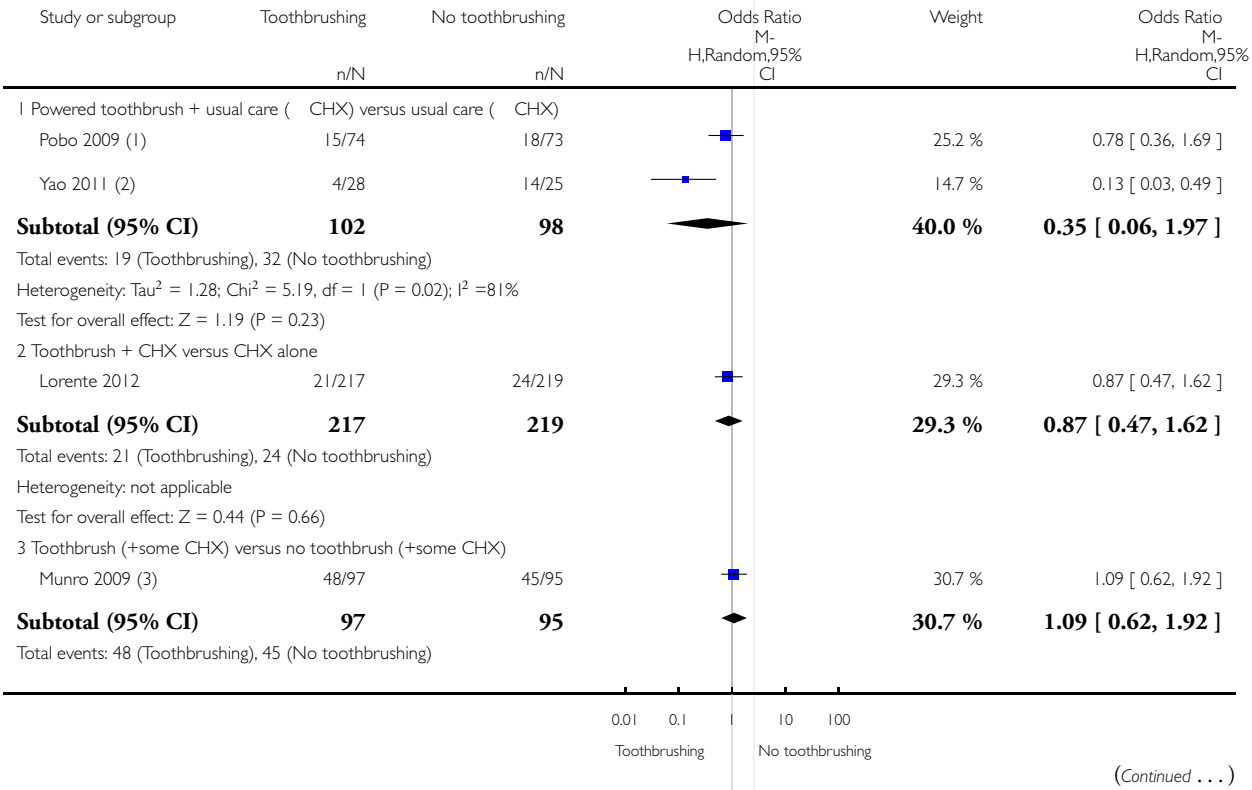



## Analysis 2.1. Comparison 2 Toothbrushing versus no toothbrushing, Outcome 1 Incidence of VAP.

Review: Oral hygiene care for critically ill patients to prevent ventilator-associated pneumonia

Comparison: 2 Toothbrushing versus no toothbrushing

Outcome: 1 Incidence of VAP

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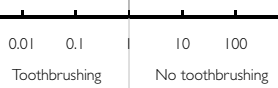
| Study or subgroup | Toothbrushing n/N | No toothbrushing n/N | Odds Ratio M-H,Random,95% CI | Weight | Odds Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.29 (P = 0.77) | | | | | |
| **Total (95% CI)** | **416** | **412** | | **100.0 %** | **0.69 [ 0.36, 1.29 ]** |
| Total events: 88 (Toothbrushing), 101 (No toothbrushing) | | | | | |
| Heterogeneity: $Tau^2$ = 0.26; $Chi^2$ = 8.44, df = 3 (P = 0.04); $I^2$ =64% | | | | | |
| Test for overall effect: Z = 1.17 (P = 0.24) | | | | | |
| Test for subgroup differences: $Chi^2$ = 1.58, df = 2 (P = 0.45), $I^2$ =0.0% | | | | | |




(1) CHX in both groups

(2) No CHX in either group

(3) Study with factorial design and equal exposure to CHX in both groups

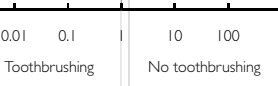
### Analysis 2.2. Comparison 2 Toothbrushing versus no toothbrushing, Outcome 2 Mortality.

Review: Oral hygiene care for critically ill patients to prevent ventilator-associated pneumonia

Comparison: 2 Toothbrushing versus no toothbrushing

Outcome: 2 Mortality

| Study or subgroup | Toothbrushing n/N | No toothbrushing n/N | Odds Ratio M-H,Random,95% CI | Weight | Odds Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| 1 Powered toothbrush+ usual care versus usual care | | | | | |
| Pobo 2009 (1) | 16/74 | 23/73 | | 18.1 % | 0.60 [ 0.29, 1.26 ] |
| Yao 2011 | 3/28 | 0/25 | | 1.1 % | 7.00 [ 0.34, 142.52 ] |
| **Subtotal (95% CI)** | **102** | **98** | | **19.2 %** | **1.32 [ 0.14, 12.90 ]** |
| Total events: 19 (Toothbrushing), 23 (No toothbrushing) | | | | | |
| Heterogeneity: $Tau^2$ = 1.85; $Chi^2$ = 2.48, df = 1 (P = 0.12); $I^2$ =60% | | | | | |
| Test for overall effect: Z = 0.24 (P = 0.81) | | | | | |
| 2 Toothbrush + CHX versus CHX alone | | | | | |
| Munro 2009 | 12/48 | 13/44 | | 11.7 % | 0.79 [ 0.32, 1.99 ] |

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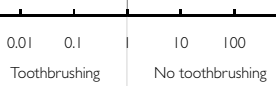
| Study or subgroup | Toothbrushing n/N | No toothbrushing n/N | Odds Ratio M-H,Random,95% CI | Weight | Odds Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| Lorente 2012 | 62/217 | 69/219 | | 59.2 % | 0.87 [ 0.58, 1.31 ] |
| **Subtotal (95% CI)** | **265** | **263** | | **70.9 %** | **0.86 [ 0.59, 1.25 ]** |
| Total events: 74 (Toothbrushing), 82 (No toothbrushing) | | | | | |
| Heterogeneity: $Tau^2$ = 0.0; $Chi^2$ = 0.03, df = 1 (P = 0.86); $I^2$ =0.0% | | | | | |
| Test for overall effect: Z = 0.81 (P = 0.42) | | | | | |
| 3 Toothbrush alone versus no treatment | | | | | |
| Munro 2009 | 10/49 | 9/51 | | 9.9 % | 1.20 [ 0.44, 3.25 ] |
| **Subtotal (95% CI)** | **49** | **51** | | **9.9 %** | **1.20 [ 0.44, 3.25 ]** |
| Total events: 10 (Toothbrushing), 9 (No toothbrushing) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.35 (P = 0.73) | | | | | |
| **Total (95% CI)** | **416** | **412** | | **100.0 %** | **0.85 [ 0.62, 1.16 ]** |
| Total events: 103 (Toothbrushing), 114 (No toothbrushing) | | | | | |
| Heterogeneity: $Tau^2$ = 0.0; $Chi^2$ = 3.22, df = 4 (P = 0.52); $I^2$ =0.0% | | | | | |
| Test for overall effect: Z = 1.01 (P = 0.31) | | | | | |
| Test for subgroup differences: $Chi^2$ = 0.49, df = 2 (P = 0.78), $I^2$ =0.0% | | | | | |




(1) CHX in both groups

### Analysis 2.3. Comparison 2 Toothbrushing versus no toothbrushing, Outcome 3 Duration of ventilation.

Review: Oral hygiene care for critically ill patients to prevent ventilator-associated pneumonia

Comparison: 2 Toothbrushing versus no toothbrushing

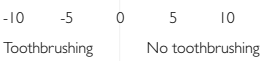
Outcome: 3 Duration of ventilation

| Study or subgroup | Toothbrushing N | Mean(SD) | No toothbrushing N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 Toothbrush + CHX versus CHX alone | | | | | | | |
| Lorente 2012 | 217 | 9.18 (14.13) | 219 | 9.93 (15.39) | | 32.5 % | -0.75 [ -3.52, 2.02 ] |
| Pobo 2009 | 74 | 8.9 (5.8) | 73 | 9.8 (6.1) | | 67.5 % | -0.90 [ -2.82, 1.02 ] |
| **Subtotal (95% CI)** | **291** | | **292** | | | **100.0 %** | **-0.85 [ -2.43, 0.73 ]** |

Heterogeneity: $Chi^2 = 0.01$, df = 1 (P = 0.93); $I^2 = 0.0\%$

Test for overall effect: Z = 1.06 (P = 0.29)

Test for subgroup differences: Not applicable




### Analysis 2.4. Comparison 2 Toothbrushing versus no toothbrushing, Outcome 4 Duration of ICU stay.

Review: Oral hygiene care for critically ill patients to prevent ventilator-associated pneumonia

Comparison: 2 Toothbrushing versus no toothbrushing

Outcome: 4 Duration of ICU stay

| Study or subgroup | Toothbrushing N | Mean(SD) | No toothbrushing N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 Toothbrush + CHX versus CHX alone | | | | | | | |
| Lorente 2012 | 217 | 12.07 (15.55) | 219 | 13.04 (17.27) | | 48.0 % | -0.97 [ -4.05, 2.11 ] |
| Pobo 2009 | 74 | 12.9 (8.7) | 73 | 15.5 (9.6) | | 52.0 % | -2.60 [ -5.56, 0.36 ] |
| **Subtotal (95% CI)** | **291** | | **292** | | | **100.0 %** | **-1.82 [ -3.95, 0.32 ]** |

Heterogeneity: $Chi^2 = 0.56$, df = 1 (P = 0.46); $I^2 = 0.0\%$

Test for overall effect: Z = 1.67 (P = 0.095)

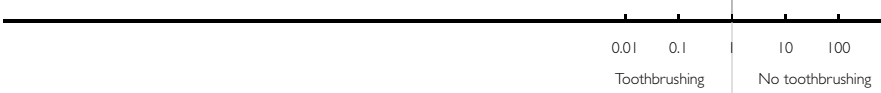
### Analysis 2.5. Comparison 2 Toothbrushing versus no toothbrushing, Outcome 5 Colonisation with VAP associated organisms (Day 5).

Review: Oral hygiene care for critically ill patients to prevent ventilator-associated pneumonia

Comparison: 2 Toothbrushing versus no toothbrushing

Outcome: 5 Colonisation with VAP associated organisms (Day 5)

| Study or subgroup | Toothbrushing n/N | No toothbrushing n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 versus CHX alone | | | | | |
| Needleman 2011 | 5/10 | 11/18 | | 100.0 % | 0.82 [ 0.40, 1.68 ] |
| **Subtotal (95% CI)** | **10** | **18** | | **100.0 %** | **0.82 [ 0.40, 1.68 ]** |
| Total events: 5 (Toothbrushing), 11 (No toothbrushing) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.55 (P = 0.59) | | | | | |
| Test for subgroup differences: Not applicable | | | | | |



### Analysis 2.6. Comparison 2 Toothbrushing versus no toothbrushing, Outcome 6 Plaque score.

Review: Oral hygiene care for critically ill patients to prevent ventilator-associated pneumonia

Comparison: 2 Toothbrushing versus no toothbrushing

Outcome: 6 Plaque score

| Study or subgroup | Toothbrushing N | Mean(SD) | No toothbrushing N | Mean(SD) | Std. Mean Difference IV,Fixed,95% CI | Weight | Std. Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 Powered toothbrush versus usual care | | | | | | | |
| Needleman 2011 (1) | 18 | 0.75 (0.5027) | 9 | 1.35 (0.5074) | | 33.4 % | -1.15 [ -2.02, -0.29 ] |
| Yao 2011 (2) | 25 | 2.51 (0.91) | 24 | 3.73 (1.06) | | 66.6 % | -1.22 [ -1.83, -0.60 ] |
| **Total (95% CI)** | **43** | | **33** | | | **100.0 %** | **-1.20 [ -1.70, -0.70 ]** |

Heterogeneity: $Chi^2 = 0.01$, df = 1 (P = 0.91); $I^2 = 0.0\%$

Test for overall effect: Z = 4.68 (P < 0.00001)

Test for subgroup differences: Not applicable


(1) CHX in both groups

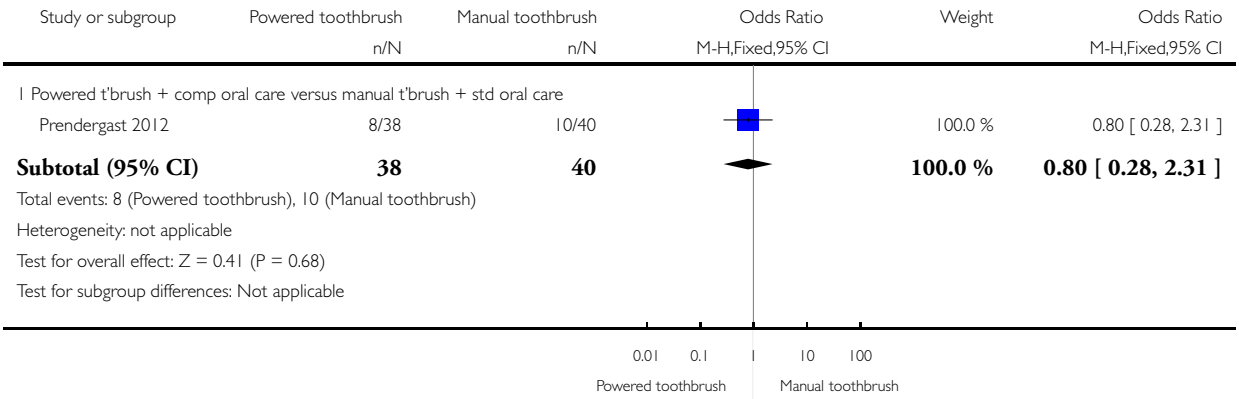
(2) No CHX in either group

### Analysis 3.1. Comparison 3 Powered toothbrush versus manual toothbrush, Outcome 1 Incidence of VAP.

Review: Oral hygiene care for critically ill patients to prevent ventilator-associated pneumonia

Comparison: 3 Powered toothbrush versus manual toothbrush

Outcome: 1 Incidence of VAP

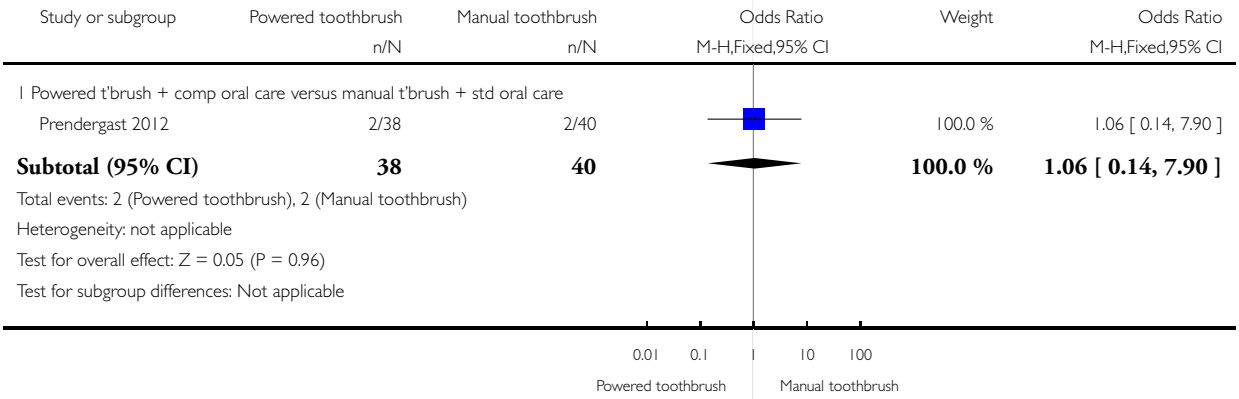



### Analysis 3.2. Comparison 3 Powered toothbrush versus manual toothbrush, Outcome 2 Mortality.

Review: Oral hygiene care for critically ill patients to prevent ventilator-associated pneumonia

Comparison: 3 Powered toothbrush versus manual toothbrush

Outcome: 2 Mortality

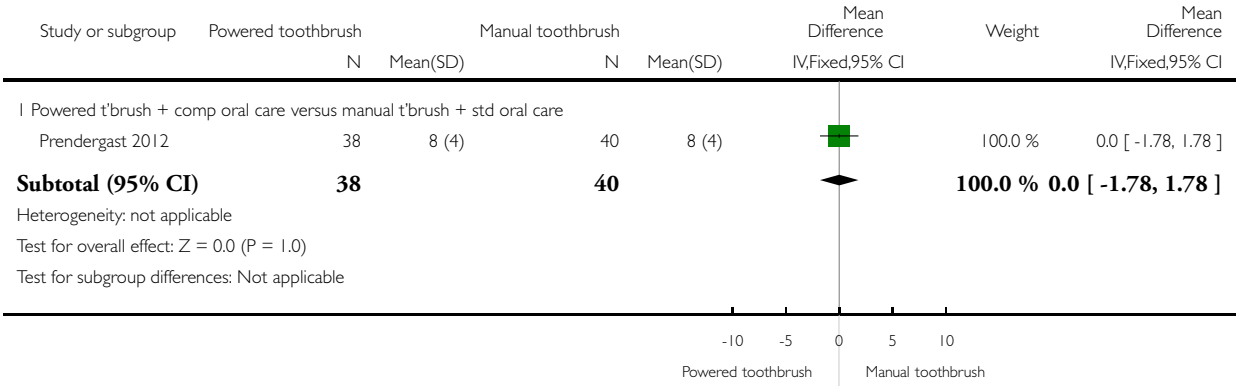


### Analysis 3.3. Comparison 3 Powered toothbrush versus manual toothbrush, Outcome 3 Duration of ventilation.

Review: Oral hygiene care for critically ill patients to prevent ventilator-associated pneumonia

Comparison: 3 Powered toothbrush versus manual toothbrush

Outcome: 3 Duration of ventilation

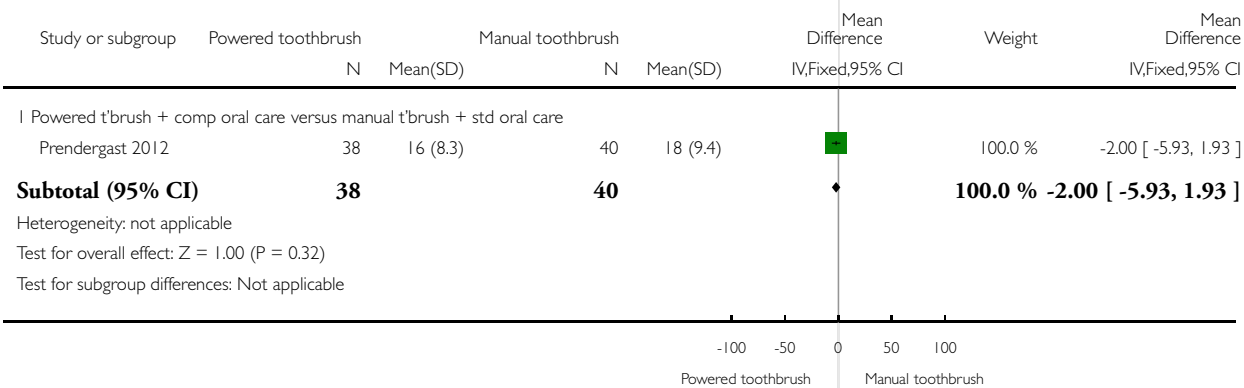



### Analysis 3.4. Comparison 3 Powered toothbrush versus manual toothbrush, Outcome 4 Duration of ICU stay.

Review: Oral hygiene care for critically ill patients to prevent ventilator-associated pneumonia

Comparison: 3 Powered toothbrush versus manual toothbrush

Outcome: 4 Duration of ICU stay

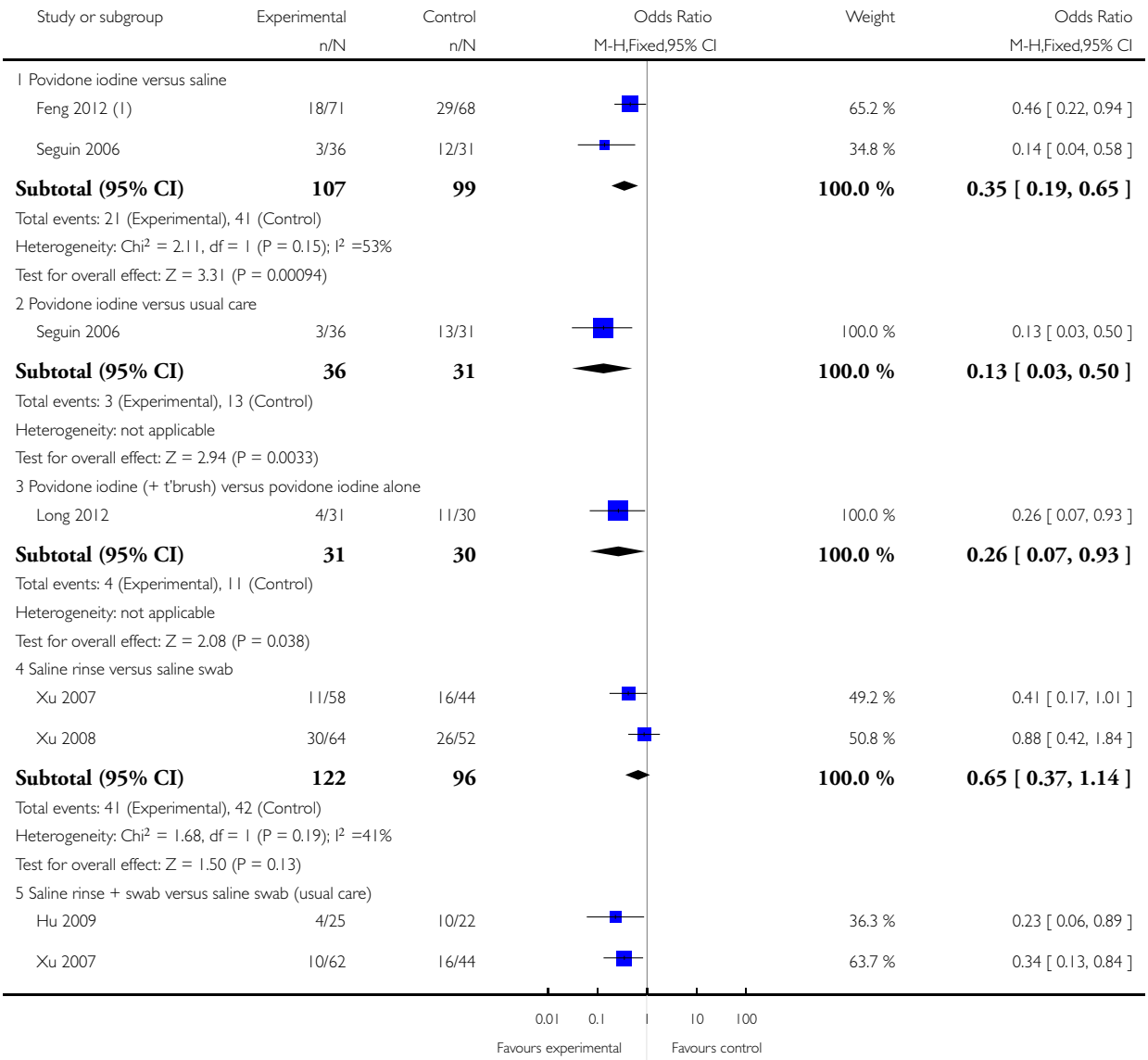


### Analysis 4.1. Comparison 4 Other oral care solutions, Outcome 1 Incidence of VAP.

Review: Oral hygiene care for critically ill patients to prevent ventilator-associated pneumonia

Comparison: 4 Other oral care solutions

Outcome: 1 Incidence of VAP

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| Study or subgroup | Experimental n/N | Control n/N | Odds Ratio M-H,Fixed,95% CI | Weight | Odds Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| **Subtotal (95% CI)** | **87** | **66** | | **100.0 %** | **0.30 [ 0.14, 0.63 ]** |
| Total events: 14 (Experimental), 26 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 0.21, df = 1 (P = 0.64); $I^2$ =0.0% | | | | | |
| Test for overall effect: Z = 3.14 (P = 0.0017) | | | | | |
| 6 Saline rinse versus usual care | | | | | |
| Caruso 2009 | 14/130 | 31/132 | | 77.5 % | 0.39 [ 0.20, 0.78 ] |
| Seguin 2006 | 12/31 | 13/31 | | 22.5 % | 0.87 [ 0.32, 2.41 ] |
| **Subtotal (95% CI)** | **161** | **163** | | **100.0 %** | **0.50 [ 0.29, 0.88 ]** |
| Total events: 26 (Experimental), 44 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 1.64, df = 1 (P = 0.20); $I^2$ =39% | | | | | |
| Test for overall effect: Z = 2.41 (P = 0.016) | | | | | |
| 7 Bicarbonate rinse versus water | | | | | |
| Berry 2011 | 4/76 | 4/78 | | 100.0 % | 1.03 [ 0.25, 4.27 ] |
| **Subtotal (95% CI)** | **76** | **78** | | **100.0 %** | **1.03 [ 0.25, 4.27 ]** |
| Total events: 4 (Experimental), 4 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.04 (P = 0.97) | | | | | |
| 8 Triclosan rinse versus saline | | | | | |
| Zhao 2012 | 73/162 | 82/162 | | 100.0 % | 0.80 [ 0.52, 1.24 ] |
| **Subtotal (95% CI)** | **162** | **162** | | **100.0 %** | **0.80 [ 0.52, 1.24 ]** |
| Total events: 73 (Experimental), 82 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 1.00 (P = 0.32) | | | | | |
| 9 Furacilin versus povidone iodine | | | | | |
| Feng 2012 (2) | 8/65 | 18/71 | | 100.0 % | 0.41 [ 0.17, 1.03 ] |
| **Subtotal (95% CI)** | **65** | **71** | | **100.0 %** | **0.41 [ 0.17, 1.03 ]** |
| Total events: 8 (Experimental), 18 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 1.90 (P = 0.058) | | | | | |
| 10 Furacilin versus saline | | | | | |
| Feng 2012 (3) | 8/65 | 29/68 | | 100.0 % | 0.19 [ 0.08, 0.46 ] |
| **Subtotal (95% CI)** | **65** | **68** | | **100.0 %** | **0.19 [ 0.08, 0.46 ]** |
| Total events: 8 (Experimental), 29 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 3.70 (P = 0.00021) | | | | | |


(1) Toothbrushing in both groups

(2) Toothbrushing in both groups

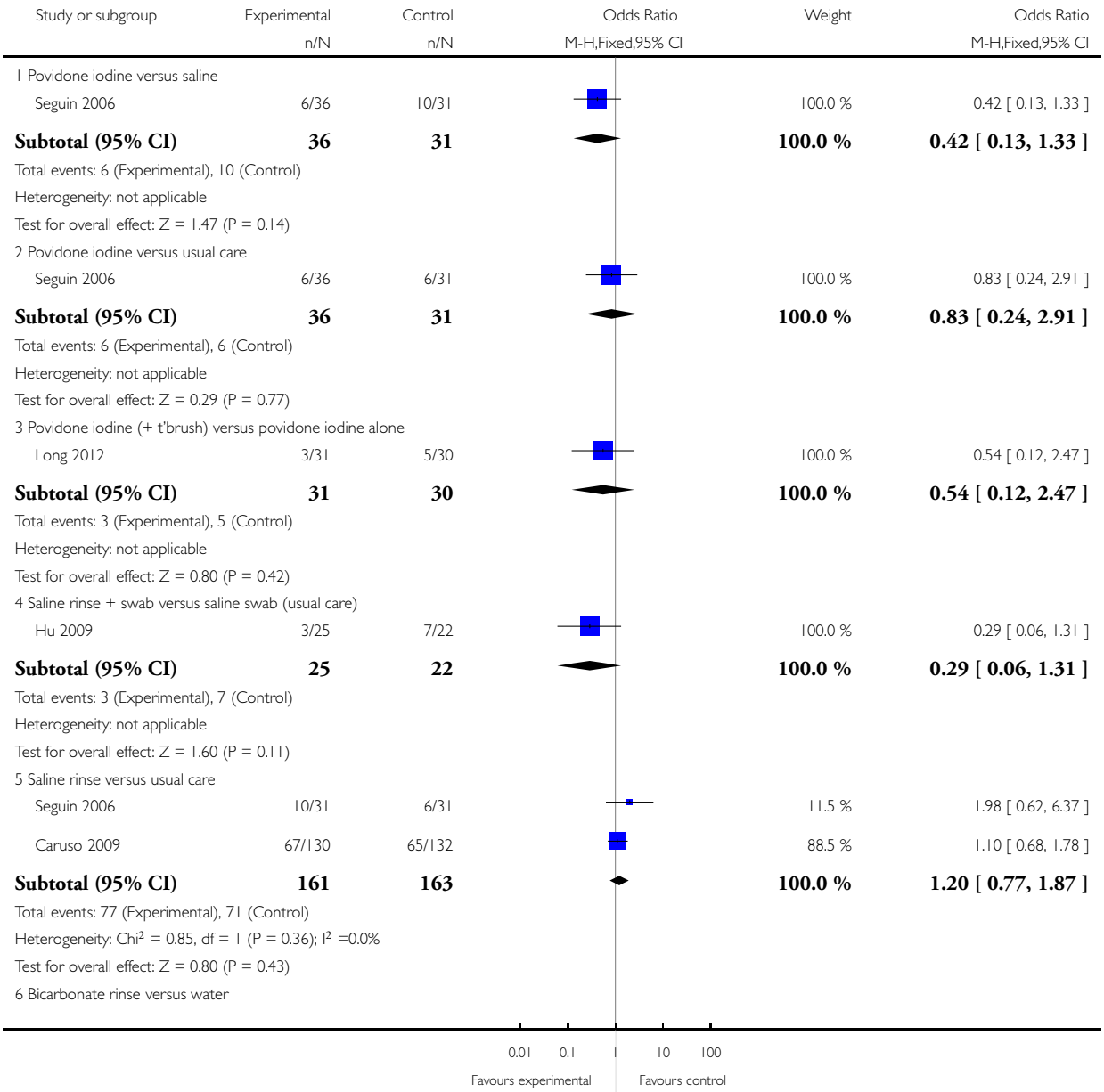
(3) Toothbrushing in both groups

## Analysis 4.2. Comparison 4 Other oral care solutions, Outcome 2 Mortality.

Review: Oral hygiene care for critically ill patients to prevent ventilator-associated pneumonia

Comparison: 4 Other oral care solutions

Outcome: 2 Mortality

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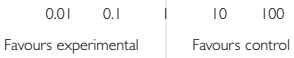
(. . . *Continued*)

| Study or subgroup | Experimental n/N | Control n/N | Odds Ratio M-H,Fixed,95% CI | Weight | Odds Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Berry 2011 | 13/76 | 4/78 | | 100.0 % | 3.82 [ 1.18, 12.30 ] |
| **Subtotal (95% CI)** | **76** | **78** | | **100.0 %** | **3.82 [ 1.18, 12.30 ]** |
| Total events: 13 (Experimental), 4 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 2.24 (P = 0.025) | | | | | |
| Test for subgroup differences: Chi² = 11.08, df = 5 (P = 0.05), I² =55% | | | | | |



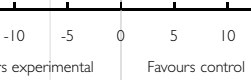

### Analysis 4.3. Comparison 4 Other oral care solutions, Outcome 3 Duration of ventilation.

Review: Oral hygiene care for critically ill patients to prevent ventilator-associated pneumonia

Comparison: 4 Other oral care solutions

Outcome: 3 Duration of ventilation

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 Povidone iodine versus saline | | | | | | | |
| Seguin 2006 | 36 | 9 (8) | 31 | 10 (6) | | 100.0 % | -1.00 [ -4.36, 2.36 ] |
| **Subtotal (95% CI)** | **36** | | **31** | | | **100.0 %** | **-1.00 [ -4.36, 2.36 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 0.58 (P = 0.56) | | | | | | | |
| 2 Povidone iodine versus usual care | | | | | | | |
| Seguin 2006 | 36 | 9 (8) | 31 | 12 (11) | | 100.0 % | -3.00 [ -7.67, 1.67 ] |
| **Subtotal (95% CI)** | **36** | | **31** | | | **100.0 %** | **-3.00 [ -7.67, 1.67 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 1.26 (P = 0.21) | | | | | | | |
| 3 Povidone iodine (+ t'brush) versus povidone iodine alone | | | | | | | |
| Long 2012 | 31 | 10.29 (1.93) | 30 | 10.16 (1.7) | | 100.0 % | 0.13 [ -0.78, 1.04 ] |
| **Subtotal (95% CI)** | **31** | | **30** | | | **100.0 %** | **0.13 [ -0.78, 1.04 ]** |
| Heterogeneity: not applicable | | | | | | | |

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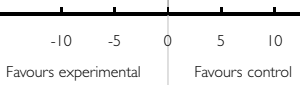
| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Test for overall effect: Z = 0.28 (P = 0.78) | | | | | | | |
| 4 Saline versus usual care | | | | | | | |
| Caruso 2009 | 130 | 11.2 (11.2) | 132 | 11.1 (9) | | 76.2 % | 0.10 [ -2.36, 2.56 ] |
| Seguin 2006 | 31 | 10 (6) | 31 | 12 (11) | | 23.8 % | -2.00 [ -6.41, 2.41 ] |
| **Subtotal (95% CI)** | **161** | | **163** | | | **100.0 %** | **-0.40 [ -2.55, 1.75 ]** |
| Heterogeneity: $Chi^2$ = 0.66, df = 1 (P = 0.42); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 0.36 (P = 0.72) | | | | | | | |
| 5 Saline rinse + swab versus saline swab | | | | | | | |
| Hu 2009 | 25 | 12.45 (1.17) | 22 | 16.36 (4.52) | | 100.0 % | -3.91 [ -5.85, -1.97 ] |
| **Subtotal (95% CI)** | **25** | | **22** | | | **100.0 %** | **-3.91 [ -5.85, -1.97 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 3.94 (P = 0.000081) | | | | | | | |
| 6 Saline rinse versus saline swab | | | | | | | |
| Xu 2008 | 64 | 22.5 (11.1) | 52 | 33.3 (15.8) | | 100.0 % | -10.80 [ -15.88, -5.72 ] |
| **Subtotal (95% CI)** | **64** | | **52** | | | **100.0 %** | **-10.80 [ -15.88, -5.72 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 4.16 (P = 0.000031) | | | | | | | |
| 7 Triclosan rinse versus saline | | | | | | | |
| Zhao 2012 | 162 | 8.96 (1.09) | 162 | 14.2 (2.37) | | 100.0 % | -5.24 [ -5.64, -4.84 ] |
| **Subtotal (95% CI)** | **162** | | **162** | | | **100.0 %** | **-5.24 [ -5.64, -4.84 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 25.57 (P < 0.00001) | | | | | | | |

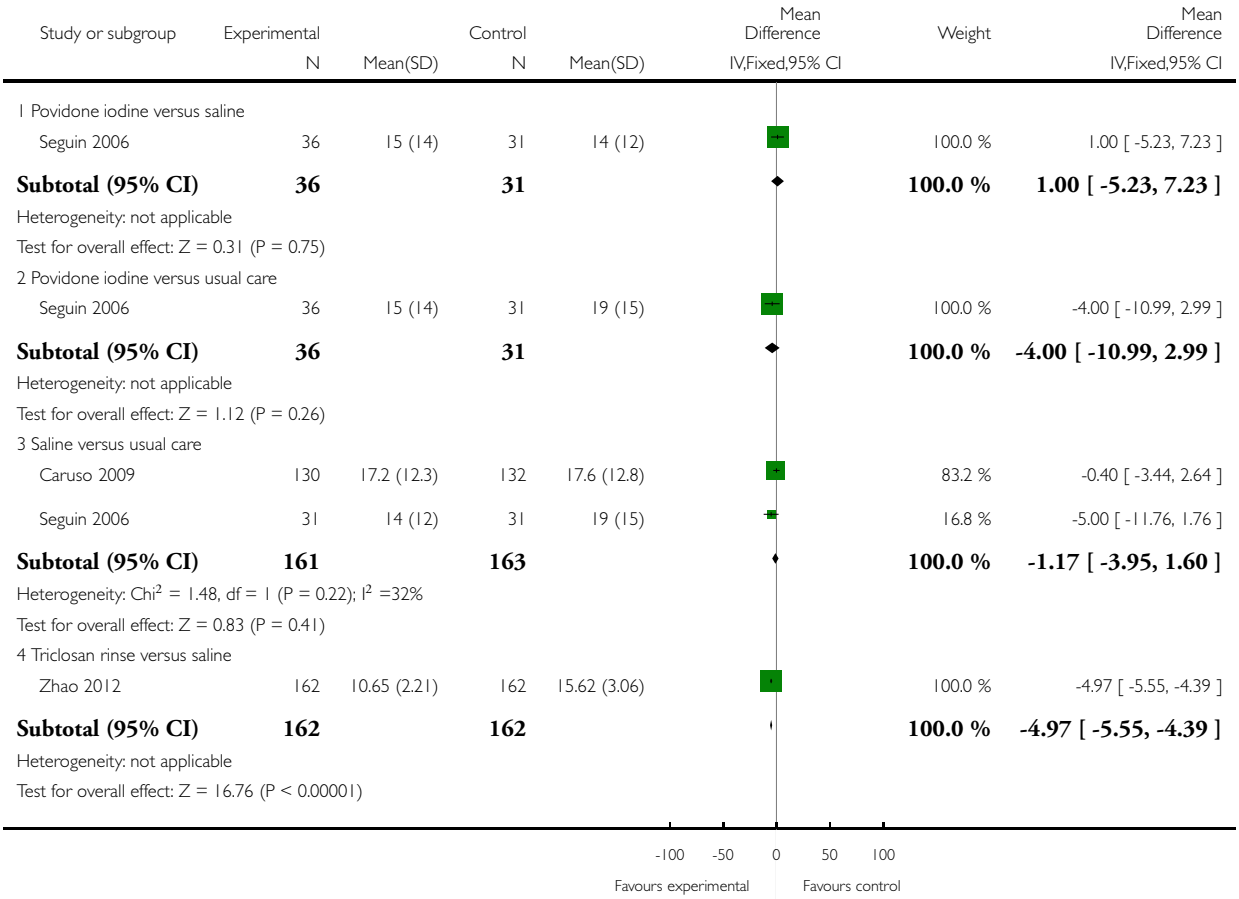


### Analysis 4.4. Comparison 4 Other oral care solutions, Outcome 4 Duration of ICU stay.

Review: Oral hygiene care for critically ill patients to prevent ventilator-associated pneumonia

Comparison: 4 Other oral care solutions

Outcome: 4 Duration of ICU stay

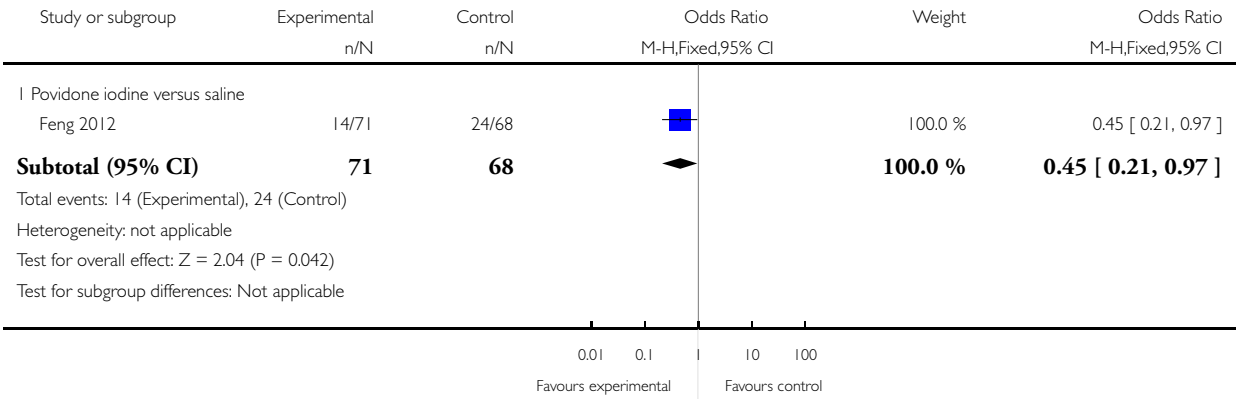


### Analysis 4.5. Comparison 4 Other oral care solutions, Outcome 5 Positive cultures.

Review: Oral hygiene care for critically ill patients to prevent ventilator-associated pneumonia

Comparison: 4 Other oral care solutions

Outcome: 5 Positive cultures




## ADDITIONAL TABLES

**Table 1. Other outcome data from included studies**

| Comparison | Outcome | Data | Effect estimate (95% CI) |
|---|---|---|---|
| CHX versus placebo/control ( Berry 2011) | Microbial colonisation | There was no significant difference in comparison of change in microbial growth from day 1 to day 4 between CHX and control groups | |
| Toothbrushing versus none ( Bopp 2006) | Incidence of VAP | 0/2 cases in toothbrushing group and 1/3 case in control group | |
| | Duration of ventilation | Mean 5.5 days (SD 0.3896) n = 2 in toothbrushing group and mean 5 days (SD 0.8051) n = 3 | |
| | Duration of ICU stay | Mean 18 days (SD 1.6695) n = 2 in toothbrushing group and mean 10.3 days (SD 2.6971) n = 3 | |

**Table 1. Other outcome data from included studies** (*Continued*)

| | | | |
|---|---|---|---|
| CHX versus placebo/control ( Grap 2004) | Microbial colonisation | Positive cultures in 3/11 patients in CHX spray group, 3/12 patients in CHX swab group and 4/11 patients in control group over the study period | |
| CHX versus placebo (Koeman 2006) | Mortality | Hazard ratio | HR 1.12 (0.72 to 1.17) |
| | Oral microbial colonisation | Hazard ratio, Gram positive organisms<br>Hazard ratio, Gram negative organisms | HR 0.695 (0.606 to 0.796) (Gram positive)<br>HR 0.826 (0.719 to 0.950) (Gram negative) |
| CHX spray versus CHX spray + toothbrush versus usual care (McCartt 2010) | Mean CPIS at 72 hours compared to baseline | CHX spray: CPIS score at 72 hours mean 4.88 (SD 2.14) n = 24<br>CHX spray + toothbrush: CPIS score at 72 hours mean 5.00 (SD 1.84) n = 24<br>Usual care: CPIS score at 72 hours mean 5.19 (SD 1.56) n = 21 | CHX spray versus usual care P = 0.58<br>CHX + toothbrushing versus usual care P = 0.71<br>Experimental groups combined versus usual care P = 0.57 |
| Powered toothbrush + CHX versus CHX alone (Roca Biosca 2011) | Plaque index | Mean in toothbrush group 1.68 (n = 29) and mean in control group 1.91 (n = 32)<br>No estimates of variance but reported that P = 0.7 (no difference) | |
| | Incidence of VAP | Odds ratio 0.78 (95% CI 0.36 to 1.68, P = 0.56) | |
| CHX (once daily or twice daily) versus placebo (Scannapieco 2009) | Plaque index | No difference between the 3 groups (data presented graphically) | |

CHX = chlorhexidine; CI = confidence interval; CPIS = Clinical Pulmonary Infection Score; HR = hazard ratio; ICU = intensive care unit; SD = standard deviation; VAP = ventilator-associated pneumonia

# APPENDICES

## Appendix 1. Cochrane Oral Health Group's Trials Register search strategy

#1 ((critical* AND ill*):ti,ab) AND (INREGISTER)
#2 ((depend* and patient*):ti,ab) AND (INREGISTER)
#3 (("critical care" or " intensive care" or ICU or CCU):ti,ab) AND (INREGISTER)
#4 ((intubat* or ventilat*):ti,ab) AND (INREGISTER)
#5 ((#1 or #2 or #3 or #4)) AND (INREGISTER)
#6 ((pneumonia or "nosocomial infect*" or VAP):ti,ab) AND (INREGISTER)
#7 (#5 and #6) AND (INREGISTER)

## Appendix 2. Cochrane Central Register of Controlled Trials (CENTRAL) search strategy

#1 MeSH descriptor Critical illness this term only
#2 (critical* in All Text near/6 ill* in All Text)
#3 (depend* in All Text near/6 patient* in All Text)
#4 MeSH descriptor Critical care this term only
#5 (intensive-care in All Text or "intensive care" in All Text or critical-care in All Text or "critical care" in All Text)
#6 ICU in Title, Abstract or Keywords
#7 ((intubat* in All Text near/5 patient* in All Text) or (ventilat* in All Text near/5 patient* in All Text))
#8 (#1 or #2 or #3 or #4 or #5 or #6 or #7)
#9 (VAP in Title, Abstract or Keywords or VAP in Title, Abstract or Keywords)
#10 "nosocomial infection*" in Title, Abstract or Keywords
#11 MeSH descriptor Pneumonia, Ventilator-Associated this term only
#12 pneumonia in All Text
#13 (#9 or #10 or #11 or #12)
#14 MeSH descriptor Oral health this term only
#15 MeSH descriptor Oral hygiene explode all trees
#16 MeSH descriptor Dentifrices explode all trees
#17 MeSH descriptor Mouthwashes explode all trees
#18 MeSH descriptor Periodontal diseases explode all trees
#19 periodont* in All Text
#20 ("oral care" in All Text or "oral health" in All Text or oral-health in All Text or "mouth care" in All Text or "oral hygien*" in All Text or oral-hygien* in All Text or "dental hygien*" in All Text or decontaminat* in All Text)
#21 (mouthwash* in All Text or mouth-wash* in All Text or mouth-rins* in All Text or mouthrins* in All Text or "oral rins*" in All Text or oral-rins* in All Text or "artificial saliva" in All Text or "saliva substitut*" in All Text or ( (denture* in All Text near/6 clean* in All Text) or toothpaste* in All Text) or dentifrice* in All Text)
#22 (#14 or #15 or #16 or #17 or #18 or #19 or #20 or #21)
#23 (#8 and #13)
#24 (#22 and #23)

## Appendix 3. MEDLINE via OVID search strategy

1. CRITICAL ILLNESS/
2. (critical$ adj5 ill$).mp.
3. (depend$ adj5 patient$).mp.
4. INTENSIVE CARE/
5. ("intensive care" or intensive-care or "critical care" or critical-care).mp.
6. ICU.mp. or CCU.ti,ab.
7. ((intubat$ or ventilat$) adj5 patient$).mp.
8. or/1-7
9. PNEUMONIA, VENTILATOR-ASSOCIATED/
10. pneumonia.ti,ab.
11. VAP.ti,ab.
12. "nosocomial infection".mp.
13. or/9-12
14. exp ORAL HYGIENE/
15. exp DENTIFRICES/
16. MOUTHWASHES/
17. ANTI-INFECTIVE AGENTS, LOCAL/
18. Cetylpyridinium/
19. Chlorhexidine/
20. Povidone-Iodine/
21. ("oral care" or "mouth care" or "oral hygien$" or oral-hygien$ or "dental hygien$").ti,ab.
22. (mouthwash$ or mouth-wash$ or mouth-rins$ or mouthrins$ or "oral rins$" or oral-rins$ or toothpaste$ or dentifrice$ or toothbrush$ or chlorhexidine$ or betadine$ or triclosan$ or cepacol or Corsodyl or Peridex or Hibident or Prexidine or Parodex or Chlorexil or Peridont or Eludril or Perioxidin or Chlorohex or Savacol or Periogard or Chlorhexamed or Nolvasan or Sebidin or Tubulicid or hibitane).mp.
23. (antiseptic$ or antiinfect$ or "local microbicide$" or "topical microbicide$").mp.
24. or/14-23
25. 8 and 13 and 24

## Appendix 4. EMBASE via OVID search strategy

1. CRITICAL ILLNESS/
2. (critical$ adj5 ill$).mp.
3. (depend$ adj5 patient$).mp.
4. INTENSIVE CARE/
5. ("intensive care" or intensive-care or "critical care" or critical-care).mp.
6. (ICU or CCU).ti,ab.
7. ((intubat$ or ventilat$) adj5 patient$).mp.
8. or/1-7
9. PNEUMONIA, VENTILATOR-ASSOCIATED/
10. pneumonia.ti,ab.
11. VAP.ti,ab.
12. "nosocomial infection".mp.
13. or/9-12
14. exp ORAL HYGIENE/
15. exp DENTIFRICES/
16. MOUTHWASHES/
17. ANTI-INFECTIVE AGENTS, LOCAL/
18. Cetylpyridinium/
19. Chlorhexidine/
20. Povidone-Iodine/

21. ("oral care" or "mouth care" or "oral hygien$" or oral-hygien$ or "dental hygien$").ti,ab.
22. (mouthwash$ or mouth-wash$ or mouth-rins$ or mouthrins$ or "oral rins$" or oral-rins$ or toothpaste$ or dentifrice$ or toothbrush$ or chlorhexidine$ or betadine$ or triclosan$ or cepacol or Corsodyl or Peridex or Hibident or Prexidine or Parodex or Chlorexil or Peridont or Eludril or Perioxidin or Chlorohex or Savacol or Periogard or Chlorhexamed or Nolvasan or Sebidin or Tubulicid or hibitane).mp.
23. (antiseptic$ or antiinfect$ or "local microbicide$" or "topical microbicide$").mp.
24. or/14-23
25. 8 and 13 and 24
The above subject search was linked to the Cochrane Oral Health Group filter for EMBASE via OVID:
1. random$.ti,ab.
2. factorial$.ti,ab.
3. (crossover$ or cross over$ or cross-over$).ti,ab.
4. placebo$.ti,ab.
5. (doubl$ adj blind$).ti,ab.
6. (singl$ adj blind$).ti,ab.
7. assign$.ti,ab.
8. allocat$.ti,ab.
9. volunteer$.ti,ab.
10. CROSSOVER PROCEDURE.sh.
11. DOUBLE-BLIND PROCEDURE.sh.
12. RANDOMIZED CONTROLLED TRIAL.sh.
13. SINGLE BLIND PROCEDURE.sh.
14. or/1-13
15. ANIMAL/ or NONHUMAN/ or ANIMAL EXPERIMENT/
16. HUMAN/
17. 16 and 15
18. 15 not 17
19. 14 not 18

## Appendix 5. CINAHL via EBSCO search strategy

S25 S14 and S24
S24 S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23
S23 (antiseptic* or antiinfect* or "local microbicide*" or "topical microbicide*")
S22 (mouthwash* or mouth-wash* or mouth-rins* or mouthrins* or "oral rins*" or oral-rins* or toothpaste* or dentifrice* or toothbrush* or chlorhexidine* or betadine* or triclosan* or cepacol or Corsodyl or Peridex or Hibident or Prexidine or Parodex or Chlorexil or Peridont or Eludril or Perioxidin or Chlorohex or Savacol or Periogard or Chlorhexamed or Nolvasan or Sebidin or Tubulicid or hibitane)
S21 ("oral care" or "mouth care" or "oral hygien*" or oral-hygien* or "dental hygien*")
S20 (MH Povidone-Iodine)
S19 (MH Chlorhexidine)
S18 (MH "Antiinfective Agents, Local")
S17 MH MOUTHWASHES
S16 (MH "DENTIFRICES+")
S15 (MH "Oral Hygiene+")
S14 S8 AND S13
S13 S9 or S10 or S11 or S12
S12 TI pneumonia or AB pneumonia
S11 MH PNEUMONIA, VENTILATOR-ASSOCIATED
S10 TI "nosocomial infection" and AB "nosocomial infection"
S9 TI VAP or AB VAP
S8 S1 or S2 or S3 or S4 or S5 or S6 or S7

S7 ((intubat* N5 patient*) or (ventilat* N5 patient*))
S6 TI ICU or AB ICU or TI CCU or AB CCU
S5 (intensive-care or "intensive care" or critical-care or "critical care")
S4 MH CRITICAL CARE
S3 (depend* N6 patient*)
S2 (critical* N6 ill*)
S1 MH CRITICAL ILLNESS

## Appendix 6. LILACS via BIREME Virtual Health Library search strategy

(Mh Critical illness or "Enfermedad Crítica" or "Estado Terminal" or "critical illness$" or Mh Intensive care or "Cuidados Intensivos" or "Terapia Intensiva" or "critical care" or "intensive care" or "ICU" or "CCU" or intubate$ or ventilate$) [Words] and (Mh Pneumonia, Ventilator-Associated or "Neumonia Asociada al Ventilador" or "Pneumonia Associada à Ventilação Mecânica" or (ventilator AND pneumonia)) [Words] and (Mh Oral hygiene or "oral hygiene" or "Higiene Bucal" or "oral care" or "mouth care" or mouthwash$ or mouthrins$ or toothpaste$ or dentifrice$ or chlorhexidine or betadine or triclosan or Clorhexidina or Clorexidina or "Antisépticos Bucales" or "Antissépticos Bucais" or "Cepillado Dental" or "Escovação Dentária" or antiseptic$ or antiinfective$)

## Appendix 7. Chinese Biomedical Literature Database search strategy

#1 缺省[智能]:危重 -限定:1978-2012

#2 缺省:ICU -限定:1978-2012

#3 缺省:VAP -限定:1978-2012

#4 缺省:插管 -限定:1978-2012
#5 #4 or #3 or #2 or #1

#6 缺省:口 腔护理

#7 缺省[智能]:口 腔清洁

#8 缺省:口 腔卫生

#9 缺省[智能]:刷牙
#10 #9 or #8 or #7 or #6
#11 #10 and #5

#12 缺省[智能]:随机

#13 缺省:随机对照
#14 #13 or #12
#15 #14 and #11

## Appendix 8. China National Knowledge Infrastructure search strategy

#1 数据库: 中国期刊全文数据库 检索条件: ((题名=VAP) 或者 (摘要=ICU) 或者 (题名=危重))并且(摘要=呼吸机相关性肺炎) 或者 (摘要=插管) (模糊匹配);2003-2012;全部期刊;时间排序; 单库检索

#2 数据库: 中国期刊全文数据库 检索条件: (题名=口 腔护理) 或者 (摘要=口 腔去污染) 或者 (题名=口 腔清洁) 或者 (摘要=刷牙) 或者 (主题=口 腔卫生) (模糊匹配);时间排序; 单库检索(结果中 检索)

#3 数据库: 中国期刊全文数据库 检索条件: (题名=随机对照) 或者 (摘要=随机) 或者 (题名=随机对照实验) 或者 (摘要=随机分配) 或者 (主题=随机隐藏) (模糊匹配);时间排序; 单库检索(结果中 检索)

## Appendix 9. Wan Fang Database search strategy

1. ((全部字段 =(模糊匹配) "危重") ) ; 按相关度排序
2. ((全部字段 =(模糊匹配) "ICU") ) ; 按相关度排序
3. ((全部字段 =(模糊匹配) "VAP") ) ; 按相关度排序
4. ((全部字段 =(模糊匹配) "口腔") ) ; 按相关度排序
5. ((全部字段 =(模糊匹配) "刷牙") ) ; 按相关度排序
6. ((全部字段 =(模糊匹配) "去污染") ) ; 按相关度排序
7. ((全部字段 =(模糊匹配) "洗必泰") ) ; 按相关度排序
8. ((全部字段 =(模糊匹配) "口腔冲洗") ) ; 按相关度排序
9. ((全部字段 =(模糊匹配) "危重") ) 或 ((全部字段 =(模糊匹配) "ICU") ) 或 ((全部字段 =(模糊匹配) "VAP") )
10. ((全部字段 =(模糊匹配) "口腔") ) 或 ((全部字段 =(模糊匹配) "刷牙") ) 或 ((全部字段 =(模糊匹配) "去污染") ) 或 ((全部字段 =(模糊匹配) "洗必泰") ) 或 ((全部字段 =(模糊匹配) "口腔冲洗") )
11. ( ((全部字段 =(模糊匹配) "口腔") ) 或 ((全部字段 =(模糊匹配) "刷牙") ) 或 ((全部字段 =(模糊匹配) "去污染") ) 或 ((全部字段 =(模糊匹配) "洗必泰") ) 或 ((全部字段 =(模糊匹配) "口腔冲洗") ) ) 与 ( ((全部字段 =(模糊匹配) "口腔") ) 或 ((全部字段 =(模糊匹配) "刷牙") ) 或 ((全部字段 =(模糊匹配) "去污染") ) 或 ((全部字段 =(模糊匹配) "洗必泰") ) 或 ((全部字段 =(模糊匹配) "口腔冲洗") ) 与 ((全部字段 =(模糊匹配) "危重") ) 或 ((全部字段 =(模糊匹配) "ICU") ) 或 ((全部字段 =(模糊匹配) "VAP") ) )

## Appendix 10. OpenGrey search strategy

"oral health" or "oral hygiene" or "oral care" or "mouth care" or "dental hygiene" or mouthwash* or mouth-wash or mouthrinse* or mouth-rinse* or "artificial saliva" or "saliva substitute*" or toothpaste* or dentifrice* or periodontic* or periodontal
AND
"critical care" or "intensive care" or ICU or "critical illness" or intubated or ventilated

## Appendix 11. ClinicalTrials.gov search strategy

ventilator and pneumonia and "oral hygiene"

## CONTRIBUTIONS OF AUTHORS

Zongdao Shi and Huixu Xie: As joint first authors, conceiving, designing and co-ordinating the protocol, preparing a draft of the review.

Sue Furness: Contact author, updating background, revising inclusion criteria, screening search results, extracting data, assessing risk of bias, conducting meta-analysis and revising the text of the review.

Helen Worthington: Screening search results, extracting data, assessing risk of bias, conducting meta-analysis.

Ian Needleman: Updating background and revising inclusion criteria, extracting data, assessing risk of bias, contributing to the discussion section.

Ping Wang, Huixu Xie, Qi Zhang: Undertaking searches, screening search results, appraising risk of bias, extracting data.

E Chen and Yan Wu, Ian Needleman: Appraising quality of those papers for which Xie and Wang disagreed, participating in the discussion prior to preparation of the first draft.

Linda Ng: Electronic and handsearching for nursing journal articles.

## DECLARATIONS OF INTEREST

Ian Needleman is the first author of one of the studies included in this review. The assessment of risk of bias and the data extraction of this study was undertaken by two other review authors.

None known.

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## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Clarifications were made to the criteria for studies eligible to be included in this review.

- Participants in trials should not have a respiratory infection at baseline.

- The interventions to be included in this review must include an oral hygiene care component. Trials where the intervention being evaluated was a type of suction system or variation of method, timing, or place where mechanical ventilation was introduced (e.g. emergency room or ICU) were excluded.

- Minimum duration of mechanical ventilation of 48 hours, in order for the diagnosis of nosocomial pneumonia, diagnosed either during period of ventilation or within 48 hours of extubation, to be considered ventilator-associated pneumonia.

- Outcome of mortality defined as either all cause ICU mortality or where this was not available, all cause 30-day mortality. We considered that the effect of the underlying condition(s) on mortality would be similar in each randomised treatment group during this period.

- In order to avoid duplication, trials where the intervention was selective decontamination of the digestive tract with antibiotics were excluded as these interventions are included in another Cochrane review (D'Amico 2009).

- Likewise trials where the intervention was probiotics were excluded as these interventions are included in another Cochrane review (Hao 2011).

The text in the methods section of this review about the risk of bias assessment has been updated in line with the latest version of the *Cochrane Hanbook for Systematic Reviews of Interventions* and additional details about the process followed have been added.