Prevention of ventilator-associated pneumonia with oral antiseptics: a systematic review and meta-analysis

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Summary

Background We did a systematic review and random effects meta-analysis of randomised trials to assess the effect of oral care with chlorhexidine or povidone-iodine on the prevalence of ventilator-associated pneumonia versus oral care without these antiseptics in adults.

Methods Studies were identified through PubMed, CINAHL, Web of Science, CENTRAL, and complementary manual searches. Eligible studies were randomised trials of mechanically ventilated adult patients receiving oral care with chlorhexidine or povidone-iodine. Relative risks (RR) and 95% CIs were calculated with the Mantel-Haenszel model and heterogeneity was assessed with the I^2 test.

Findings 14 studies were included (2481 patients), 12 investigating the effect of chlorhexidine (2341 patients) and two of povidone-iodine (140 patients). Overall, antiseptic use resulted in a significant risk reduction of ventilator-associated pneumonia (RR 0·67; 95% CI 0·50–0·88; p=0·004). Chlorhexidine application was shown to be effective (RR 0·72; 95% CI 0·55–0·94; p=0·02), whereas the effect resulting from povidone-iodine remains unclear (RR 0·39; 95% CI 0·11–1·36; p=0·14). Heterogeneity was moderate (I^2=29%; p=0·16) for the trials using chlorhexidine and high (I^2=67%; p=0·08) for those assessing povidone-iodine use. Favourable effects were more pronounced in subgroup analyses for 2% chlorhexidine (RR 0·53, 95% CI 0·31–0·91), and in cardiosurgical studies (RR 0·41, 95% CI 0·17–0·98).

Interpretation This analysis showed a beneficial effect of oral antiseptic use in prevention of ventilator-associated pneumonia. Clinicians should take these findings into account when providing oral care to intubated patients.

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Introduction

Ventilator-associated pneumonia is defined as pneumonia in people who have a device to continuously assist or control respiration through a tracheostomy or by endotracheal intubation within 48 h before the onset of infection, inclusive of the weaning period.[1] Affecting 10–30% of mechanically ventilated patients, this type of pneumonia is one of the most frequent nosocomial infections in intensive care units.[2,3] Depending on the casemix, disease severity, microorganisms involved, and adequacy of anti-infective management, the attributable mortality (mortality in exposed patients in excess to mortality in matched unexposed patients) can exceed 50%.[4] Moreover, ventilator-associated pneumonia is an important cause of morbidity, increased use of health-care resources, and excess cost.[3] As such, prevention of this disease is a priority in quality improvement programmes in intensive care units[5,6] and plenty of efforts have been taken to elucidate the effect of distinct preventive measures.[7–9]

The most important mechanism for development of ventilator-associated pneumonia is aspiration of colonised oropharyngeal secretions into the lower respiratory tract.[10] Oral bacterial colonisation results from accumulation of debris in the oral cavity. Adequate salivary flow is an important factor for maintainance of oral health through its antimicrobial, lubricating, and buffering properties. In intubated patients, however, a constantly open mouth and the use of drugs such as antihypertensives, anticholinergics, antipsychotics, and diuretics predispose for xerostomia and subsequent reduction in salivary immune factors. Additionally, an endotracheal tube can hamper thorough inspection of the oral cavity and limit access for oral care.[11,12]

Reduction of the number of oral microorganisms might hold a potential for prevention of ventilator-associated pneumonia.[13,14] Both chlorhexidine and povidone-iodine have been proposed as powerful antiseptic drugs against oral bacteria, but studies aiming to determine the most effective product, its optimum concentration, and frequency of use have yielded inconclusive results. We did a systematic review and subsequent meta-analysis postulating that oral care with chlorhexidine or povidone-iodine reduced the occurrence of ventilator-associated pneumonia in mechanically ventilated adults compared with absence of oral care or oral care with a placebo, saline 0·9%, or another active product.

Methods

Search strategy

Our systemic search for relevant publications included the electronic databases PubMed, CINAHL, Web of Science, and The Cochrane Central Register of Controlled Trials (CENTRAL). We searched combinations of the keywords "oral care", "oral health", "oral hygiene", "oral

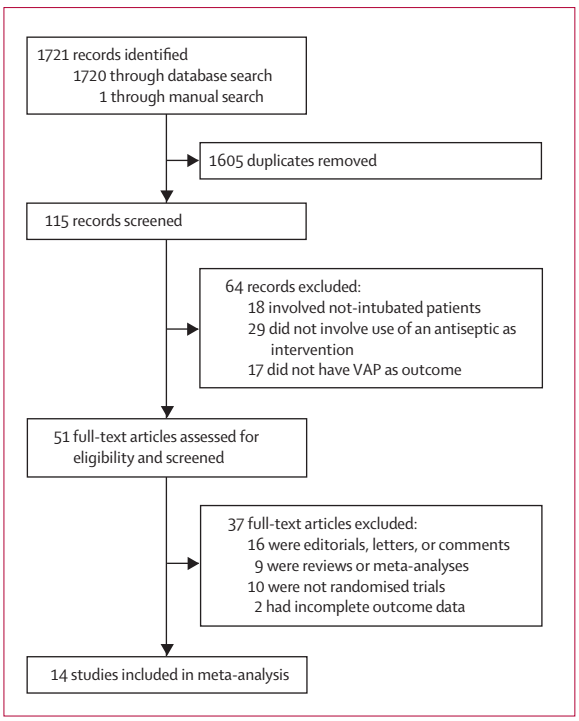

Figure 1: **Summary of literature search and study selection**
VAP=ventilator-associated pneumonia.

decontamination", "antiseptics", "intubation", "(mechanical) ventilation", "ventilator-associated pneumonia", "prevention", "reduction", "pneumonia", "respiratory (tract) infection", "chlorhexidine", "iodine", "betadine", "povidone", and "nosocomial pneumonia". We included articles in English, French, or Dutch published from January, 1975 to February, 2011. We identified unpublished studies in conference abstracts or in registers of clinical trials (ClinicalTrials.gov and Current Controlled trials). We also consulted bibliographies of relevant articles, science citation index, and Google Scholar.

For **ClinicalTrials.gov** see http://www.clinicaltrials.gov

For **Current Controlled Trials** see http://www.controlled-trials.com

For **Google Scholar** see http://www.googlescholar.com

Study selection

We narrowed the list of publications obtained to studies meeting our predetermined inclusion criteria. Thereby, we included only randomised controlled trials of mechanically ventilated adult patients receiving oral care with chlorhexidine or povidone-iodine. We excluded studies in which antibiotics were used as experimental intervention for oral decontamination. We included standard oral care, use of a placebo, or another product for oral care as control interventions. We retained only studies reporting rates of ventilator-associated pneumonia as outcome. Two investigators (NB and KVdV) did a first broad selection based on study title, under close supervision of the principal investigator (SB) who is a content expert. To allow further narrowing, four independent reviewers (KVdV, SB, SL, NB) screened the selected abstracts, each masked to the results of the others' selection. Mostly, all reviewers decided unanimously. In one case of disagreement, assessment of eligibility was done by mutual consideration.

Data extraction

Categories of extracted data included author and year of publication, settings and study populations, inclusion and exclusion criteria, definitions and diagnosis of ventilator-associated pneumonia, intervention in the study and the control group, and prevalence of the disease. The concentration of the antiseptic used and the application method were also extracted from the studies if available. Prevalence was registered as the proportion of patients with ventilator-associated pneumonia to the total number of patients, in both study and control groups. When important data were missing, the author was contacted. Secondary outcome variables were extracted for the systematic review, but not included in the meta-analysis.

Quality assessment

The quality of the included randomised trials was assessed by two reviewers (NB and KVdV) with a validated checklist of the Dutch Cochrane Centre, and subsequently appraised by another reviewer (SL).[15] Criteria for quality assessment included the use of (blinded) randomisation and masking of patient, practitioner, or assessor. Applicability was assessed in terms of comparability of the groups at baseline, loss-to-follow-up, intention-to-treat analysis, comparability of treatment, and overall assessment of the quality of the study. An additional quality check included assessment of the sample size, definition of inclusion and exclusion criteria, and clear definition of outcomes.

Statistical analysis

We did a random-effects meta-analysis using Review Manager 5.0 (Cochrane Collaboration, 2008) following the Mantel-Haenszel model to obtain relative risks (RR) and 95% CIs. We assessed clinical heterogeneity by comparing protocol, populations, and methodology of the studies included. We assessed statistical heterogeneity using the I^2 statistic that measures the degree of inconsistency across studies; it results in a 0–100% range quantifying the proportion of variation in the effect, which is due to inter-study variation. We predefined heterogeneity ($I^2 \leq 25\%$ for low, $25\% < I^2 < 50\%$ for moderate, and $I^2 \geq 50\%$ for high). We constructed a funnel plot to assess publication bias and did sensitivity analysis by different subgroup analyses. A p value of less than 0·05 was used to denote statistical significance.

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

	Setting	Inclusion	Exclusion	Diagnosis VAP	Intervention	Control	Blinded
De Riso et al (1996)[18]	Cardiothoracic (open heart surgery)	CABG, valve surgery, septal surgery, cardiac-tumour excision, or combinations	Intraoperative death, preoperative infection or intubation, pregnancy, heart and lung transplant recipients, hypersensitivity to CHX	New or progressing pulmonary infiltrate, fever, leucocytosis, and purulent tracheobronchial secretions	CHX 0·12% 15 mL oral rinse twice a day, start preoperatively and continue postoperatively until discharge from ICU or death (n=173)	Placebo (n=180)	Yes
Fourrier et al (2000)[13]	Medico-surgical ICU	Age >18 years, medical condition suggesting ICU stay ≥5 days, mechanically ventilated by orotracheal or nasotracheal intubation or tracheostomy	Edentulous patients	Temperature >38°C or <36°C, infiltrates on chest radiographs, leucocytosis (>10×10³ cells per μL) or leucopenia (<3×10³ cells per μL), positive culture from tracheal aspirate or positive culture of BAL, or both	CHX 0·2% gel three times a day during ICU stay (n=30)	Standard oral care: mouth rinsing with bicarbonate isotonic serum, oropharyngeal sterile application four times a day (n=30)	Yes
Houston et al (2002)[20]	Cardiothoracic (open heart surgery)	Patients after CABG or valve surgery requiring cardiopulmonary bypass, or both	Intraoperative death, pregnancy, preoperative documented respiratory infection	New or progressing pulmonary infiltrate, fever, leucocytosis, positive microbial culture results	CHX 0·12% 15 mL oral rinse twice a day, start preoperatively until 10 days postoperative or until extubation, tracheostomy, death, or diagnosis pneumonia (n=270)	Listerine (phenolic mixture) 15 mL oral rinse twice a day (n=291)	No
Chua et al (2004)[27]	Medical, surgical, neurological, neurosurgical and central ICU	Mechanically ventilated adults (>18 years), seen within 24 h of intubation	Nosocomial pneumonia, hyperthyroidism, hypersensitivity to povidone-iodine	As defined by CDC[28]	PVP-I 1% three times a day and teeth cleaning once a day (n=22)	Placebo and teeth cleaning once a day (n=20)	Yes
Grap et al (2004)[14]	Surgical trauma ICU, neuroscience ICU, emergency department	Age >18 years, endotracheally intubated and mechanically ventilated	Edentulous patients	CPIS >6	CHX 0·12% 2 mL single application (n=7)	Standard oral care (n=5)	Yes
Macnaughton et al (2004)[22]	Mixed surgical-medical ICU	Patients requiring ventilatory support for at least 48 h	Treatment for infections at admission of ICU, hypersensitivity to CHX	Leukocytosis, fever >38°C, deterioration in oxygenation or chest signs, new consolidation on chest radiograph, substantial bacterial growth on BAL, CPIS >6	CHX 0·2% twice a day (n=91)	Placebo (n=88)	Yes
Fourrier et al (2005)[19]	ICUs	Age >18 years, medical condition suggesting ICU stay ≥5 days, mechanically ventilated by orotracheal or nasotracheal intubation	Patients with tracheostomy, or hospitalised for >48 h before ICU admission, edentulous patients, facial trauma, postsurgical and requiring specific oropharyngeal care, allergy to CHX	Temperature >38°C or <36°C, new infiltrates on chest radiographs, leucocytosis (>10×10³ cells per μL) or leucopenia (<3×10³ cells per μL), positive quantitative culture from tracheal aspirate or BAL, or both	CHX 0·2% gel three times a day until day 28; toothbrushing was not allowed (n=114)	Placebo (n=114)	Yes
Bopp et al (2006)[17]	Critical-care unit	Orally or nasally intubated patients	Patients on metronidazole, allergy to CHX, sensitivity to alcohol, risk for infective endocarditis, history or presence of various comorbidities; or admitted to hospital with pneumonia and subsequently intubated	VAP was diagnosed by a physician, criteria are not specified	CHX 0·12% twice a day until extubation, toothbrushing with CHX (n=2)	Standard oral care twice a day with foam swab, hydrogen peroxide and oral lubricant (n=3)	No
Koeman et al (2006)[21]	Mixed and surgical ICUs	Age >18 years, requiring mechanical ventilation for ≥48 h	Pre-admission immunocompromised status, pregnancy, physical condition not allowing oral application of study medication	New, persistent or progressive infiltrate on chest radiograph and at least three of four criteria: fever >38°C or <35·5°C, leucocytosis (>10×10³ cells per μL) or leucopenia (<3×10³ cells per μL), purulent aspect of tracheal aspirate, positive semiquantitative culture from tracheal aspirate	CHX 2% paste four times a day until diagnosis VAP, death, extubation, or withdrawal of consent (n=127)	Placebo (n=130)	Yes
Seguin et al (2006)[16]	Surgical ICU	Adult patients >18 years, severe closed head trauma, expected to need mechanical ventilation for >2 days	Admitted to ICU >12 h after initial trauma with facial, thoracic, abdominal, or spinal injuries, reaction to iodine, respiratory disease, infiltrates on chest radiograph, need for curative antibiotics	New, pulmonary infiltrate on chest radiograph and two of the following: fever >38°C or <36°C, purulent endotracheal aspirate, leucocytosis (>10×10³ cells per μL) or leucopenia (<3×10³ cells per μL), bacterological culture growth BAL	Povidone-iodine 10% six times a day (n=36)	Standard care without instillation but with aspiration of secretions six times a day (n=31) or nasopharynx and oropharynx rinsing with 60 mL of saline solution six times a day (n=31)	No

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	Setting	Inclusion	Exclusion	Diagnosis VAP	Intervention	Control	Blinded
(Continued from previous page)							
Tantipong et al (2008)[23]	ICU	Adult patients >18 years, mechanically ventilated	Pneumonia, allergy to CHX	New, persistant, or progressive infiltrate on chest radiograph and at least three of four criteria: fever >38°C or <35·5°C, leucocytosis (>10×10³ cells per μL) or leucopenia (<3×10³ cells per μL), purulent tracheal aspirate, positive semiquantitative culture from tracheal aspirate	CHX 2% 15 mL solution four times a day with toothbrushing (n=102)	Saline, with the same oral care procedure (n=105)	No
Scannapieco et al (2009)[26]	Trauma ICU	Adult patients >18 years, intubated and mechanically ventilated within 48 h of admission	Witnessed aspiration, confirmed diagnosis of postobstructive pneumonia, known hypersensitivity to CHX, absence of consent, diagnosed thrombocytopenia (<40×10³ platelets per μL or an INR >2, or both, or other coagulopathy), do not intubate order, pregnancy, legal incarceration, transfer from another ICU, oral mucositis, immunosuppression (either-HIV or drug induced), and re-admission to the ICU	Upon suspicion of pneumonia, lung secretions analysis by bqBAL by use of a mini-BAL technique with >10⁴ CFU/mL of a target PRP in bqBAL fluid or a positive pleural fluid culture in the absence of previous pleural instrumentation regarded as positive evidence for diagnosis of pneumonia	CHX 0·12% once a day plus placebo (n=58) or CHX 0·12% twice a day (n=58)	Placebo twice a day (n=59)	Yes (double-blind)
Panchabhai et al (2009)[25]	Mixed ICU	All patients admitted to the ICU during the 8-month study period	Pregnancy, pneumonia on hospital admission, patients in whom oral care was contraindicated or with history of allergy to CHX	Nosocomial pneumonia was defined by two independent, masked reviewers: development of new persistent alveolar infiltrates on chest radiograph; >38°C; leucocytosis (>12×10³ WBCs per μL), and purulent sputum developing >48 h after ICU admission with worsening of hypoxaemia on arterial blood gas analysis; all parameters were essential for the diagnosis; semiquantitative cultures obtained by the protected non-bronchoscopic mini-BAL technique were considered positive with >10³ CFU per mL. A positive culture was not essential for the diagnosis of pneumonia	10 mL CHX 0·2% twice a day (n=88)	10 mL 0·01% potassium permanganate twice a day (n=82)	No
Bellissimo-Roderigues et al (2009)[24]	Mixed ICU	All patients admitted to the ICU with a prospective length of stay >48 h, regardless of whether they received mechanical ventilation	Previous CHX hypersensitivity, pregnancy, formal indication for CHX use or prescription of another oral topical medication.	As defined by CDC[28]	CHX 0·12% 15 mL after mechanical cleaning three times a day (n=64)	Placebo 15 mL after mechanical cleaning three times a day (n=69)	Yes (double-blind)

VAP=ventilator-associated pneumonia. CABG=coronary artery bypass grafting. CHX=chlorhexidine. ICU=intensive care unit. BAL=bronchoalveolar lavage. CDC=US Centers for Disease Control and Prevention. PVP-I=povidone-iodine. CPIS=clinical pulmonary infection score. INR=international normalised ratio. bqBAL= blind quantitative bronchoalveolar lavage. CFU=colony forming units. PRP=potential respiratory bacterial pathogen. WBC=white blood cell.

Table: **Study characteristics of subpopulations included**

Results

See Online for webappendix

Our broad search strategy yielded 1720 abstracts (873 in PubMed, 502 in Web of Science, 78 in CINAHL, and 267 in CENTRAL). After elimination of identical publications and studies that did not meet inclusion criteria, 13 studies[13,14,16–26] were selected. Scanning of reference lists yielded one additional study.[27] As a result, 14 studies published in English between January, 1996 and February, 2011 consisting of 2481 patients were included in the systematic review (figure 1). Construction of funnel plot did not show publication bias (webappendix p 1).

All studies included were randomised trials, nine of which used a blinded design.[13,14,18,19,21,22,24,26,27] 12 trials including 2341 patients assessed the effectiveness of oral chlorhexidine,[13,14,17–26] two trials comprising 140 patients involved the use of povidone-iodine.[16,27] Most studies included patients in mixed intensive-care units.[13,14,17,19,21–25,27] Two reports,[18,20] however, accounting for 36·8% (914 of 2481)

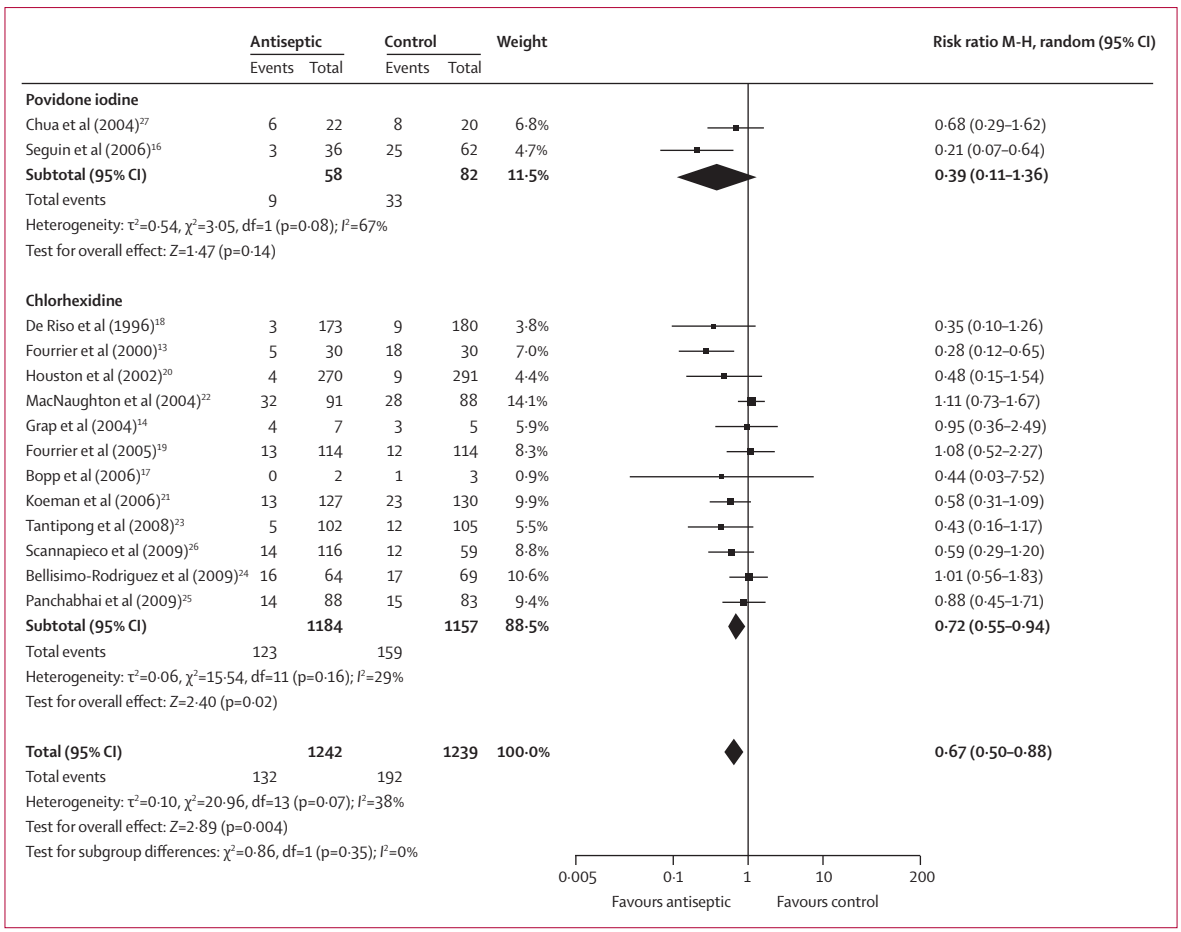

Figure 2: **Overall effect of oral antiseptic use on the prevalence of ventilator-associated pneumonia, and subanalysis of chlorhexidine versus povidone-iodine use**
M-H=Mantel-Haenszel test.

of the population for the meta-analysis, exclusively included cardiosurgical patients, and two others pertained to patients from a trauma or surgical intensive-care unit.[16,26] Sample sizes varied considerably (table).

With regard to interventions, Seguin and colleagues[16] randomly assigned patients in the intervention group to receive oral care with either povidone-iodine or saline. For the present meta-analysis, the patients treated with povidone-iodine were considered the intervention group, and were compared with the joint saline and standard regimen groups (controls). Also, a study group combining the use of chlorhexidine and colistin (Koeman and colleagues)[21] was excluded from the present analysis. Scannapieco and colleagues[26] randomly assigned their study patients to (1) a control group with placebo administration twice daily; (2) an experimental group with 0·12% chlorhexidine once daily and placebo application once daily; and (3) an additional experimental group with 0·12% chlorhexidine administration twice daily. For the present analysis, both groups in which patients were given chlorhexidine 0·12% were considered as experimental groups.

Interventions varied considerably between studies. Teeth were brushed before application of antiseptics,[17,23,27] oral rinse with 15 mL chlorhexidine was applied with a sponge swab for 30 s,[18,20] chlorhexidine gel was given after rinse of the mouth and oropharyngeal aspiration,[13,19] chlorhexidine was used as a spray or swab,[11] or multiple interventions were combined.[23] Koeman and colleagues[21] applied chlorhexidine paste 2 cm bilaterally in the mouth after removal of remnants of the previous dose with a gauze moistened with saline 0·9%. In the study by Panchabhai and colleagues,[25] application of chlorhexidine 0·12% was preceded by oral and pharyngeal suction of pooled secretions, and by swabbing of the oral cavity, teeth, palate, buccal spaces, posterior pharyngeal wall, and hypopharynx with normal saline solution. Nurses trained in the study protocol gave 15 mL chlorhexidine 0·12% after mechanical cleaning of the mouth.[24] Chlorhexidine was also applied with a rinse-saturated oral foam applicator.[26]

Seguin and colleagues[16] rinsed the nasopharynx and oropharynx with 20 mL povidone-iodine 10% reconstituted in a 60 mL solution with sterile water, followed by

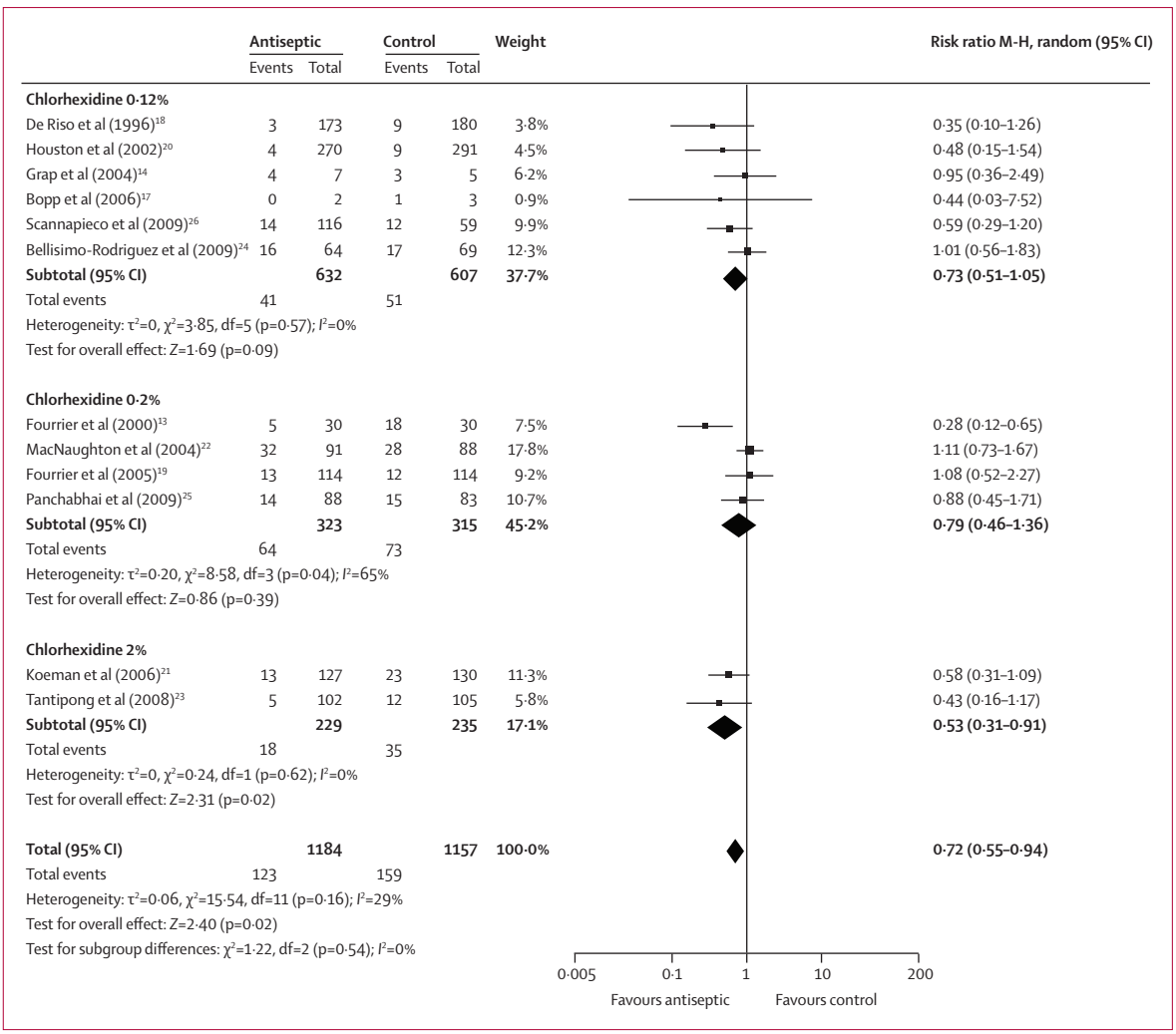

Figure 3: **Subanalysis of 2%, 0·2%, and 0·12% chlorhexidine concentrations**

aspiration of oropharyngeal secretions. Chua and colleagues[27] rinsed the oropharyngeal area with cotton pledgets soaked in 15–20 mL sterile water, then swabbed the entire oropharyngeal mucosa and part of the endotracheal tube with cotton pledgets soaked in povidone-iodine 1%.

Chlorhexidine was used at concentrations of 0·12%,[14,17,18,20,24,26] 0·2%,[13,19,22,25] and 2%,[21] and povidone-iodine at 1%[27] and 10%.[16] Frequency of antiseptic application varied from once[14,26] or twice a day,[17,18,20,22,25,26] over three[13,19,24,27] and four[21,23] to six times a day.[16] Chlorhexidine was applied as oral rinse, foam, gel, or paste and povidone-iodine as oral rinse only. Duration of oral care varied greatly between studies and was not always reported.

In the chlorhexidine studies, patients in the control group were given a placebo (n=640),[18,19,21,22,24,26] standard oral care (n=38),[13,14,17] saline 0·9% (n=105),[23] potassium permanganate 0·01% (n=82),[25] or the phenolic oral rinse Listerine (Johnson & Johnson Limited; n=291; table 1).[20] In the povidone-iodine studies, patients in the control group were given a placebo (n=20),[27] saline,[16] or 'standard' oral care (n=62).[16] The definition of standard oral care varied noticeably between trials.

Age older than 18 years was specified as inclusion criterion in eight studies (table 1).[13,14,16,19,21,23,26,27] All others[17,18,20,22,24,25] also included adults only but did not specify the lower age limit for inclusion. Exclusion criteria varied widely. With regard to diagnostic criteria, Grap and colleagues[14] used the Clinical Pulmonary Infection Score (CPIS) for definition of ventilator-associated pneumonia. The other studies applied the US Centers for Disease Control and Prevention (CDC) definitions for nosocomial pneumonia[18,20,24,27] or similar definitions.[13,16,19,21–23] Bopp and colleagues[17] reported no diagnostic criteria. Nosocomial pneumonia was defined by two independent, masked reviewers in the study by Panchabhai and colleagues.[25] Scannapieco and

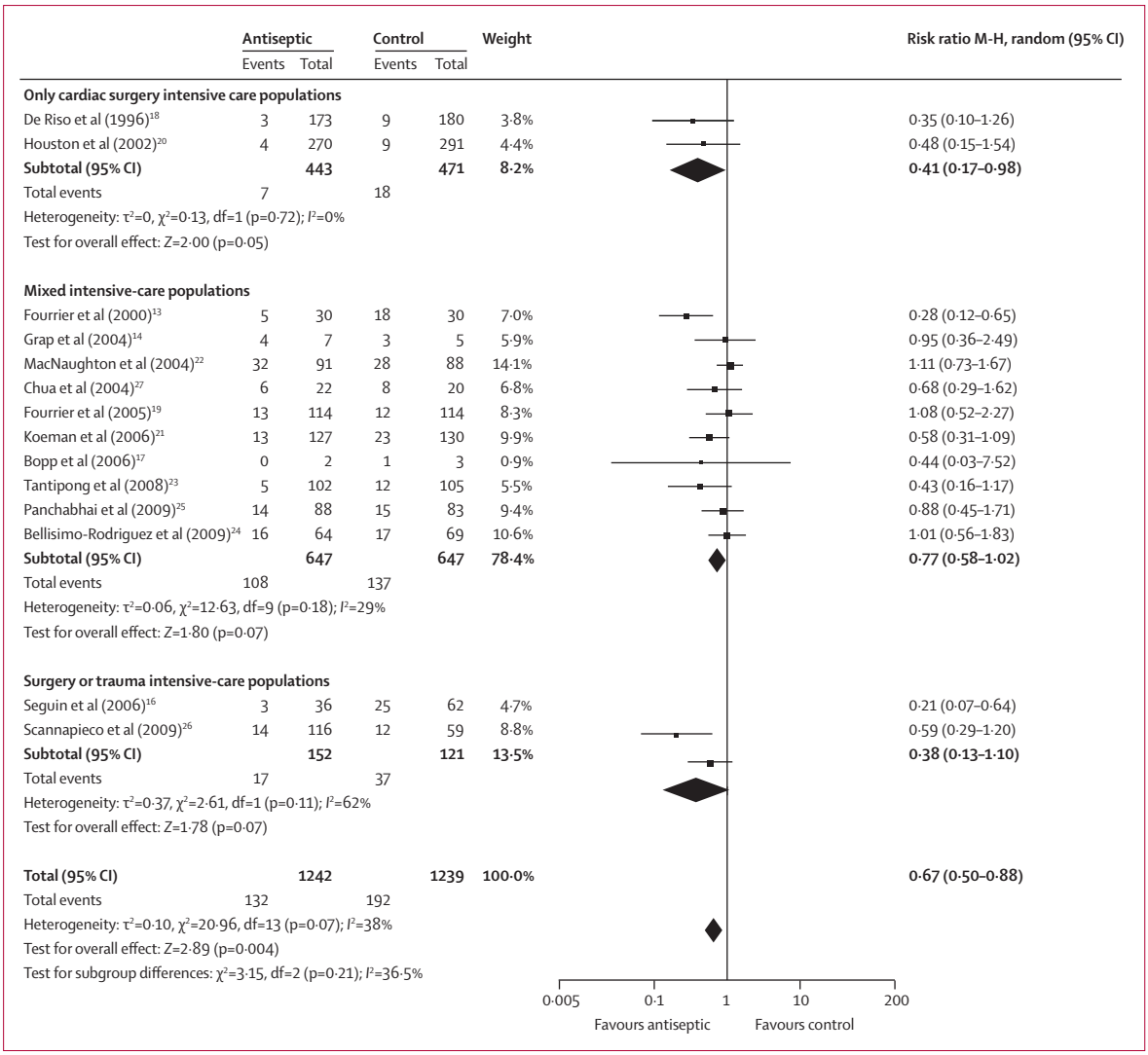

Figure 4: **Subanalysis following type of intensive-care unit**

colleagues[26] based their diagnosis on microbiological assessment of lung secretions.

Two studies[18,20] done in cardiothoracic intensive-care units reported antibiotic administration perioperatively and until 48 h postoperatively. Stress ulcer prophylaxis,[18,25] semirecumbent body position with head of bed elevation of 30°,[16,21,23,25] daily assessment for readiness for extubation,[25] deep vein thromboprophylaxis,[25] and regular emptying of condensate from ventilator tubing[25] were also reported. Although, even if not mentioned, these are components of standard care and, as such, were probably applied as part of routine practice.

In a medico-surgical intensive-care unit, Fourrier and colleagues[13] reported prevalences of ventilator-associated pneumonia of 17% (five of 30 patients) in the interventional group and 60% (18 of 30 patients) in the control group, accounting for 10·7 and 32·3 episodes of ventilor-associated pneumonia per 1000 ventilator-days, respectively (p<0·05; relative risk [RR] reduction 53%). In the study by Koeman and colleagues[21] 52 patients were diagnosed with ventilator-associated pneumonia (13 [10%] of 127 patients in the chlorhexidine group and 23 [18%] of 130 in the control group; the remaining 16 [13%] patients were given a combination of chlorhexidine 2% and colistin 2% as part of an intervention group. This group was not included in our study). Tantipong and colleagues[23] reported five (4·9%) of 102 patients with the disease in the chlorhexidine group and 12 (11·4%) of 105 patients in the control group (RR 0·43, 95% CI 0·16–1·17; p=0·08) with a mean number of seven cases per 1000 ventilator-days in the intervention group and 21 per 1000 ventilator-days in the control group (p=0·04).

In the povidone-iodine study by Seguin and colleagues[16] a significant decrease (p=0·001) in the rate of pneumonia in surgical patients was shown in the intervention group

(three [8%] of 36 patients [95% CI 0–17] versus 12 [39%] of 31 patients [95% CI 22–56] in the control group [p=0·003] and 13 [42%] of 31 patients [95% CI 25–59] in the saline and the standard regimen groups [p=0·001]).[16] In the povidone-iodine study by Chua and colleagues[27] in a mixed intensive-care unit, the rates of pneumonia did not differ between both groups (p=0·58).

We did a meta-analysis of all 14 retrieved studies[13,14,16–27] to assess the pooled effect of oral care with topical chlorhexidine or povidone-iodine on the occurrence of ventilator-associated pneumonia. This analysis showed an important reduction of the disease (p=0·004; figure 2), with a moderate statistical heterogeneity. Subgroup analysis based on type of antiseptic showed a significant reduction in cases of ventilator-associated pneumonia in the chlorhexidine studies, but the effect resulting from povidone-iodine remains unclear (figure 2). The povidone-iodine subanalysis was based on fewer studies, and also showed a larger heterogeneity and broader CIs (figure 2).

To determine the most effective chlorhexidine concentration, subgroup analyses included chlorhexidine 2%,[21,23] 0·2%[13,19,22,25] and 0·12%.[14,17,18,20,24,26] Chlorhexidine 2% was to be associated with a significant risk reduction with a low heterogeneity (figure 3). This protective effect of chlorhexidine was less strong at lower concentrations, with an RR of 0·79 chlorhexidine 0·2% and 0·73 for chlorhexidine 0·12%, and with broad 95% CIs enclosing RR 1 (nil effect; figure 3). Results from the studies assessing the use of chlorhexidine 0·12%, however, showed true homogeneity.

Given their specific profile in terms of infection control, the use of chlorhexidine in all concentrations was compared between cardiosurgical,[18,20] mixed,[13,14,17,19,21–25] and surgical or trauma intensive-care unit populations.[16,26] This analysis showed a significant risk reduction associated with the intervention in cardiosurgical patients (figure 4). The two cardiosurgical studies[18,20] were homogeneous. In both groups of non-cardiosurgical patients, the risk reduction was not significant (figure 4). Subanalyses considering blinded[13,14,18,19,21,22,24,26,27] studies showed a RR of 0·73 (95% CI 0·54–1·00) and those considering non-blinded[16,17,20,23,25] studies a RR of 0·50 (95% CI 0·29–0·87; data not shown).

Discussion

This meta-analysis of 14 randomised trials providesstrong evidence that oral care with chlorhexidine or povidone-iodine effectively reduces rates of ventilator-associated pneumonia when compared with oral care without these antiseptics. This effect was most prominent for chlorhexidine 2%. For chlorhexidine 0·12%, which is currently the recommended dosage by the CDC for cardiosurgical patients,[29] the risk reduction was not significant. With regard to povidone-iodine application, only two rather small studies with higher statistical heterogeneity could be assessed. Although the evidence was not statistically convincing, the risk reduction associated with povidone-iodine use was substantial. As such, povidone-iodine might become a worthy alternative for chlorhexidine, which is currently regarded as the gold standard,[30] without the disadvantage of brown-staining teeth in chronic use.[31] Larger and standardised comparative studies are necessary to obtain more conclusive results for the use of povidone-iodine in oral care.

The strengths of this analysis include the comprehensive search for relevant randomised trials, four-fold screening, assessment of methodological quality, and use of the random-effects model. This study is limited, however, by the clinical and statistical heterogeneity between the trials included. Although this lack of homogeneity was clinically perceived as substantial, statistically it was moderate in the overall meta-analysis (I^2=38%), and no evidence of heterogeneity (I^2=0%) was reported in the subanalyses of studies on cardiosurgical patients (figure 4), and those assessing chlorhexidine at concentrations of 0·12% and 2% (figure 3). Heterogeneity is an inherent problem in systematic reviews and meta-analyses.[32] It results from variation in sample sizes, baseline characteristics of the populations, study protocols and definitions used, diagnostic criteria, and study outcomes (positive or negative). Furthermore, substantial clinical heterogeneity can be expected with regard to associated prevention measures. In the selected studies, information about prevention of ventilator-associated pneumonia—other than oral care—was rather scarce or absent. Besides, heterogeneity was also identified within studies, since different frequencies of care or combinations of interventions were applied.[17,19] Although various subgroup analyses were done to elucidate the heterogeneity, insufficient data were available to analyse the effect of frequency of antiseptic application, its form, or whether teeth were brushed in combination with the intervention. Although it can be assumed that combination of different interventions for oral care might act synergetically, further research is needed to identify their specific attributable benefit on the prevention of the disease.

During our literature search, we identified other studies[33–36] assessing the effect of chlorhexidine on occurrence of ventilator-associated pneumonia. These studies, however, did not meet our inclusion criteria, or the provided data were incomplete. Because we were unable to obtain the necessary data, these studies could not be included. Although effects are unlikely to be less explicit in blinded studies, our subanalysis of these trials still showed a 27% risk reduction, which proved to be very close to statistical significance.

Cardiosurgical patients benefited considerably from topical antiseptic use. In both studies including this category of patients,[18,20] the intervention consisted of application of chlorhexidine 0·12%. Cardiosurgical patients have nevertheless a specific profile in terms of infection control, which hampers comparison with critically ill patients in general. Most often, cardiac

surgery is an elective procedure. As such, cardiosurgical patients are usually in better physical condition than are general patients in intensive-care units. Those requiring valve surgery are moreover submitted to a thorough preoperative dental and oral control, and to tooth extraction if required. Also, cardiosurgical patients are intubated in the operating theatre under optimum and controlled conditions, whereas critically ill patients are more often emergently intubated, in less optimum circumstances. Considering all the above, it is not surprising that the beneficial effects from oral care on occurrence of ventilator-associated pneumonia in cardiosurgical patients (RR 0·41) largely exceed those in mixed intensive-care-unit patients (RR 0·77). Finally, cardiosurgical patients generally have less confounders and experience a shorter period of mechanical ventilation than do medical or trauma patients. Thereby, oral antiseptics could be assumed to be more successful in the prevention of early onset compared with late onset ventilator-associated pneumonia, occurring 5 days or more after endotracheal intubation. Due to a lack of available data, however, the present review remains inconclusive on this issue.

Our meta-analysis is the first to include studies assessing povidone-iodine. Moreover, it includes five studies that have not been included in any previous meta-analysis.[23–27] Previous meta-analyses assessing the effect of oral antiseptics on rates of ventilator-associated pneumonia[37–40] had different scopes. Chan and colleagues[37] assessed, besides antiseptics, the effect of oral antibiotics on rates of ventilator-associated pneumonia. Chlebicki and Safdar,[38] Kola and Gastmeier,[39] and Pineda and colleagues[40] focused on oral care with chlorhexidine only. In conclusion, this meta-analysis provides strong evidence of the beneficial effect of oral antiseptics in the prevention of ventilator-associated pneumonia, especially in cardiosurgical patients and with use of 2% chlorhexidine.

Conflicts of interest

We declare that we have no conflicts of interest.

Contributors

SB conceived and designed the study, contributed to the search of published work, and the acquisition of data. KVDV contributed to the search of published work, data acquisition, and data analysis. SL contributed to the search of published work and data acquisition, and drafted the report. NB contributed to the search of published work, the data analysis and data interpretation, and reviewed the report. DV critically revised the report and made substantial contributions on the final manuscript. All contributors approved the final version.

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