PJSS PHILIPPINE JOURNAL OF SURGICAL SPECIALTIES

Oral Hygiene for Improving Surgical Outcomes: A Systematic Review and Meta-analysis

Marie Carmela Lapitan, MD[1,2]; Joshua Vincent Baroña, MD[1]; Giselle Celine Cerrillo-Villanueva, MD[1] and Brian Buckley, PhD[1]

[1] Department of Surgery, College of Medicine, University of the Philippines Manila
[2] Institute of Clinical Epidemiology, National Institutes of Health, University of the Philippines Manila

Introduction: Nosocomial infections such as surgical site infections (SSI) and postoperative pneumonia significantly contribute to a patient's morbidity and mortality. This systematic review and meta-analysis evaluate the effectiveness of oral hygiene programs in reducing the incidence of nosocomial infections and related postoperative complications among all surgical patients.
Methods: The systematic review and meta-analysis were conducted in line with the Cochrane Handbook for Systematic Reviews of Interventions. Medline and the Cochrane controlled trials (CENTRAL) databases were searched. Two review authors independently selected the trials and extracted the outcome data. The risk of bias of each included study was assessed independently by two review authors using the tool recommended in the Cochrane Handbook for Systematic Reviews of Interventions. Meta-analysis was performed when more than one trial reported the same outcome for the same comparison.
Results: 29 systematic reviews and 59 randomized controlled trials were included in the review. Thirty-two trials compared chlorhexidine with placebo, 7 trials povidone iodine with placebo, 7 trials topical antibiotics with placebo, 1 trial essential oils with placebo, 3 trials other agents with placebo, and 5 trials toothbrushing with no toothbrushing. Five trials compared one agent with another agent, and 1 trial compared dosings and frequencies of chlorhexidine use. Chlorhexidine was associated with a reduced risk of nosocomial infection, nosocomial pneumonia, ventilator-associated pneumonia (VAP), and shorter hosptial stay, and no significant impact on surgical site infection rates, ventilator days and mortality. Povidone iodine did not show any significant benefit on reducing VAP rates, ventilator days, ICU days, or mortality when compared against placebo. Hexetidine,when compared with placebo showed similar incidences of VAP. Topical oral antibiotics did not provide significant reduction on VAP rates, ventilator days, ICU days and mortality rates, compared with placebo.
Conclusion: Oral hygiene offers benefits in terms of lower rates of nosocomial infection, nosocomial pneumonia, ventilator-associated pneumonia, surgical site infection, shorter ICU stay, less ventilator days and lower oral colonization / colony counts.

Nosocomial infections such as surgical site infections (SSI) and postoperative pneumonia significantly contribute to a patient's morbidity and mortality. They increase length of hospital stay and need for medications, leading to additional health care costs and use of health care resources.[1] Nosocomial respiratory infections account for approximately 10-15% of all hospital acquired infections, with 20-50% mortality among affected patients.[2]

Among the proposed mechanisms causing nosocomial infections among surgical patients, swallowing and aspiration of pathogenic microorganisms in the oral cavity is of particular interest.[3] Oral secretions are also contaminated by dental plaque colonized with respiratory pathogens.[4] Patients in the intensive care unit (ICU) setting are at increased risk of accumulating dental plaque and subsequently also at risk for ventilator-associated pneumonia. This is due to the hundred-fold increase in the number of bacteria in oropharyngeal fluid among mechanically ventilated patients, whether by oral intubation or by tracheostomy when compared with levels prior to intubation.[5] Apart from having swallowing difficulties, inadequate oral hygiene and lack of self-care, this is also impacted by administration of medications, compromised immune system, dehydration and hyposalivation.[6]

Previous research has evaluated the potential of oral hygiene management in preventing nosocomial infections and postoperative complications, much of it in cardiac and thoracic surgery patients. In a systematic review evaluating perioperative systematic oral hygiene among patients who underwent elective thoracic surgery,

all studies pointed to the reduction of the number of postoperative infections as a result of systematic decontamination of the nasopharynx and/or oropharynx.[2] Two systematic reviews found that oral chlorhexidine was effective for the prevention of nosocomial pneumonia and ventilator-associated pneumonia in the adult population of the cardiothoracic intensive care unit.[1,7] Subgroup analysis suggested that cardiac surgery patients had the greatest benefit from oral antiseptic use (RR 0.41; 95% CI 0.17-0.98, p=0.05).[7] The Center of Disease Control of America recommends the use of chlorhexidine at a concentration of 0.12% among patients undergoing cardiovascular surgery for the prevention of pneumonia during the pre-operative period.[8]

Evidence of the effectiveness of oral hygiene in preventing infection among the general surgical population is less well-documented. One study reported that perioperative oral hygiene reduced SSI risk after colorectal surgery and subsequently shortened hospital stays, and emphasized that perioral management should commence as soon as surgery is contemplated.[3] In a separate study, a lack of preoperative oral management in patients undergoing hepatectomy was significantly associated with an increased risk of SSI (OR=10.17, p=0.035).[9]

Currently, there are no standard definitions of oral hygiene methods, which vary among institutions and include but are not limited to: mechanical aids to remove plaque and debris from the oral cavity (eg. toothbrushing, swabbing with water); topical or chemical disinfection to reduce colonization (eg. mouthwashes, sprays, liquids, or gels); a combination of mechanical and topical disinfection (eg. swabbing with an antiseptic, toothbrushing with antibacterial toothpaste, or daily toothbrushing plus antiseptic rinse); and professional dental care (eg. aided toothbrushing, suctioning to remove excess fluid). Antiseptics include agents such as saline, chlorhexidine, povidone-iodine and cetylpyridium. These measures have no specified duration or frequency and can be administered by caregivers, nurses, dental care professionals, or dentists.[10]

This systematic review and meta-analysis evaluates the effectiveness of oral hygiene programs in reducing the incidence of nosocomial infections and related postoperative complications among all surgical patients, with a view to providing a comprehensive overview of the current evidence base and inform guideline recommendations to the surgical community.

This report presents the findings of the systematic review in brief. The full report, including detailed assessments of the quality of the evidence, all meta-analyses and forest plots, and discussion are available in the online appendix.

Methods

Only randomized controlled trials were included in the review. To ensure a strong evidence base, the authors included studies with several population types: studies with only surgical patients (i.e. operative cases and non-operative cases usually attended to by surgeons, such as trauma cases), excluding dental surgery cases; studies with mixed surgical and medical populations; studies with ICU populations, which may be primarily medical but which did not specifically exclude surgical patients. Since the focus of this review is informing decisions about oral hygiene interventions for surgical patients, where meta-analysis was possible these populations were considered both separately and together to assess whether interventions were more or less effective in different types of population.

Studies that compared the oral hygiene programs using various oral agents, techniques and various combinations of such, with placebo or usual care, or with any other of the interventions were included. Oral care agents such as, but not limited to, chlorhexidine, povidone-iodine, oral topical antibiotics, essential oil-based mouthwash, and hexetidine, were included. The authors included studies that considered the following outcomes: nosocomial infection, nosocomial pneumonia, ventilator-associated pneumonia (VAP), surgical site infection (SSI), ventilator days, ICU stay, mortality, adverse events, and oral colony count.

The systematic review and meta-analysis was conducted in line with the Cochrane Handbook for Systematic Reviews of Interventions.[11] Medline and the Cochrane controlled trials (CENTRAL) databases were searched for all relevant publications, with no time restriction. The following terms were used: oral hygiene,

oral care, oral health, mouthwash, mouthrinse, nosocomial infection, nosocomial infection, nosocomial pneumonia, respiratory infection, surgical site infection. The search was restricted to clinical trials and systematic reviews, which were checked for additional studies. Two review authors independently screened the titles and abstracts for eligibility. The full texts of all potentially eligible records were retrieved and screened independently by two review authors.

Two review authors independently extracted the outcome data of included studies. Study characteristics were obtained by one review author and a second review author checked the data for accuracy. (Study characteristics are reported in full in the online appendix). The risk of bias of each included study was assessed independently by two review authors using the tool recommended in the Cochrane Handbook for Systematic Reviews of Interventions.[11] This included the assessment of bias in six domains: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting. Other sources of bias were also noted. At all stages, disagreements were resolved by discussion or by consulting a third review author.

Meta-analysis was performed when more than one trial reported the same outcome for the same comparison. The authors conducted intention-to-treat analyses were possible, and otherwise conducted available case analysis. No data were imputed. For dichotomous/ categorical outcomes, they used risk ratios (RR). For continuous outcomes, they used mean difference (MD) or standardized mean difference (SMD) with corresponding 95% confidence intervals (CIs). A fixed effects model was used to calculate pooled estimates of treatment effect across similar studies. When visual or statistical heterogeneity was demonstrated, a random effects model was used. Heterogeneity between studies was assessed by visual inspection of plots of the data, the Chi^2 Q test for heterogeneity and the I^2 statistics. They considered substantial heterogeneity present if I^2 was greater than 50%. They used funnel plots to assess heterogeneity of study effects if 10 or more studies investigating a particular outcome were included. For studies with more than two intervention groups, only the intervention groups relevant to the review were selected, or groups were combined to create a single pair-wise comparison where possible. Where meta-analysis was not possible, they used a narrative synthesis approach.

Results

Search Results

The database search identified 3,171 citations, of which 2,845 articles were excluded based on the title or abstract. Following the removal of 163 duplicates, 163 full text articles were assessed for eligibility. Of these, 75 were excluded based on eligibility criteria and a total of 88 articles were included: 29 systematic reviews and 59 randomized controlled trials. No additional trials were identified upon review of the systematic reviews and these were subsequently excluded from further analysis. The Preferred Reporting Items for Systematic Review and Meta-analyses flow diagram of the study selection process is shown in Figure 1.

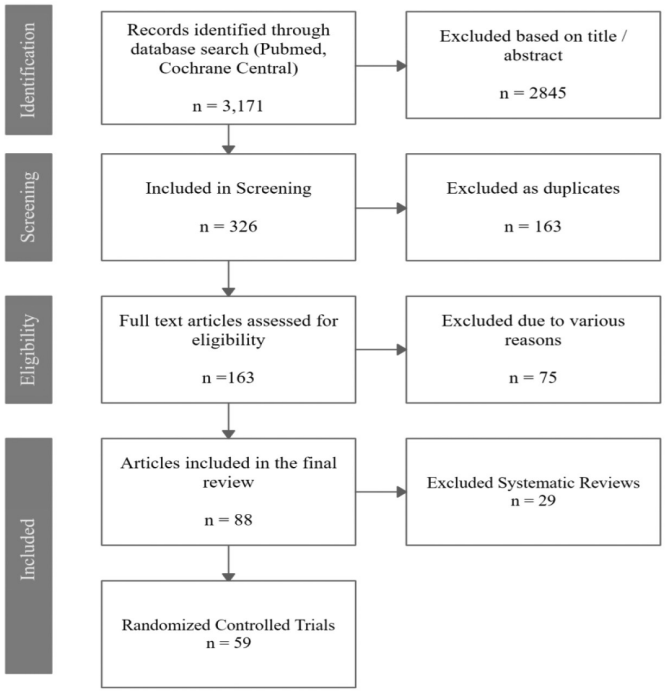

Figure 1. Preferred reporting items for systematic review and meta-analyses flow diagram of the study selection process.

Included Studies

Of all the 59 RCTs included, 15 involved surgical populations, 16 were mixed, and 22 involved predominantly medical or unspecified patients. Thirty-two trials compared chlorhexidine with placebo, 7 trials povidone iodine with placebo, 7 trials topical antibiotics with placebo, 1 trial essential oils with placebo, 3 trials other agents with placebo, and 5 trials toothbrushing with no toothbrushing. Five trials compared one agent with another agent, and 1 trial compared dosings and frequencies of chlorhexidine use. Outcomes assessed were nosocomial infection, nosocomial pneumonia, ventilator-associated pneumonia, surgical site infection, mortality, ventilator days, ICU days, and adverse events. All articles were published in English. The characteristics of included studies are reported in the online appendix.

Overall Quality of the Evidence

Twelve out of 59 studies (20.34%) have a low risk of bias in all domains. Sixteen studies (27.12%) have an unclear risk of bias in at least one domain, while the rest (31/59 or 52.54%) have high risk of bias in at least one domain. The risk of bias per domain for the included studies overall is summarized in Figure 2. The risk of bias for each included study is reported in the forest plots and the characteristics of studies table in the online appendix.

Intervention Outcomes

Use of Oral Care Agents

Chlorhexidine versus placebo / usual care

Thirty-two trials compared chlorhexidine (2644 patients) with placebo or usual care (2624 patients). Five studies, four with only surgical patients, reported on the incidence of nosocomial infection. Pooled analysis of all 5 studies suggested a significantly reduced risk of nosocomial infection with the use of chlorhexidine. Subgroup analysis showed similar results across population types.[12-16]

Twenty-two studies, the majority involving mixed surgical and medical populations, reported on nosocomial pneumonia. Pooled analysis of all studies suggested that chlorhexidine significantly reduced the risk of nosocomial pneumonia. Subgroup analysis showed similar results across population types.[12-16, 17,18-33]

Twenty-seven studies involving all population types reported on ventilator-associated pneumonia. Pooled analysis of all studies suggested a significantly reduced risk of ventilator associated pneumonia with the use of chlorhexidine. Subgroup analysis showed similar results across population types.[13,15-31,33-41]

Four studies in surgical populations reported on surgical site infection (SSI). Pooled analysis of all studies suggested no significant reduction of the risk of SSI with the use of chlorhexidine.[12,13,15,42]

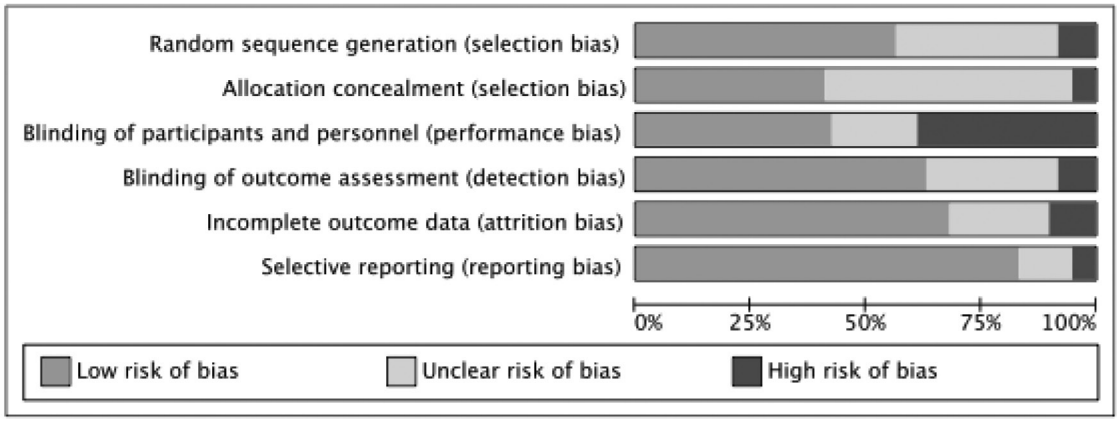

Figure 2. Overall graph on quality of the evidence.

Eight studies involving all population types reported on mechanical ventilation days. Pooled analysis of all studies suggested no significant effect on ventilator days with the use of chlorhexidine, although the trend was towards benefit. Subgroup analysis suggested no significant effect for any population type, but suggested the trend was towards benefit from use of chlorhexidine in the surgical and ICU populations and the opposite in the mixed population.[15,17,19,23-25, 31,43]

Seven studies involving all population types reported on ICU days. Pooled analysis of all studies suggested a significantly shorter ICU stay with the use of chlorhexidine. Subgroup analysis revealed differences between population types: while a significant reduction in ICU days was seen in surgical and ICU patients, little or no difference was seen in the mixed population.[13,15-17,23-25]

Twenty studies involving all population types reported on mortality. Pooled analysis of all studies suggested no benefit with the use of chlorhexidine. Subgroup analysis showed similar results across population types.[12-16, 18,19,21-26,28,29,31,33,34,36,38]

Three studies involving all population types reported on adverse events. Pooled analysis of all studies suggested a significantly increased risk of adverse events with chlorhexidine. Random effects analysis did not change this result. Subgroup analysis revealed differences between population types: while there was a trend towards reduced adverse events with chlorhexidine in ICU patients, the opposite was the case for surgical and mixed populations. Reported adverse events were minor and included burning sensation and oral mucosa irritation, local urticaria, and teeth discoloration.[12,29,44]

Eleven studies involving all population types (1236 chlorhexidine, 1239 placebo/usual care) reported on colonization with respiratory pathogens. One study reported quantitative colony counts of pathogens, which suggested that chlorhexidine was more effective in reducing anaerobic than aerobic bacteria counts (1865 times decrease versus 13 times decrease) after five minutes of washing and an overall lower absolute number of intra-oral bacterial counts compared to normal saline.[42] Nine studies reported only the qualitative presence or absence of respiratory pathogens, with six reporting a decrease in the number of positive cultures for Gram-positive bacteria in the chlorhexidine group compared to the placebo group[13,15, 23-25, 28], while there was little or no difference in the other studies.[16,29,33] Outcome reporting was unclear in one study.[31]

Povidone iodine vs placebo / usual care

Seven trials compared povidone iodine (333 patients) and placebo or usual care (362 patients). Four studies involving all population types reported on ventilator-associated pneumonia. Pooled analysis of all studies suggested that povidone iodine conferred no benefit. Subgroup analysis based on population type suggested povidone iodine was associated with greater benefit in surgical patients than in other populations.[43,45-47]

Three studies involving all population types reported ventilator days. Pooled analysis of all studies suggested a significant reduction in ventilator days with the use of povidone iodine. Subgroup analysis suggested that while povidone iodine was associated with a benefit in the mixed and ICU patients, there was little or no difference in surgical patients.[46-48]

Two studies (surgical, mixed) reported on ICU days. Pooled analysis of the studies suggested povidone iodine was associated with little or no benefit. Subgroup analysis showed similar results across population types.[43,46]

Three studies (surgical, mixed) reported on mortality. Pooled analysis of all studies suggested no benefit was associated with the use of povidone iodine. Subgroup analysis showed similar results across population types.[43,46,48]

Three small studies reported significant reductions in aerobic and anaerobic oral cavity bacterial counts associated with povidone iodine in surgical patients.[42,49,50] One study reported a decreased cuff contamination associated with povidone iodine in medical patients.[47]

No included studies comparing povidone iodine and placebo/usual care reported on nosocomial infections, nosocomial pneumonia or adverse events.

Hexetidine versus placebo / usual care

No clinical trial was identified that investigated the effectiveness of hexetidine mouthwashes against placebo/usual care in surgical patients or in hospital populations that include surgical patients.

One small randomized trial compared chlorhexidine and hexetidine among critically-ill patients, with 13 patients receiving hexetidine and 14 receiving chlorhexidine.[62] The methodological quality of the study was generally poor. The study, published only as an abstract, was at high risk for performance bias due to lack of blinding, and was uncertain in three domains of randomization, allocation concealment, and blinding of outcome assessors. The study reported similar incidences of VAP in both groups. It was observed that there was a tendency for a faster recovery (defined as a decline in Clinical Pulmonary Infection Score) among patients who received chlorhexidine.[62]

Topical antibiotics versus placebo / usual care

Seven studies compared topical antibiotics with placebo or usual care. Pooled analyses of the studies suggested no significant reduction in ventilator-associated pneumonia[45,52-55], ventilator days[54-55], ICU days[54-56] or mortality.[52-55,57]

Two small studies reported on colonization with respiratory pathogens. One study reported a significant reduction in aerobic and anaerobic oral cavity counts using 1% cetrimide solution vs placebo.[42] In the second study, the use of methylcellulose sodium carboxy paste containing 2% polymyxin E, 2% tobramycin and 2% amphotericin B showed significantly less acquired lower respiratory tract and intra-abdominal infections compared to the control group. Acquired infections caused by Gram-positive (28 vs 45) and Gram-negative (6 vs 40) bacteria were isolated less in the study group than in the control group.[57] No included study comparing oral topical antibiotics and placebo/usual care reported on nosocomial infections or nosocomial pneumonia rates.

Evaluations of other agents, one agent versus another, or dosing and frequency comparisons.

Studies of varying sizes and methodological quality were identified that evaluated other comparisons : phenolic mixture (Listerine® mouthwash) versus sterile water; toothbrushing followed by chlorhexidine swab with or without oral probiotics; 0.5% alpha-bisabolol mouthwash, 0.12% chlorhexidine and 0.5% alpha-bisabolol mouthwash and 0.12% chlorhexidine mouthwash; chlorhexidine rinse and a solution of a phenolic mixture; 1% cetrimide solution and 0.9% sodium chloride; chlorhexidine and hexetidine; 0.12% chlorhexidine combined with sodium bicarbonate mouthwash and sterile water; sodium bicarbonate mouthwash and sterile water; antiobiotic mouthwash containing 500mg neomycin and 500mg erythromycin and placebo; 0.2% chlorhexidine and 2% chlorhexidine. None of the studies observed differences in the effectiveness of the evaluated interventions. Results are reported in the online appendix.[22,42,44,58-62]

Toothbrushing vs No Toothbrushing

Five trials compared toothbrushing and no toothbrushing. All five studies, involving all population types, reported on ventilator-associated pneumonia. Pooled analysis of all studies suggested that toothbrushing was not associated with a significant reduction in the risk of VAP, although the trend was towards benefit. In subgroup analysis, there was a significant reduction in risk of VAP in one small trial involving surgical patients (RR 0.26, 95% CI 0.10-0.67), but not in other populations.[36, 38, 63-65]

Three studies involving all population types reported on ventilator days. Pooled analysis of all studies suggested that toothbrushing was not associated with a significant reduction in ventilator days. Subgroup analysis showed similar results across population types.[38,63,64]

Three studies involving all population types reported on ICU days. Pooled analysis of all studies suggested that toothbrushing was not associated with a significant reduction in ICU days. Subgroup analysis showed similar results across population types.[38,63,64]

Five studies involving all population types reported on mortality. Pooled analysis of all five studies suggested that toothbrushing was not associated with benefit. Subgroup analysis showed similar results across population types.[36,38,63-65]

One study reported on adverse events. No adverse events were reported amongst 74 ICU patients who underwent toothbrushing and 73 patients in the control group who received only standard oral care with gauze impregnated with 20 ml of 0.12% chlorhexidine.[38]

Table 1. Outcomes from studies evaluating the use of oral care agents.

Outcome	Studies (n)	Intervention patients (n)	Control patients (n)	Quality	Effect RR (95% CI) or MD (95% CI)
Chlorhexidine versus placebo / usual care					
Nosocomial infection	5	2644	2624	Moderate heterogeneity. Low RoB across most domains.	RR 0.64 (0.54, 0.76)
Nosocomial pneumonia	22	2111	2228	Low heterogeneity. Low RoB across most domains. No publication bias detected.	RR 0.78 (0.68, 0.89)
Ventilator-associated pneumonia	27	2087	2049	Low heterogeneity. Mixed RoB: 6 studies at low risk across all domains, 11 with high risk in at least one domain. No publication bias detected.	RR 0.73 (0.65, 0.83)
Surgical site infection	4	914	903	>50% heterogeneity. Mixed RoB: 2 studies at low risk across all domains, 1 at unclear risk for allocation concealment, 1 at high risk for two domains.	RR 0.62 (0.23, 1.71)*
Ventilator days	8	954	886	Low heterogeneity. Low RoB across most domains, 2 studies at high risk for at least one domain.	MD -0.05 (-0.14, 0.04)
ICU days	7	982	968	Moderate heterogeneity. Low RoB across most domains, 2 studies at high risk for at least one domain.	MD -0.64 (-0.76, -0.52)
Mortality	20	2263	2236	Low heterogeneity. Low RoB across most domains, 8 studies at high risk for at least one domain. No publication bias detected.	RR 1.08 (0.95, 1.22)
Adverse events	3	385	386	>50% heterogeneity. Mixed RoB: 1 study at low risk across all domains, 1 at unclear risk of selection bias, 1 at high risk of performance bias.	RR 2.83 (1.03, 7.76)*
Povidone Iodine versus placebo / usual care					
Ventilator-associated pneumonia	4	269	255	>50% heterogeneity. Mixed RoB: 1 study at low risk across all domains, 3 at high risk for at least one domain.	RR 0.61 (0.30, 1.26)*
Ventilator days	3	80	104	>50% heterogeneity. Mixed RoB: 1 study at low risk across all domains, 2 at high risk for at least one domain.	MD -0.86 (-2.45, 0.74)*
ICU days	2	114	103	Low heterogeneity. Mixed RoB: 1 study at low risk across all domains, 1 at high risk for at least one domain.	0.35 (-3.90, 3.21)
Mortality	3	136	158	Low heterogeneity. Mixed RoB: 2 studies at low risk across all domains, 1 at high risk for at least one domain.	RR 1.04 (0.74, 1.46)
Topical antibiotics versus placebo / usual care					
Ventilator-associated pneumonia	5	594	640	>50% heterogeneity. Low RoB across most domains, 2 studies at high risk for at least one domain.	RR 0.65 (0.42, 1.02)*
Ventilator days	3	138	113	Low heterogeneity. Mixed RoB: 1 study at low risk across all domains, 2 at high risk for at least one domain.	MD -2.24 (-4.84, 0.37)
ICU days	3	138	113	Moderate heterogeneity. Mixed RoB: 1 study at low risk across all domains, 2 at high risk for at least one domain.	MD -2.4 (-5.62, 0.83)
Mortality	5	578	616	Low heterogeneity. Mixed RoB: 2 studies at low risk across all domains, 1 at unclear risk of bias in at least one domain, 2 at high risk for at least one domain.	RR 0.98 (0.81, 1.18)

*Random effects model used due to I^2 >50%

One study reported on colony count in patients who received either gauze cleansing with 0.12% chlorhexidine and oral cavity injection either with or without manual toothbrushing and reported little or no difference in the detection of gram-positive cocci or gram-negative organisms.[64]

Other interventions

Studies of varying sizes and methodological quality were identified that evaluated other comparisons: dental care provided by a dental surgeon versus application of 2% topical chlorhexidine; toothbrushing with 0.02% povidone iodine combined with cephem antibiotics versus combined povidone iodine and cephem antibiotics alone; saline rinse versus saline swab or cotton balls. Results are reported in the online appendix.[50,66-69]

The forest plots of the pooled analyses of the outcomes are in the online appendix.

Discussion

While the effectiveness of oral hygiene interventions in preventing nosocomial infections in surgical patients has been evaluated previously, much of the research has focused on cardiac and thoracic surgery.[1,2,7] This review sought to evaluate the effectiveness of oral hygiene in preventing nosocomial infections in the wider surgical population.

The largest body of evidence related to the use of chlorhexidine compared with placebo or usual care. Multiple meta-analyses highlighted its effectiveness in reducing the risk of nosocomial infection, nosocomial pneumonia, ventilator-associated pneumonia and in reducing ICU days both in surgical patients specifically and in the wider hospital populations that include surgical patients. Pooled analyses did not support its effectiveness in reducing surgical site infections, ventilator days or mortality, although non-significant trends often indicated some benefit. Overall, studies that could not be pooled supported its effectiveness in reducing pathogen counts. Although chlorhexidine was associated with an increase in adverse events, these were minor. These findings are in line with previous more limited reviews of the evidence.[1,7]

A much smaller body of evidence considered the effectiveness of povidone iodine compared with placebo or usual care. Pooled analyses suggested povidone iodine was associated with a reduction in ventilator days, but

Table 2. Outcomes from studies evaluating toothbrushing or combination interventions.

Toothbrushing versus no toothbrushing					
Outcome	Studies (n)	Intervention patients (n)	Control patients (n)	Quality	Effect RR (95% CI) or MD (95% CI)
Ventilator-associated pneumonia	5	447	442	>50% heterogeneity. Mixed RoB: 5 studies at unclear risk for at least one domain, 4 at high risk for at least one domain.	RR 0.69 (0.44, 1.09)*
Ventilator days	3	319	317	Low heterogeneity. Mixed RoB: 2 studies at unclear risk for at least one domain, 2 at high risk for at least one domain.	MD -0.87 (-2.41, 0.68)
ICU days	3	319	317	Low heterogeneity. Mixed RoB: 2 studies at unclear risk for at least one domain, 2 at high risk for at least one domain.	MD -1.60 (-3.40, 0.21)
Mortality	5	400	398	Low heterogeneity. Mixed RoB: 5 studies at unclear risk for at least one domain, 4 at high risk for at least one domain.	RR 0.96 (0.75, 1.22)

*Random effects model used due to I^2 >50%

with little or no difference for ventilator-associated pneumonia, ICU days or mortality. Overall, studies that could not be pooled supported its effectiveness in reducing pathogen counts. No studies reported on nosocomial infections, nosocomial pneumonia or adverse events.

A similarly small body of evidence considered the effectiveness of topical antibiotic preparations compared with placebo or usual care, which indicated little or no benefit in terms of ventilator-associated pneumonia, ventilator days, ICU days or mortality, although there was a non-significant trend in favor of topical antibiotics in reducing ventilator-associated pneumonia. In general, studies that could not be pooled supported its effectiveness in reducing pathogen counts. No studies reported on nosocomial infections, nosocomial pneumonia rates, adverse events or mortality.

In general, other individual studies that evaluated other agents, one agent versus another, or dosing and frequency comparisons did not report differences in the effectiveness of the evaluated interventions.

Overall, the few studies that considered the effectiveness of toothbrushing reported little or no difference in ventilator-associated pneumonia, ventilator days, ICU days, adverse events, mortality or detection of pathogens, although one very small trial indicated that toothbrushing reduced the risk of ventilator-associated pneumonia in surgical patients.

Implications in Practice

Oral hygiene among surgical patients, particularly in the perioperative phase of their care, should be part of standard care. Based on the available evidence and the significant benefit demonstrated in this review, chlorhexidine appears to be the oral agent of choice. However, alternative oral agents may still be considered, particularly povidone iodine, hexetidine, and essential oil-based mouthwash, as there is evidence, albeit limited, that shows similar potential.

Available data on oral topical antibiotics showed a trend towards benefit, but given their potential impact on antimicrobial resistance, their use must be carefully considered unless clear benefits are established.

Toothbrushing is beneficial and desirable for many reasons and may also confer added protection against nosocomial infections, and should thus be part of patients' normal self-care. However, given the limited evidence of its effectiveness as nosocomial infection prophylaxis in patients who are unable to brush their own teeth, it may be considered as an optional component of oral hygiene care, due to the additional burden it places on already busy and often insufficient skilled nursing staff.

Implications for Research

As well as highlighting the value of chlorhexidine in improving outcomes in surgical patients, the review reveals substantial gaps in the evidence. Hexetidine is another widely available antiseptic with a wide spectrum of actions against Gram-positive and Gram-negative bacteria that may have similar potential, yet it has not been studied in a randomized trial. There is little evidence-based information on the most effective durations of oral hygiene interventions, or on the value or otherwise of patient assessment to best target prophylactic oral care.

Of note, relatively few studies have been conducted specifically in general surgical populations, and few report on outcomes of particular interest in surgical patients such as surgical site infections and general nosocomial infections. Yet, given the acceptability and safety of oral hygiene interventions and the availability of participants, these would be relatively simple trials to conduct compared with many others.

Toothbrushing, gargling, swabbing of the oral cavity and other maneuvers can be easily performed by the conscious patient, but can be labor intensive, especially for the health workers who will be performing these procedures on unconscious, obtunded or intubated patients. Other maneuvers require specialized care from skilled health practitioners such as ICU nurses or dental hygiene practitioners. Research on techniques that can easily and properly be performed by health care workers, not necessarily skilled health practitioners, are of interest.

The majority of included studies have methodological issues such as lack of assessor-blinding. Future research should conform to higher methodological quality.

Conclusions

Oral hygiene offers benefits in terms of lower rates of nosocomial infection, nosocomial pneumonia, ventilator-associated pneumonia, surgical site infection, shorter ICU stay, less ventilator days and lower oral colonization / colony counts. Several oral care agents have demonstrated benefits in improving outcomes, with chlorhexidine having a clear benefit in reducing the incidence of nosocomial infection.

References

1. Rabello F, Araújo VE, Magalhães S. Effectiveness of oral chlorhexidine for the prevention of nosocomial pneumonia and ventilator-associated pneumonia in intensive care units: Overview of systematic reviews. Int J Dent Hyg 2018; 16(4): 441-9. doi:10.1111/idh.12336
2. Pedersen PU, Larsen P, Håkonsen SJ. The effectiveness of systematic perioperative oral hygiene in reduction of postoperative respiratory tract infections after elective thoracic surgery in adults: a systematic review. JBI Database System Rev Implement Rep 2016; 14(1): 140-73. doi:10.11124/jbisrir-2016-80.
3. Nobuhara H, Yanamoto S, Funahara M, Matsugu Y, Hayashida S, Soutome S, Kawakita A, Ikeda S, Itamoto T and Umeda M. Effect of perioperative oral management on the prevention of surgical site infection after colorectal cancer surgery. Medicine 2018; 97(40): e12545.
4. Nicolosi L, del Carmen Rubio M, Martinez C, Gonzalez N and Cruz M. Effect of oral hygiene and 0.12% chlorhexidine gluconate oral rinse in preventing ventilator-associated pneumonia after cardiovascular surgery. Respiratory Care 2018; 59(4): 504-9.
5. Funahara M, Yanamoto S, Ueda M, Suzuki T, Ota Y, Nishimaki F, Kurita H, Yamakawa N, Kirita T, Okura M, Mekaru Y, Arakaki K and Umeda M. Prevention of surgical site infection after oral cancer surgery by topical tetracycline. Medicine 2017; 96(48): e8891.
6. Sato J, Goto J, Harahashi A, Murata T, Hata H, Yamazaki Y, Satoh A, Notani K and Kitagawa Y. Oral health care reduces the risk of postoperative surgical site infection in inpatients with oral squamous cell carcinoma. Supportive Care in Cancer 2010; 19(3): 409-6.
7. Spreadborough P, Lort S, Pasquali S, et al. A systematic review and meta-analysis of perioperative oral decontamination in patients undergoing major elective surgery. Perioper Med (Lond). 2016;5:6. Published 2016 Mar 22. doi:10.1186/s13741-016-0030-7
8. Tablan O, Anderson L, Besser R, Bridges C and Hajjeh R. Guidelines For Preventing Health-Care--Associated Pneumonia, 2003. [online] Cdc.gov. Available at: <https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5303a1.htm> [Accessed 8 September 2020].
9. Hasegawa T, Takeda D, Tanaka M, et al. Effects of preoperative dental examination and oral hygiene instruction on surgical site infection after hepatectomy: a retrospective study [published online ahead of print, 2020 May 18]. Support Care Cancer. 2020;10.1007/s00520-020-05525-7. doi:10.1007/s00520-020-05525-7
10. Liu C, Cao Y, Lin J, et al. Oral care measures for preventing nursing home-acquired pneumonia. Cochrane Database Syst Rev 2018;9(9):CD012416. Published 2018 Sep 27. doi:10.1002/14651858.CD012416.pub2
11. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions v.5.0.2. The Cochrane Collaboration 2011. http://www.cochrane-handbook.org/. Accessed February 2014
12. D'Journo XB, Falcoz PE, Alifano M, Le Rochais JP, D'Annoville T, Massard G, Regnard JF, Icard P, Marty-Ane C, Trousse D, Doddoli C, Orsini B, Edouard S, Million M, Lesavre N, Loundou A, Baumstarck K, Peyron F, Honoré S, Dizier S, Charvet A, Leone M, Raoult D, Papazian L, Thomas PA. Oropharyngeal and nasopharyngeal decontamination with chlorhexidine gluconate in lung cancer surgery: a randomized clinical trial. Intensive Care Med 2018 May;44(5):578-87. doi: 10.1007/s00134-018-5156-2. Epub 2018 Apr 18. PMID: 29671041.
13. DeRiso AJ 2nd, Ladowski JS, Dillon TA, Justice JW, Peterson AC. Chlorhexidine gluconate 0.12% oral rinse reduces the incidence of total nosocomial respiratory infection and nonprophylactic systemic antibiotic use in patients undergoing heart surgery. Chest 1996;109(6):1556-61. doi: 10.1378/chest.109.6.1556. PMID: 8769511.
14. Nicolosi LN, del Carmen Rubio M, Martinez CD, Gonzalez NN, Cruz ME. Effect of oral hygiene and 0.12% chlorhexidine gluconate oral rinse in preventing pneumonia after cardiovascular surgery. Respir Care 2014;59:504
15. Segers P, Speekenbrink RG, Ubbink DT, van Ogtrop ML, de Mol BA. Prevention of nosocomial infection in cardiac surgery by decontamination of the nasopharynx and oropharynx with chlorhexidine gluconate: a randomized controlled trial. JAMA 2006; 296(20): 2460-6. doi: 10.1001/jama.296.20.2460. PMID: 17119142.
16. Cabov T, Macan D, Husedzinović I, et al. The impact of oral health and 0.2% chlorhexidine oral gel on the prevalence of nosocomial infections in surgical intensive-care patients: a randomized placebo-controlled study. Wien Klin Wochenschr. 2010;122(13-14):397-404. doi:10.1007/s00508-010-1397-y
17. Grap MJ, Munro CL, Hamilton VA, Elswick RK, Sessler CN, Ward KR. Early, single chlorhexidine application reduces ventilator-associated pneumonia in trauma patients. Hear Lung J Acute Crit Care 2011; 40(5):e115-e122. doi:10.1016/j.hrtlng.2011.01.006
18. Jácomo AD, Carmona F, Matsuno AK, Manso PH, Carlotti AP. Effect of oral hygiene with 0.12% chlorhexidine gluconate on the incidence of nosocomial pneumonia in children undergoing cardiac surgery. Infect Control Hosp Epidemiol 2011; 32(6):591-6. doi: 10.1086/660018. PMID: 21558772.

19. Scannapieco FA, Yu J, Raghavendran K, et al. A randomized trial of chlorhexidine gluconate on oral bacterial pathogens in mechanically ventilated patients. Crit Care 2009;13(4):1-12. doi:10.1186/cc7967
20. Zaiton H, Elshamy K, Elesawy F, Sultan M. Effect of implementing an oral care protocol in minimizing rate of ventilator-associated pneumonia among mechanically ventilated patients at Mansoura emergency hospital. J Am Sci 2012; 8: 503-14.
21. Bellissimo-Rodrigues F, Bellissimo-Rodrigues WT, Viana JM, Teixeira GC, Nicolini E, Auxiliadora-Martins M, Passos AD, Martinez EZ, Basile-Filho A, Martinez R. Effectiveness of oral rinse with chlorhexidine in preventing nosocomial respiratory tract infections among intensive care unit patients. Infect Control Hosp Epidemiol 2009; 30(10): 952-8. doi: 10.1086/605722. PMID: 19743899.
22. Berry A, Davidson P, Masters J, Rolls K and Ollerton R. Effects of three approaches to standardized oral hygiene to reduce bacterial colonization and ventilator associated pneumonia in mechanically ventilated patients: A randomised control trial. International Journal of Nursing Studies 2011; 48(6): 681-8.
23. Fourrier F, Cau-Pottier E, Boutigny H, Roussel-Delvallez M, Jourdain M, Chopin C. Effects of dental plaque antiseptic decontamination on bacterial colonization and nosocomial infections in critically ill patients. Intensive Care Med 2000; 26(9): 1239-47. doi:10.1007/s001340000585
24. Fourrier F, Dubois D, Pronnier P, et al. Effect of gingival and dental plaque antiseptic decontamination on nosocomial infections acquired in the intensive care unit: a double-blind placebo-controlled multicenter study. Crit Care Med 2005; 33(8): 1728-35. doi:10.1097/01.ccm.0000171537.03493.b0
25. Koeman M, van der Ven AJ, Hak E, et al. Oral decontamination with chlorhexidine reduces the incidence of ventilator-associated pneumonia. Am J Respir Crit Care Med 2006; 173(12): 1348-55. doi:10.1164/rccm.200505-820OC
26. Kusahara DM, Peterlini MA, Pedreira ML. Oral care with 0.12% chlorhexidine for the prevention of ventilator-associated pneumonia in critically ill children: randomised, controlled and double blind trial. Int J Nurs Stud. 2012;49(11):1354-1363. doi:10.1016/j.ijnurstu.2012.06.005
27. MacNaughton P, Bailey J, Donlin N. Intensive Care Med. A randomized controlled trial assessing efficacy of oral chlorhexidine in ventilated patients: European Society of Intensive Care Medicine 2004; 30(suppl): S5–S18
28. Panchabhai TS, Dangayach NS, Krishnan A, Kothari VM, Karnad DR. Oropharyngeal cleansing with 0.2% chlorhexidine for prevention of nosocomial pneumonia in critically ill patients: an open-label randomized trial with 0.01% potassium permanganate as control. Chest 2009; 135(5): 1150-6. doi: 10.1378/chest.08-1321. PMID: 19420193.
29. Tantipong H, Morkchareonpong C, Jaiyindee S, Thamlikitkul V. Randomized controlled trial and meta-analysis of oral decontamination with 2% chlorhexidine solution for the prevention of ventilator-associated pneumonia. Infect Control Hosp Epidemiol 2008; 29(2): 131-6. doi:10.1086/526438
30. Bopp M, Darby M, Loftin KC, Broscious S. Effects of daily oral care with 0.12% chlorhexidine gluconate and a standard oral care protocol on the development of nosocomial pneumonia in intubated patients: a pilot study. J Dent Hyg 2006 Summer; 80(3):9. Epub 2006 Jul 1. PMID: 16953990.
31. Özçaka Ö, Başoğlu OK, Buduneli N, Taşbakan MS, Bacakoğlu F, Kinane DF. Chlorhexidine decreases the risk of ventilator-associated pneumonia in intensive care unit patients: a randomized clinical trial. J Periodontal Res 2012; 47(5): 584-92. doi: 10.1111/j.1600-0765.2012.01470.x. Epub 2012 Feb 29. PMID: 22376026.
32. Rujipong P, Lekutai S, Pinyopasakul W, Rungruanghiranya S. The effect of using an oral care clinical nursing practice guideline on oral hygiene status and ventilator-associated pneumonia in intubated patients. J Nurs Sci 2009;27(Suppl 2):57-63
33. Sebastian MR, Lodha R, Kapil A, Kabra SK. Oral mucosal decontamination with chlorhexidine for the prevention of ventilator-associated pneumonia in children - a randomized, controlled trial. Pediatr Crit Care Med 2012; 13(5): e305-e310. doi:10.1097/PCC.0b013e31824ea119
34. Meinberg MC, Cheade Mde F, Miranda AL, Fachini MM, Lobo SM. The use of 2% chlorhexidine gel and toothbrushing for oral hygiene of patients receiving mechanical ventilation: effects on ventilator-associated pneumonia. Uso de clorexidina 2% gel e escovação mecânica na higiene bucal de pacientes sob ventilação mecânica: efeitos na pneumonia associada a ventilador. Rev Bras Ter Intensiva 2012; 24(4): 369-74. doi:10.1590/s0103-507x2012000400013
35. Chen QL, Ye XF, Jiang YZ, Yan MQ. Application of new oral care method to orotracheal intubation. Fujian Med J 2008; 30(5): 155-7.
36. Munro CL, Grap MJ, Jones DJ, McClish DK, Sessler CN. Chlorhexidine, toothbrushing, and preventing ventilator-associated pneumonia in critically ill adults. Am J Crit Care 2009; 18 (5): 428-37. doi: 10.4037/ajcc2009792.
37. Nie HM & Lv CM. The effect of chlorhexidine tooth brushing on prevention of ventilator-related pneumnia. Contemporary Nurses Specialist (China) 2011; 1: 95–6.
38. Pobo A, Lisboa T, Rodriguez A, et al. A randomized trial of dental brushing for preventing ventilator-associated pneumonia. Chest 2009; 136(2): 433-9. doi:10.1378/chest.09-0706
39. Tuon FF, Gavrilko O, Almeida S, Sumi ER, Alberto T, Rocha JL, Rosa EA. Prospective, randomised, controlled study evaluating early modification of oral microbiota following admission to the intensive care unit and oral hygiene with chlorhexidine. J Glob Antimicrob Resist 2017; 8: 159-63. doi: 10.1016/j.jgar.2016.12.007. Epub 2017 Feb 20. PMID: 28216018.
40. Zhou W, Wang SL and Zhang P-W. Oral chlorhexidine on ventilator-associated pneumonia. J Hosp Inf 2009; 19: 1383-4.
41. Zhu L. Application of chlorhexidine oral care to prevent ventilator-associated pneumonia. Guide to Chinese Medicine 2011; 9, 142-3.

42. Kosutic D, Uglesic V, Perkovic D, Persic Z, Solman L, Lupi-Ferandin S, Knezevic P, Sokler K, Knezevic G. Preoperative antiseptics in clean/contaminated maxillofacial and oral surgery: prospective randomized study. Int J Oral Maxillofac Surg 2009; 38(2): 160-5. doi: 10.1016/j.ijom.2008.11.023. Epub 2009 Jan 22. PMID: 19167188.
43. Seguin P, Laviolle B, Dahyot-Fizelier C, et al. Effect of oropharyngeal povidone-iodine preventive oral care on ventilator-associated pneumonia in severely brain-injured or cerebral hemorrhage patients: a multicenter, randomized controlled trial. Crit Care Med 2014; 42(1): 1-8. doi:10.1097/CCM.0b013e3182a2770f
44. Zand F, Zahed L, Mansouri P, Dehghanrad F, Bahrani M, Ghorbani M. The effects of oral rinse with 0.2% and 2% chlorhexidine on oropharyngeal colonization and ventilator associated pneumonia in adults' intensive care units. J Crit Care 2017; 40: 318-22. doi: 10.1016/j.jcrc.2017.02.029. Epub 2017 Mar 1. PMID: 28320561.
45. Feng S, Sun X, Chen Y. Application of different mouthwashes in oral nursing for patients with orotracheal intubation. China Med Pharm 2012; 8(2):100-1.
46. Seguin P, Tanguy M, Laviolle B, Tirel O, Mallédant Y. Effect of oropharyngeal decontamination by povidone-iodine on ventilator-associated pneumonia in patients with head trauma. Crit Care Med 2006; 34(5): 1514-9. doi:10.1097/01.CCM.0000214516.73076.82
47. Takeyasu Y, Yamane GY, Tonogi M, Watanabe Y, Nishikubo S, Serita R, Imura K. Ventilator-associated pneumonia risk decreased by use of oral moisture gel in oral health care. Bull Tokyo Dent Coll 2014; 55(2): 95-102. doi: 10.2209/tdcpublication.55.95. PMID: 24965954
48. Chua JVDE, Sison CMC, Berba RP. The efficacy of povidone-iodine oral rinse in preventing ventilator-associated pneumonia: a randomized, double-blind, placebo-controlled (VAPOR) trial: preliminary report. Philipp J Microbiol Infect Dis 2004; 33: 153-61.
49. Okuda M, Kaneko Y, Ichinohe T, Ishihara K, Okuda K. Reduction of potential respiratory pathogens by oral hygienic treatment in patients undergoing endotracheal anesthesia. J Anesth 2003; 17(2): 84-91. doi:10.1007/s005400300022
50. Sato M, Yoshihara A, Miyazaki H. Preliminary study on the effect of oral care on recovery from surgery in elderly patients [published correction appears in J Oral Rehabil 2007; 34(1): 77]. J Oral Rehabil 2006; 33(11): 820-6. doi:10.1111/j.1365-2842.2006.01634.x
51. Zouka M, Soultati I, Hari H, Pourzitaki C, Paroutsidou G, Thomaidou E, et al. Oral dental hygiene and ventilator-associated pneumonia prevention in an ICU setting: Comparison between two methods (preliminary data of a randomised prospective study). Intens Care Med 2010; 36: S103
52. Bergmans DC, Bonten MJ, Gaillard CA, Paling JC, van der Geest S, van Tiel FH, Beysens AJ, de Leeuw PW, Stobberingh EE. Prevention of ventilator-associated pneumonia by oral decontamination: a prospective, randomized, double-blind, placebo-controlled study. Am J Respir Crit Care Med 2001; 164(3):382-8. doi: 10.1164/ajrccm.164.3.2005003. PMID: 11500337.
53. Kollef M, Pittet D, Sánchez García M, Chastre J, Fagon JY, Bonten M, Hyzy R, Fleming TR, Fuchs H, Bellm L, Mercat A, Mañez R, Martínez A, Eggimann P, Daguerre M, Luyt CE; Prevention of Pneumonia Study (POPS-1) Trial Group. A randomized double-blind trial of iseganan in prevention of ventilator-associated pneumonia. Am J Respir Crit Care Med 2006; 173(1): 91-7. doi: 10.1164/rccm.200504-656OC. Epub 2005 Sep 28. PMID: 16192451.
54. Laggner AN, Tryba M, Georgopoulos A, Lenz K, Grimm G, Graninger W, Schneeweiss B, Druml W. Oropharyngeal decontamination with gentamicin for long-term ventilated patients on stress ulcer prophylaxis with sucralfate? Wien Klin Wochenschr 1994; 106(1): 15-9. PMID: 8135026.
55. Rios F, Maskin B, Sanez, Valiente A, Galante A, Cazes, Camaero P, Aguliar L, Peluffo G, Bendetti F, Hidalgo J, Lloria M, and Apeztegulia C. Prevention of ventilator associated pneumonia (VAP) by oral decontamination (OD): prospective, randomized, double-blind, placebo controlled study. American Thoracic Society 2005 International Conference; May 20 25; San Diego, California 2005;C95.
56. Abele-Horn M, Dauber A, Bauernfeind A, Russwurm W, Seyfarth-Metzger I, Gleich P, Ruckdeschel G. Decrease in nosocomial pneumonia in ventilated patients by selective oropharyngeal decontamination (SOD). Intensive Care Med 1997; 23(2): 187-95. doi: 10.1007/s001340050314. PMID: 9069004.
57. Kerver AJ, Rommes JH, Mevissen-Verhage EA, Hulstaert PF, Vos A, Verhoef J, Wittebol P. Prevention of colonization and infection in critically ill patients: a prospective randomized study. Crit Care Med 1988; 16(11): 1087-93. doi: 10.1097/00003246-198811000-00001. PMID: 3168500.
58. Berry AM. A comparison of Listerine and sodium bicarbonate oral cleansing solutions on dental plaque colonisation and incidence of ventilator associated pneumonia in mechanically ventilated patients: a randomised control trial. Int Crit Care Nurs 2013; 29(5): 275-81.
59. Houston S, Hougland P, Anderson JJ, LaRocco M, Kennedy V, Gentry LO. Effectiveness of 0.12% chlorhexidine gluconate oral rinse in reducing prevalence of nosocomial pneumonia in patients undergoing heart surgery. Am J Crit Care 2002; 11(6): 567-70. PMID: 12425407.
60. Klarin B, Adolfsson A, Torstensson A, Larsson A. Can probiotics be an alternative to chlorhexidine for oral care in the mechanically ventilated patient? A multicentre, prospective, randomised controlled open trial. Crit Care 2018; 22(1): 272. doi: 10.1186/s13054-018-2209-4. PMID: 30368249; PMCID: PMC6204275.
61. Amora-Silva BF, Ribeiro SC, Vieira CL, et al. Clinical efficacy of new α-bisabolol mouthwashes in postoperative complications of maxillofacial surgeries: a randomized, controlled, triple-blind clinical trial. Clin Oral Investig 2019; 23(2): 577-84. doi:10.1007/s00784-018-2464-4
62. Zouka M, Soultati I, Hari H, Pourzitaki C, Paroutsidou G, Thomaidou E, et al. Oral dental hygiene and ventilator-associated pneumonia prevention in an ICU setting: Comparison between two methods (preliminary data of a randomised prospective study). Intens Care Med 2010;36: S103

63. Yao L-Y, Chang C-K, Maa S-H, Wang C, Chen CC-H. Brushing teeth with purified water to reduce ventilator-associated pneumonia. J Nurs Res 2011;19(4):289-97. doi:10.1097/JNR.0b013e318236d05f
64. Lorente L, Lecuona M, Jiménez A, et al. Ventilator-associated pneumonia with or without toothbrushing: A randomized controlled trial. Eur J Clin Microbiol Infect Dis 2012; 31(10): 2621-9. doi:10.1007/s10096-012-1605-y
65. Long Y, MouG, Zuo Y, lv F, Feng Q, Du J. Effect of modified oral nursing method on the patients with orotracheal intubation. J Nurses Train 2012; 27(24):2290-3.
66. Bellissimo-Rodrigues WT, Menegueti MG, Gaspar GG, Nicolini EA, Auxiliadora-Martins M, Basile-Filho A, Martinez R, Bellissimo-Rodrigues F. Effectiveness of a dental care intervention in the prevention of lower respiratory tract nosocomial infections among intensive care patients: a randomized clinical trial. Infect Control Hosp Epidemiol 2014; 35(11): 1342-8. doi: 10.1086/678427. Epub 2014 Oct 2. PMID: 25333428.
67. Mo ZD, Li XL, KeMo ZD, Li XL, Ke JY, Wu JP, Chen XW. Analysis of risk factors in ventilator-associated pneumonia and preventive effect of oral care. Chinese J Nosocomiol 2016; 26(3): 698-9, 705.
68. Tang J, Chen SL, Deng JL. Efficacy of mouth cavity irrigation in prevention of ventilator-associated pneumonia. Chinese J Nosocomiol 2013; 23(17): 4119-21.
69. Xu HL. Application of improved oral nursing method to the prevention of ventilator-associated pneumonia. J Qilu Nurs 2008; 14(19):15-6.

Appendix 1 : Table of characteristics of included studies (alphabetical)

Quality Assessment (Risk of Bias)
LR = Low Risk, UR = Unknown Risk, HR = High Risk
D1: Randomization, D2: Allocation Concealment, D3: Blinding of participants and personnel, D4: Blinding on outcome assessment,
D5: Completeness of followup, D6: Other sources of bias

STUDY ID	POPULATION		INTERVENTION	CONTROL	OUTCOMES	QUALITY ASSESSMENT (RoB)						COMMENTS
	Inclusion	Exclusion				D1	D2	D3	D4	D5	D6	
Abele-Horn 1997	N = 67 Surgical population Anesthesiology ICU	Patients transferred from other hospitals and patients with obvious infections, prior antibiotic therapy, adult respiratory distress syndrome, leucopenia, or myelosuppression at the time of admission.	N = 58 2% amphotericin B, 2% tobramycin, 2% polymyxin E applied QID to palate and lower lip	N = 30 Usually did not receive any antibiotics.	Vent days, ICU days	LR	HR	HR	HR	UR	LR	
Amora-Silva 2019	N = 30 Surgical population Patients (ages 18-100 years) undergoing maxillofacial surgery Not intubated	Patients undergoing maxillofacial surgery performed elsewhere, patients who have not had a fractured dentate region, who have not been submitted to ORIF, or who have no intraoral soft tissue sutures or injuries; patients under 18 or over 100 years of age; carriers	N = 21 Test group 1: n = 11 0.5% BISA (alpha bisabolol) mouthwash Test group 2: n = 10 0.12% CHX + 0.5% BISA mouthwash	N = 9 0.12% CHX mouthwash Self administered	Colony count	UR	LR	LR	LR	LR	LR	

		of immunodeficiency, diabetes, or hematological disorders; edentulous patients; and/or with allergy to the components of the tested mouthwashes.	Self administered									
Bellissimo-Rodrigues 2009	N = 194 Mixed population All patients admitted to ICU (adult clinical and surgical patients) with expected stay > 48 hours.	Previous chlorhexidine sensitivity, pregnancy, formal indication for chlorhexidine use, prescription of another oral topical medication	N = 98 0.12% chlorhexidine applied orally TID By patients if conscious, by nurses if unconscious / ventilated	N= 96 Placebo solution, which was identical in colour, consistency, smell and taste By patients if conscious, by nurses if unconscious / ventilated	NP, VAP, Mort, Vent days, ICU days	UR	LR	LR	LR	LR	LR	
Bellissimo-Rodrigues 2014	N = 254 Unknown / medical population All adult patients admitted to a single general ICU	Excluded were pregnant patients and those with blood dyscrasia	N = 127 Dental care provided by a dental surgeon 4-5x a week in addition to oral hygiene protocol,	N = 127 Routine oral hygiene protocol 3x a day by ICU nurse followed by topical application of CHX 0.12% or 2% according	VAP, Mort, Vent days	HR	LR	UR	LR	UR	LR	

				to level of consciousness								
Bergmans 2001	N = 226 Mixed population Mixed medical / surgical age >16 years intubated within 24 h of admission and who needed mechanical ventilation with an expected duration of 2 d	Not specified	N = 87 Orabase with gentamicin, colistin, and vancomycin QID until extubation, death, limited to 21 days	N = 139 Control A: placebo in ICU with patients receiving topical antimicrobial prophylaxis Control B: placebo in ICU with no topical antimicrobial prophylaxis	VAP, Mort, Vent days, ICU days	UR	LR	LR	LR	LR	UR	
Berry 2011	N = 109 Mixed population Medical-surgical ICU aged over 15 years	Required specific oral hygiene procedures in relation to facio-maxillary or dental trauma/surgery; had been in the ICU previously during the current period of hospitalization; received irradiation or chemotherapy on admission to the ICU or in the preceding 6 weeks; or suffered an autoimmune disease.	N = 66 Test group 1: n = 33 0.2% CHX solution oral rinse BID + sterile water oral rinse two hourly Administered by ICU nurses Test group 2: n = 33 0.2% CHX solution oral rinse BID + sterile water oral	N = 43 Sterile water oral rinse two hourly Administered by ICU nurses	NP, VAP, Mort	LR	LR	HR	LR	HR	LR	

			rinse two hourly + sodium bicarbonate mouthwash rinsed two hourly Administered by ICU nurses									
Berry 2013	N = 398 Mixed population Medical-surgical ICU aged over 15 years and next of kin able to give informed consent	Required specific oral hygiene procedures following facio-maxillary or dental trauma/surgery; had received irradiation or chemotherapy on admission to the ICU or in the preceding 6 weeks; diagnosed with autoimmune disease; had previous ICU admission during current period of hospitalisation	N = 271 Test group 1: n = 138 sodium bicarbonate mouth wash + sterile water, 20 ml every 2 hours Test group 2: n = 133 Listerine mouthwash, 20 ml instilled twice a day + sterile water every 2 hours for remaining time Administered by nurses	N = 127 Sterile water mouth rinses, 20 ml every two hours. Administered by nurses	VAP	LR	LR	HR	LR	HR	HR	
Bopp 2006	N = 5 Unknown / medical population Orally and nasally intubated patients	Taking metronidazole, history of allergy to chlorhexidine, sensitive to alcohol, risk for endocarditis,	N = 2 Twice daily oral hygiene care with 0.12% chlorhexidine gluconate +	N = 3 Standard oral care 6 times daily using a suctioning soR foam	NP, VAP, ICU stay	HR	UR	UR	UR	LR	LR	Small sample size of only 5 subjects

	entering critical care unit	history of other serious illness (specified), those with pneumonia	PlaqVac suction toothbrush Administered by critical care nursing staff	swab and half strength hydrogen peroxide, plus oral lubricant Administered by critical care nursing staff								(3 control, 2 treatment)
Cabov 2010	N = 60 Unknown / medical population Non-edentulous patients admitted to the ICU, aged >18 years	Not specified	N = 30 0.2% CHX gel applied over dental, gingival, and oral surfaces after standard oral care Administered by nurses	N = 30 Placebo dental gel (same color, taste, and odor as CHX gel) Administered by nurses	NI, NP, VAP, ICU days, Mort, Colony count	LR	UR	LR	LR	HR	LR	
Chen 2008	N = 120 Unknown /medical population Admission into the ICU, orally intubated, receiving mechanical ventilation > 7 days, without oral and lung disease	Using hormone therapy; with diabetes	N = 60 Oral cavity irrigated with 50 ml GSE rinse (chlorhexidine + extracts of grapefruit + FE enzyme) then aspirated oG, QID Routine oral nursing care given OD after the first irrigation	N = 60 Oral irrigation with 50 ml saline, 4 times a day, without the combination of routine oral care	VAP	LR	UR	HR	UR	LR	UR	Treatment group received co-intervention of routine oral nursing care OD, but this was not done in the control group

Chua 2004	N = 42 Mixed population Medical 57%, surgical 12%, neurosurgical 21%	Not specified	N = 22 1% povidone iodine given as buccal swab TID	N = 20 Placebo	Mort, Vent days	LR	LR	LR	LR	LR	LR	
D'Journo 2018	N = 450 Surgical population Adults 18 years and above scheduled for major anatomical pulmonary resection surgery for primary lung cancer or suspected metastasis	Age < 18 years, lower respiratory tract infection, emergency lung resection surgery, tracheostomy, impaired swallowing, need for noninvasive ventilation (NIV) before surgery, documented hypersensitivity to CHG, previous head and neck cancer, previous thoracic surgery, and oral assessment guide score ≥ 9	N = 226 Chlorhexidine gluconate (CHG) 0.12% rinse solution for oropharyngeal decontamination and 4% CHG soap for nasopharyngeal decontamination.	N = 224 Placebo of same color, taste, and smell	NI, NP, SSI, AEs, Mort	LR	LR	LR	LR	LR	LR	
Deriso 1996	N = 353 Surgical population Patients >18 years old who underwent cardiac surgery Cardiac surgical ICU	Intraoperative death, preoperative infection or intubation, pregnancy, heart and lung transplant recipients, and known hypersensitivity to CHX	N = 173 0.12% chx gluconate oral rinse preoperatively + two times a day until ICU discharge	N = 180 Placebo of same color, taste, and smell	NI, NP, SSI, ICU days, Mort, Colony count	LR	UR	LR	LR	LR	LR	

Feng 2012	N = 204 Unknown / medical population Entry ICU, with orotracheal intubation and ventilation	Pulmonary infection, stomatitis or oral tumours before intubation, accompanied by ulcer of the digestive tract, malignant tumours of the body, taking steroids > 3 days, diabetes	N = 136 Test group 1: n = 71 Toothbrushing with 1/5000 furacilin (antibiotic) by nurses Test group 2: n = 65 Toothbrushing with 0.05% povidone iodine by nurses, then the oropharyngeal cavity was rinsed with 50 ml of the solution QID	N = 68 Toothbrushing + 0.9% saline followed by rinsing of oral cavity with 50ml saline and suctioned completely QID	VAP	UR	UR	HR	UR	LR	LR	
Fourrier 2000	N = 60 Mixed population Medical or surgical ICU, >18 years old, anticipated stay in ICU 5 days, mechanical ventilation condition suggesting an ICU stay of 5 days	Edentulous patients	N = 30 0.2% chx gel three times a day until ICU discharge Administered by nurses	N = 30 Standard oral care (mouth rinsing with bicarbonate isotonic Administered by nurses	NP, VAP, ICU days, Mort, Vent days, Colony count	LR	UR	UR	LR	LR	LR	

Fourrier 2005	N = 228 Mixed population >18 years old in medical-surgical ICU	Completely edentulous; suffering from facial trauma; postsurgical and requiring specific oropharyngeal care; and known allergy to chlorhexidine	N = 114 0.2% CHX gel TID for max 28 days Administered by nurses	N = 114 Placebo, same color, taste and smell Administered by nurses	NP, VAP, ICU days, Mort, Vent days, Colony count	LR	LR	LR	LR	LR	LR	
Grap 2011	N = 39 Surgical population Trauma ICU NSICU 38%, STICU 62%	Not specified	N = 21 Sterile application of 5 mL of 0.12% CHX solution OD	N = 18 Standard oral care without CHX	NP, VAP, ICU days, Vent days	LR	UR	HR	UR	HR	LR	
Houston 2002	N = 561 Surgical population Patients who underwent cardiac surgery	Those who died during surgery, were pregnant, had preop respiratory infection documented in medical record or as reported by the patient	N = 270 15 mL of 0.12% chx gluconate oral rinse preoperatively + two times a day for 10 days or until extubation, tracheostomy, death, or diagnosis	N = 291 Solution of a phenolic mixture	NP, VAP, Mort, Colony count	HR	UR	UR	LR	UR	LR	
Jacomo 2011	N = 160 Surgical population Children with congenital heart disease undergoing cardiac surgery, consecutively admitted in the	Not specified	N = 87 0.12% CHX gluconate solution preop and BID post operatively Administered by trained nurse or same physician (ADNJ)	N =73 Placebo solution same texture, color, flavor preoperatively and postoperatively	NP, VAP, Mort, ICU days, Vent days	LR	LR	LR	LR	LR	LR	

	PICU in the postoperative period											
Jones 1989	N = 12 Surgical population Patients undergoing elective head and neck surgery No mention of intubation or mechanical ventilation	Procedures that were intraoral and did not involve the soft tissues of the neck, upper aerodigestive tract not accessible to a topical mouthwash, white blood cell count of less than 3,500 cells/mm^3, antibiotic administration within 5 days of the procedure, history of allergic or hypersensitivity reactions to the oral or parenteral antibiotics, a serum creatine level greater than 2 mg/dl, and a serum total bilirubin level greater than 2 mg/dl.	N = 7 30-ml Antibiotic mouthwash (500mg neomycin, 500mg erythromycin) given in 4 doses over a 12-hour interval Patients instructed to swish then swallow	N = 5 Placebo flavored with wintergreen Patients instructed to swish then swallow	Colony count	LR	LR	LR	LR	LR	LR	Small sample size (7 experimental intervention, 5 placebo)

Kerver 1988	N = 149 Surgical population Patients admitted to the surgical ICU who required ICU care for >5 days	Not specified	N = 42 Methylcellulose sodiumcarboxy paste containing 2% polymyxin E, 2% tobramycin and 2% amphotericin B	N = 107 Placebo	NP, SSI, Mort, Colony count	UR	UR	HR	LR	LR	LR	
Klarin 2018	N = 137 Mixed population > 18 years old, undergoing major surgery with anticipated for mechanical ventilation	Not moribund; not having pneumonia as admission diagnosis; no fractures in the facial skeleton or the base of the skull; no oral ulcers; not immune deficient; not a carrier of HIV or viral hepatitis; not being tracheotomised	N = 69 Gauze swabs soaked in carbonated bottled water followed by application of Lp299 to the mucosal surface of oral cavity	N = 68 Toothbrush + all mucosal surfaces swabbed with moistened 1mg/ml CHX solution	VAP, Colony count, Vent days, ICU days	UR	LR	UR	LR	LR	LR	
Koeman 2006	N = 257 Mixed population Consecutive adult patients (18 yr of age) needing mechanical ventilation	Preadmission immunocompromised status; pregnancy, and the inapplicable physical condition	N = 127 CHX 2% in petroleum jelly [Vaseline]FNA, CHX 2% with COL 2% in Vaseline FNA, and Vaseline FNA QID Administered by nurses	N = 130 Placebo, same taste, smell, and consistency Administered by nurses	NP, VAP, ICU days, Mort, Vent days, Colony count	LR	LR	LR	LR	LR	LR	

Kollef 2006	N = 709 Mixed population 83% Non trauma, 27% trauma 18 yr of age or older, orally/nasally intubated	Current diagnosis of pneumonia; an absolute neutrophil count less than 1,000/mm^3; human immunodeficiency virus infection with a last known CD4 count of less than 500/mm^3; a recipient of organ trans-plantation and receiving immunosuppressive therapy; current hematologic malignancy, previously documented cystic fibrosis, severe craniofacial trauma or other medical condition expected to require imminent tracheostomy,	N = 362 Iseganan 3ml (9mg) six times daily until 14 days. Discontinued if patient develops VAP or was extubated	N = 347 Placebo	VAP, Mort	LR	LR	LR	LR	LR	LR	
Kosutic 2009	N = 120 Surgical population Patients undergoing elective intra-oral surgical procedures under local or general anesthesia	Intraoperative death, preoperative infection or intubation, pregnancy, heart and lung transplant recipients, and known hypersensitivity to CHX	N = 90 Test group 1: n = 30 1% cetrimide solution Test group 2: n = 30 1% povidone iodine	N = 30 0.9% NaCl	SSI, Colony count	UR	UR	HR	HR	LR	LR	

	No mention if mechanically ventilated		Test group 3: n = 30 0.12% chlorhexidine gluconate rinse preoperatively + two times a day until ICU discharge									
Kusahara 2012	N = 96 Mixed population Children mechanically ventilated in PICU	Newborn status, confirmed diagnosis of pneumonia at admission, known hypersensitivity to chlorhexidine, absence of parental consent, children with tracheostomies, duration of mechanical ventilation less than 48 h or children who had received tracheal intubation for more than 24 h prior to PICU admission	N = 46 0.12% CHX gel BID with teeth brushing Administered by PICU nursing team	N = 50 Placebo gel same color and odor twice daily with teeth brushing Administered by PICU nursing team	NP, VAP, Mort	LR	LR	LR	LR	LR		
Laggner 1994	N = 67 Unknown / medical population General ICU	Not specified	N = 33 Gentamicin gel QID until extubation	N = 34 Placebo	VAP, Mort, Vent days	LR	HR	LR	UR	UR	LR	

Liu 2008	N = 60 Unknown / medical population General ICU	Not specified	N = 30 0.12% chlorhexidine BID	N = 30 Saline for routine care	VAP	UR	UR	UR	UR	UR	UR	
Long 2012	N = 61 Unknown / medical population Patients aged > 18, admitted to ICU	Intubated in emergency, operations upon the oral cavity, trauma of the respiratory tract, with severe bleeding or coagulation disorders	N = 31 0.1% povidone iodine swab + toothbrushing and rinsing with 0.1% povidone iodine TID	N = 30 Swab with cotton balls soaked with 0.1% povidone iodine	VAP, Mort	UR	UR	HR	UR	LR	LR	
Lorente 2012	N = 216 Mixed population Medical-surgical ICU	Edentulous, aged < 18 years, pregnant, HIV positive, white blood cells < 1000 cells/mm3, solid or hematological tumour, immunosuppressive therapy, mechanical ventilation duration <24 hours	N = 217 0.12% chlorhexidine impregnated gauze, and oral cavity injection, followed by manual brushing of the teeth with a brush impregnated with 0.12% chlorhexidine	N = 219 0.12% chlorhexidine impregnated gauze, and oral cavity injection only	VAP, Mort, Vent days, Colony count	LR	UR	HR	LR	UR	LR	
Macnaughton 2004	N = 179 Mixed population Medical-surgical ICU, patients needing mechanical ventilation >48 hours	Treatment of infection on admission to ICU, CHX hypersensitivity	N = 91 0.2% CHX mouthwash BID administered by nurse	N = 88 Placebo of identical appearance and smell administered by nurse	NP, VAP	LR	LR	LR	LR	LR	LR	

Meinberg 2012	N = 52 Surgical population Over 18 years old, receiving mechanical ventilation, admitted at surgical ICU	Aspiration pneumonia, tracheostomy, pregnancy, and immunosuppression.	N = 28 Toothbrushing plus chlorhexidine gel 2% QID Performed by nursing team	N = 24 Toothbrushing plus placebo gel QID Performed by nursing team	VAP, Mort, Vent days, ICU days	LR	LR	LR	LR	LR	HR	Study terminated for unclear reason related to "futility"
Mo 2016	N = 210 Surgical population Patients undergoing cardiothoracic surgery receiving mechanical ventilation > 48 hours	Patients with pulmonary infections or oral diseases	N = 105 Rinse with saline for 10 minutes each time QID	N = 105 Swab with saline QID	Mort	LR	UR	HR	UR	LR	LR	
Munro 2009	N = 192 Unknown / medical population Critically ill adults (> 18) receiving mechanical ventilation in medical, surgical/trauma and neuroscience ICUs	Clinical diagnosis of pneumonia at the time of intubation, edentulous patients, patients who had a previous endotracheal intubation during the current hospital admission	N = 141 Group 1: (n = 44) a 0.12% solution of chlorhexidine gluconate 5 mL by oral swab BID provided by study personnel Group 2: (n = 49) toothbrushing (manual toothbrush) TID	N = 51 Usual care provided by study personnel	VAP, Mort, ICU stay	LR	UR	HR	UR	HR	HR	

			Group 3: (n = 48) combination care (toothbrushing TID and chlorhexidine Q12 hours) Provided by study personnel									
Nicolosi 2014	N = 300 Surgical population Patients scheduled for cardiovascular surgery Mechanically ventilated	Patients requiring emergency surgery, px who died within 48 hours after surgery, px presenting with infection before surgery, received antibiotic therapy during 30 days before surgery, patients receiving immunosuppressive therapy or who were hypersensitive to chlorhexidine gluconate, and totally edentulous patients	N =150 Toothbrushing , dental floss, rinsing with 0.12% CHX gluconate Q12 hours for 3 days	N = 150 Usual care (which includes mupirocin ointment and 3rd generation cephalosporin)	NI, NP, SSI, Mort, Vent days	HR	HR	HR	HR	LR	LR	
Nie and Lv 2009	N = 200 Unknown / medical group General ICU	Pre-intubation Respiratory tract infection, coagulation abnormalities, palsy and swallowing dysfunction The MV time <48 hours, edentulous,	N = 100 Toothbrushing with 0.12% CHX, rinse with sterile water and moisturise lips with paraffin oil BID	N = 100 Saline	VAP	UR	UR	UR	UR	UR	UR	

		orotracheal intubation recently										
Okuda 2003	N = 32 Surgical population Patients scheduled to undergo oral surgery requiring endotracheal intubation	Not specified	N = 16 Oral cleansing with 200 ml of 0.5% povidone iodine + toothbrushing followed by oral rinsing with 50ml 0.5% povidone-iodine BID after surgery.	N = 16 No oral cleansing	Colony count	UR	UR	HR	HR	LR	LR	
Ozcaka 2012	N = 61 Medical population Respiratory ICU, dentate patients Intubated and mechanically ventilated	Chemical pneumonitis; postobstructive pneumonia; hypersensitivity to CHX; thrombocytopenia; pregnancy; oral mucositis; readmission survival expectation <1 week and edentulism	N = 29 0.2% CHX swab QID Performed by ICU nurse staff	N = 32 Normal saline QID Performed by ICU nurse staff	NP, VAP, Mort, Vent days, Colony count	UR	LR	LR	LR	LR	LR	
Panchabai 2009	N = 471 Mixed population Patients admitted to the Medical-Neuro ICU	Pregnant women, patients with pneumonia (community acquired or nosocomial) on hospital admission, and patients in whom oral care was contraindicated or who had a history of	N = 224 10mL of 0.2% CHX gluconate solution oral cleansing BID + cleansing with 0.2% chlorhexidine gluconate solution BID	N = 227 0.01 potassium permanganate solution BID oropharyngeal cleansing	NP, VAP, Mort, Colony count	UR	UR	UR	LR	LR	LR	

		allergy to chlorhexidine										
Pobo 2009	N = 147 Unknown / medical population Intubated adults without evidence of pulmonary infection, expected to remain ventilated for > 48 hours	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	N = 73 Standard oral care, application of gauze containing 20 ml of 0.12% CHX was to all the oral surfaces, 10 ml of 0.12% CHX injected to the oral cavity Q8 hours Performed by nurses	N = 74 Standard oral care + toothbrushing Q8 hours Performed by nurses	VAP, SSI, Mort, Vent days	LR	LR	HR	LR	LR	LR	Possible confounding use of antibiotics - 28/73 and 25/74 in control and experimental groups receiving antibiotics at time of admission
Rios 2005	N = 96 Mixed population Medical or surgical (including trauma)	Not specified	N = 47 Polymyxin B and gentamicin gel TID until 14 hours after extubation	N = 49 Placebo	VAP, Mort, Vent days	LR	LR	LR	LR	LR	LR	

Rujipong 2009	N = 24 Unknown / medical population Critically ill patients with oral endotracheal intubation aged at least 15 years old, admitted into ICUs and general ward	(1) Cannot be placed in semi-fowler position; (2) must not have burns > 20% of total body surface; (3) Be re-intubated; (4) No teeth; (5) ulceration in oral cavity; (6) history of allergy to chlorhexidine mouthwash.	N = 12 Oral care + toothbrushing with 0.12% chlorhexidine mouthwash for 15 minutes BID Performed by researcher	N = 12 Routine oral care (cotton swabs with 0.004% chloroxylenol) for 15 minutes BID Performed by researcher	NP	LR	UR	HR	UR	UR	LR	
Sato 2006	N = 30 Surgical population age >60 years, undergoing gastrointestinal surgery	Not specified	N = 15 Toothbrushing + 0.02% povidone iodine gargle + cephem antibiotics OD by a single nurse nurse (M.S.)	N = 15 0.02% povidone iodine gargle with cephem antibiotics	Colony count	UR	UR	HR	LR	LR	LR	
Scannapieco 2009	N = 99 Surgical population Trauma ICU Expected to be intubated and mechanically ventilated within 48 hours of admission	Chemical pneumonitis; post obstructive pneumonia; hypersensitivity to CHX; thrombocytopenia; pregnant; oral mucositis;	N = 50 Oral application of 0.12% CHX BID in group 1, OD in group 2 Performed by ICU staff nurses	N = 49 Placebo (distilled water) Performed by ICU staff nurses	NP, Mort, Vent days	LR	LR	LR	LR	HR	LR	More use of antibiotics pre-study in control group

Sebastian 2012	N = 86 Medical population Medical PICU aged 3 months to 15 years who required orotracheal or nasotracheal intubation and mechanical ventilation	Mechanically ventilated for over 24 hours prior to PICU admission, with tracheostomies, with inaccessible oral cavities, and with known hypersensitivity to chlorhexidine	N = 41 0.5g of 1% CHX gel every 8 hours Administered by nursing staff	N = 45 Placebo gel same appearance, consistency, taste and smell applied every 8 hours Administered by nursing staff	NP, VAP, Mort, Colony count	LR	UR	LR	LR	LR	LR	
Segers 2006	N = 954 Surgical population Patients >18 years old scheduled to undergo cardiothoracic surgery Participants in the study did not use mechanical ventilation	Emergency procedures, preoperative infection or use of antimicrobials or both, hypersensitivity to chlorhexidine gluconate, absence of written informed consent, treatment with an alternative prophylactic regimen like selective decontamination of the digestive tract	N = 485 0.12% CHX gluconate oral rinse and nasal gel QID until extubation Applied by nurse using sponge if patient unable	N = 469 Placebo, same color, taste and smell Applied by nurse using sponge if patient unable	NI, NP, VAP, SSI, ICU days, Mort, Vent days, Colony count	LR	LR	LR	LR	LR	LR	
Seguin 2006	N = 110 Surgical population Surgical ICU Adults (> 18 years) with closed head	Admitted > 12 hours after initial trauma, those with facial, thoracic, abdominal or spinal injuries, known history of reaction to iodine or of respiratory	N = 38 Povidone iodine 10% 20ml reconstituted with 60ml sterile water to nasopharynx and oropharynx	N = 72 Control A: n = 36 Naso and oropharynx rinsed Q4 hours with 60 ml saline,	VAP, Mort, Vent days	LR	LR	HR	UR	LR	LR	

	trauma admitted to ICU	disease, chest infiltrates at admission or need for curative antibiotics	6 times daily until extubation	followed by aspiration of oropharyngeal secretions Control B: n = 36 Standard regimen + aspiration of oropharyngeal secretions Administered by nurses								
Seguin 2014	N = 150 Surgical patients > 18 years, closed traumatic brain injury	Patients in whom oral care procedure could not be performed within 12 hours after intubation, or had tetraplegia, facial trauma, pulmonary contusion involving > 1 lobe, aspiration pneumonia, current curative antimicrobial therapy, known allergy to povidone-iodine, pregnancy	N = 78 Naso and oropharyngeal rinsing with 20mL povidone iodine (10%) + injection of solution in buccal and pharyngeal cavities followed by suctioning for 2 minutes Q4 hours Administered by nurses	N = 72 Placebo administered by nurses	VAP, Mort	LR	LR	LR	LR	LR	LR	
Takeyasu 2014	N = 168 Unknown / medical population Patients on	Not specified	N = 84 Oral healthcare according to protocol using 30cc of 1%	N = 84 Oral moisture gel Performed by a nurse	VAP, Vent days, Colony count	HR	UR	UR	LR	LR	UR	Exclusion criteria not mentioned, VAP not defined,

	mechanical ventilation with oral intubation for more than 10 hours in the ICU		povidone-iodine solution / 2-fold diluted oxydol	trained by a dentist or a dental hygienist.								unorthodox method for determining colony count
Tang 2013	N = 60 Unknown / medical population Adult ICU All patients admitted to the adult ICU	Unclear	N = 30 Rinse oral cavity with saline	N = 30 Saline swab with saline cotton ball	Mort, Vent days	UR	UR	HR	UR	LR	UR	
Tantipong 2008	N = 207 Mixed population Medical 12%, surgical 50%, general medical wards 38%	Patients who had pneumonia at enrolment or who had a CHX allergy	N = 102 Toothbrushing, suctioning of oral secretions, rubbing the oropharyngeal mucosa with 15 mL of 2% CHX solution QID	N = 105 Oral care with normal saline	NP, VAP, AEs, Mort, Colony count	LR	UR	HR	LR	UR	UR	Only 60% of study participants received ventilation in ICU and only 53% of participants received MV for >48 hours
Tuon 2017	N = 16 Unknown / medical population Age >18 years, Patients identified as high probability of MV for >48h	Failure to provide written informed consent, hospitalization >24 hours, recent use of antibiotics (<1 week), recent admission to another hospital or emergency room, suspected infection	N = 8 15 ml of 2% CHX digluconate	N = 8 0.9% NaCl	VAP	UR	UR	UR	LR	LR	LR	

		in the upper or lower respiratory, and less than four culture samples										
Xu 2008	N = 116 Unknown / medical group Adults entering ICU receiving mechanical ventilation expected to last > 48 hours	Patients with pulmonary infections	N = 64 Rinsing of the oropharyngeal cavity with saline for 5 - 10 seconds, followed by suctioning aspirations repeated 5 - 10 times, BID	N = 52 Standard oral care comprising scrubbing with a cotton ball soaked in saline, BID	Vent days	UR	UR	HR	UR	LR	LR	
Yao 2011	N = 53 Surgical population Surgical ICU Expected length of ICU stay over 2 days, expected to receive mechanical ventilation for at least 48-72 hours with oral or nasal-tracheal intubation Mechanically-ventilated	Patients already presented with pneumonia were excluded.	N = 28 Standardized 7-day oral care protocol (oral cavity moisturized by 10ml purified water + toothbrushing, toothette swab, hypopaharyngeal suctioning) Administered by trained nurse	N = 25 Twice daily mock oral care Administered by trained nurse	VAP, Mort, Vent days	LR	UR	LR	LR	LR	LR	
Zaiton 2012	N = 80 Surgical ICU Mechanically ventilated	Nasal intubations, tracheotomies, ulceration or trauma in oral cavity,	N = 40 15 mL CHX diluted in 50 mL of water Q12	N = 40 Routine oral care with normal saline	NP, VAP, Vent days, ICU days	UR	UR	HR	HR	UR	LR	

	patients ages >18, with oral endotracheal intubations	bleeding tendency and documented history of hematological disorders, oral surgeries, patients who cannot place in semi-fowler position, history of allergy to chlorhexidine mouth wash, patients who receive therapy for infection in the oral cavity, and reintubated patients	hours by the researcher	0.9% OD by ICU nurses								
Zand 2017	N = 114 Unknown / medical population Patients aged 18 and above having a tracheal tube, being under mechanical ventilation for at least 48H	Pneumonia on admission, hx of allergy to CHX, inflammation of the oral mucosa or trauma to the mouth, immune disorders caused by medications or illness, suffering from burn damages, pregnant, not admitted to ICU for the first time	N = 57 0.2% CHX twice daily performed by researcher	N = 57 2% CHX twice daily performed by researcher	VAP, AEs, Vent days	UR	UR	LR	LR	LR	LR	
Zhou 2009	N = 99 Unknown / medical group ICU & CCU	Not specified	N = 46 0.5% CHX QID according to the oral care process	N = 53 Placebo	VAP	UR	UR	UR	UR	UR	UR	

Zhu 2011	N = 93 Unknown / medical group ICU, CCU Mechanical ventilation >48 hours	Not specified	N = 45 2% CHX according to the oral care process TID	N = 48 Saline	VAP	LR	UR	UR	UR	UR	UR	
Zouka 2010	N = 27 Mixed population Medical-surgical ICU	Not specified	N = 14 0.12% CHX solution in saline (3:1)	N = 13 Hexetidine 0.1% solution	NP, VAP	UR	UR	HR	UR	LR	LR	

Appendix 2: Forest Plots on Oral Hygiene for Improving Surgical Outcomes

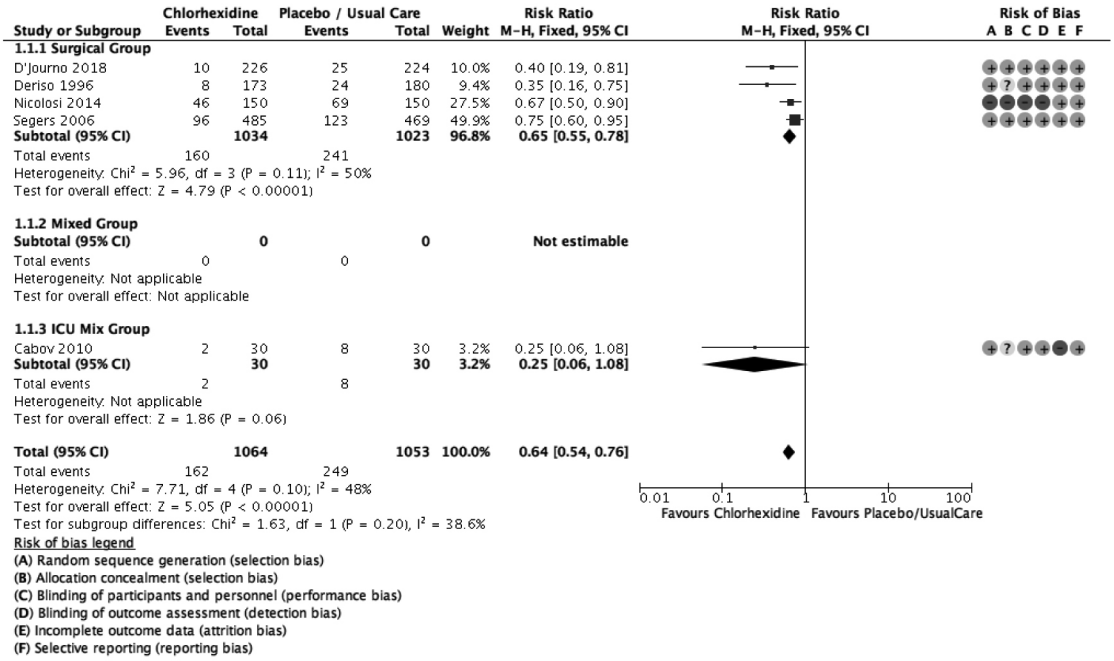

Figure 1. Chlorhexidine vs Placebo/Usual Care : Nosocomial Infection

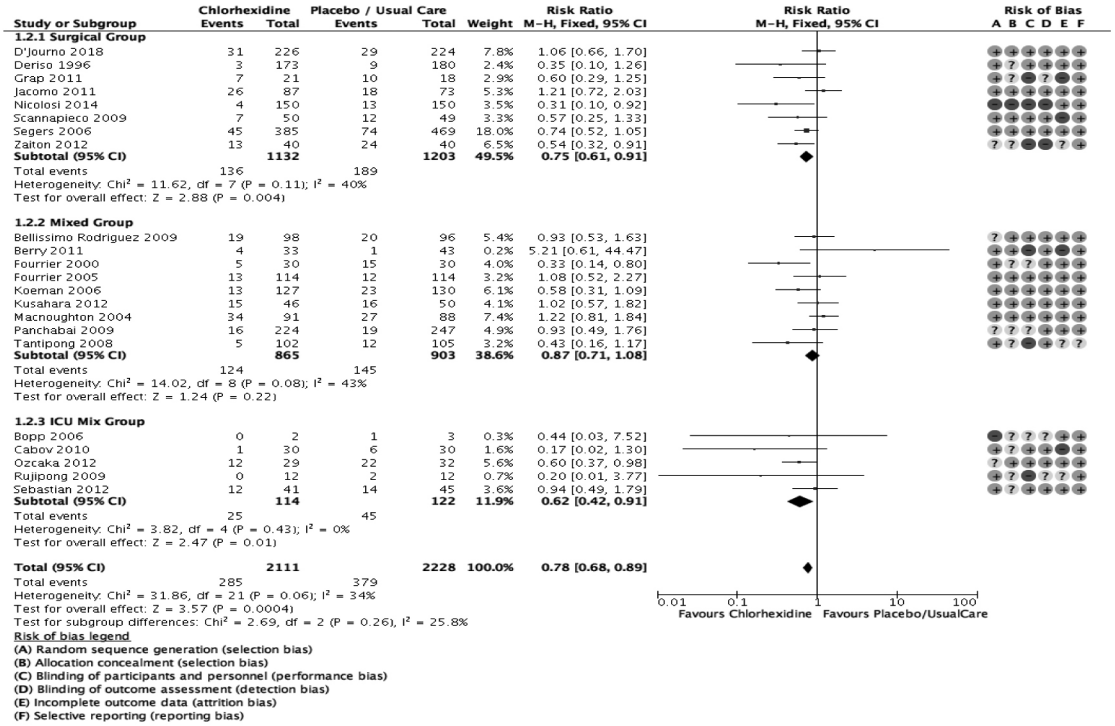

Figure 2. Chlorhexidine vs Placebo/Usual Care : Nosocomial Pneumonia

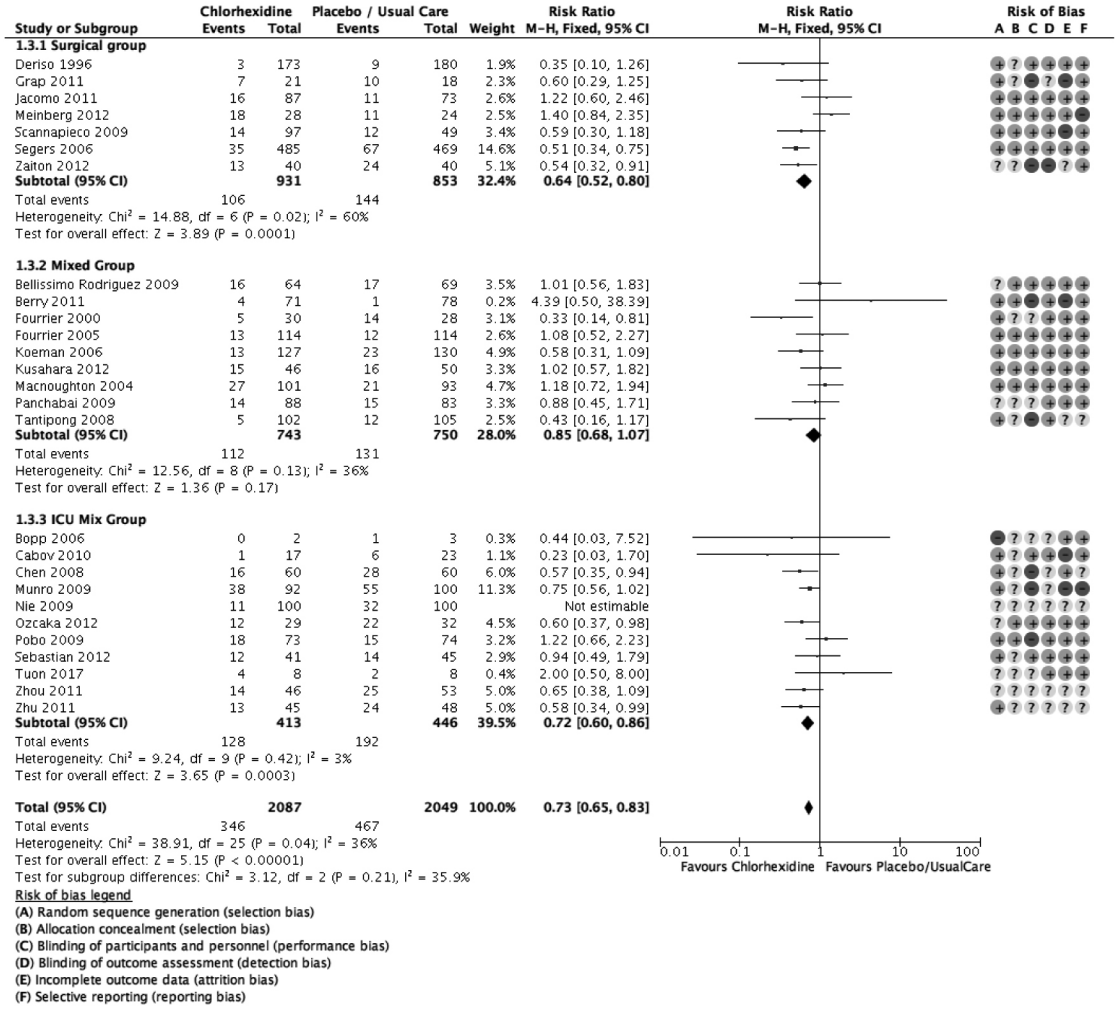

Figure 4. Chlorhexidine vs Placebo/Usual Care : Ventilator-associated pneumonia

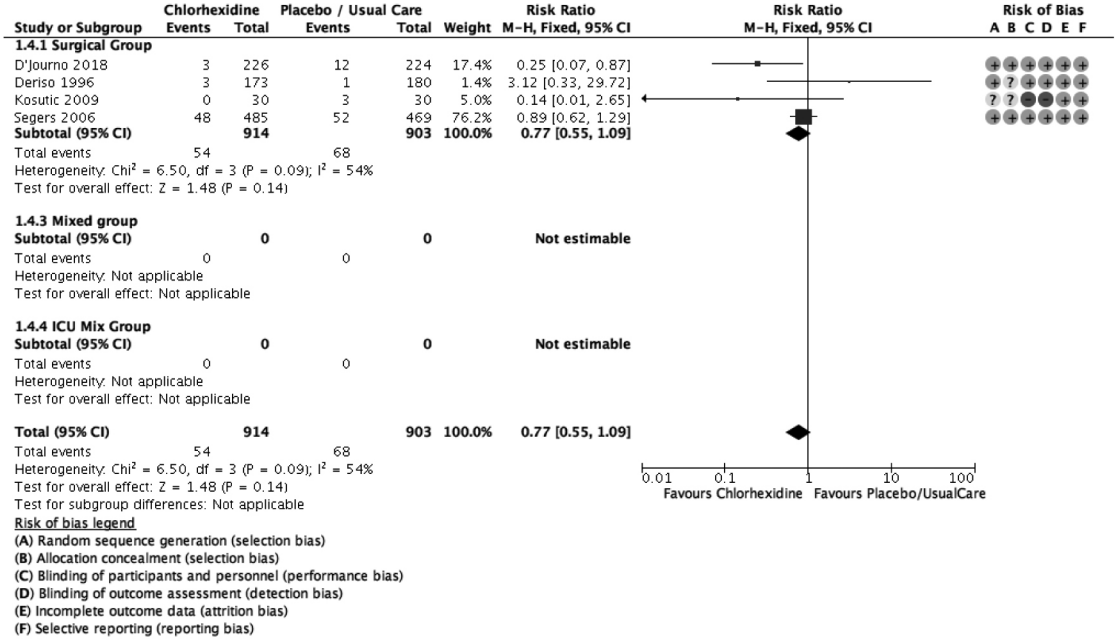

Figure 5. Chlorhexidine vs Placebo/Usual Care : Surgical Site Infection

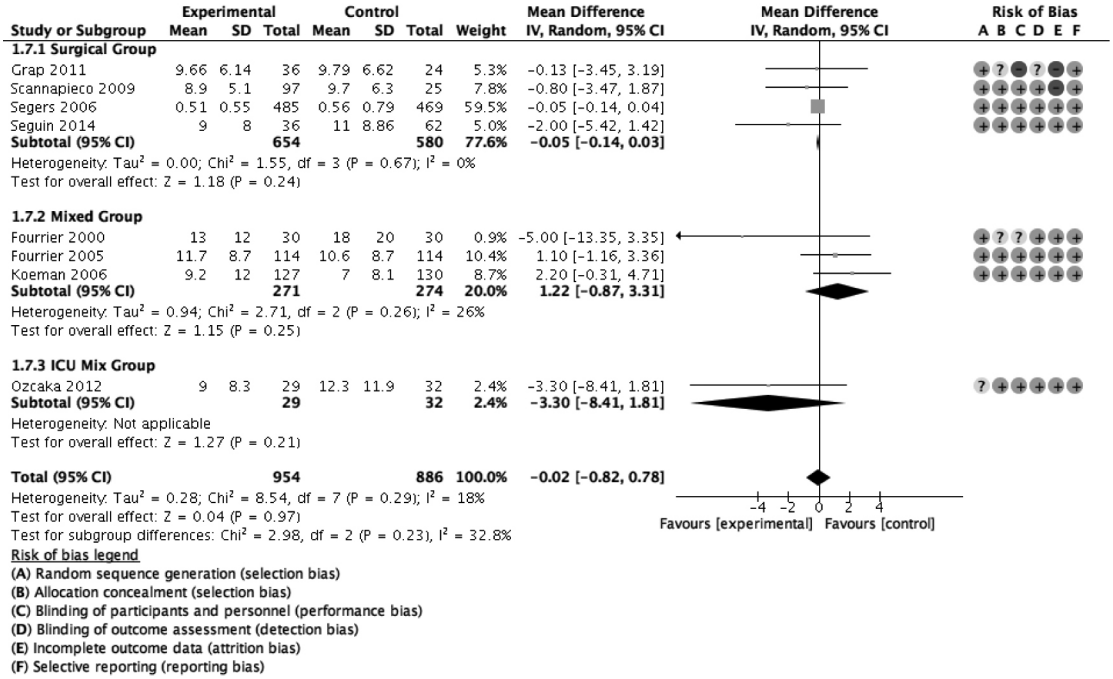

Figure 6. Chlorhexidine vs Placebo/Usual Care : Ventilator Days

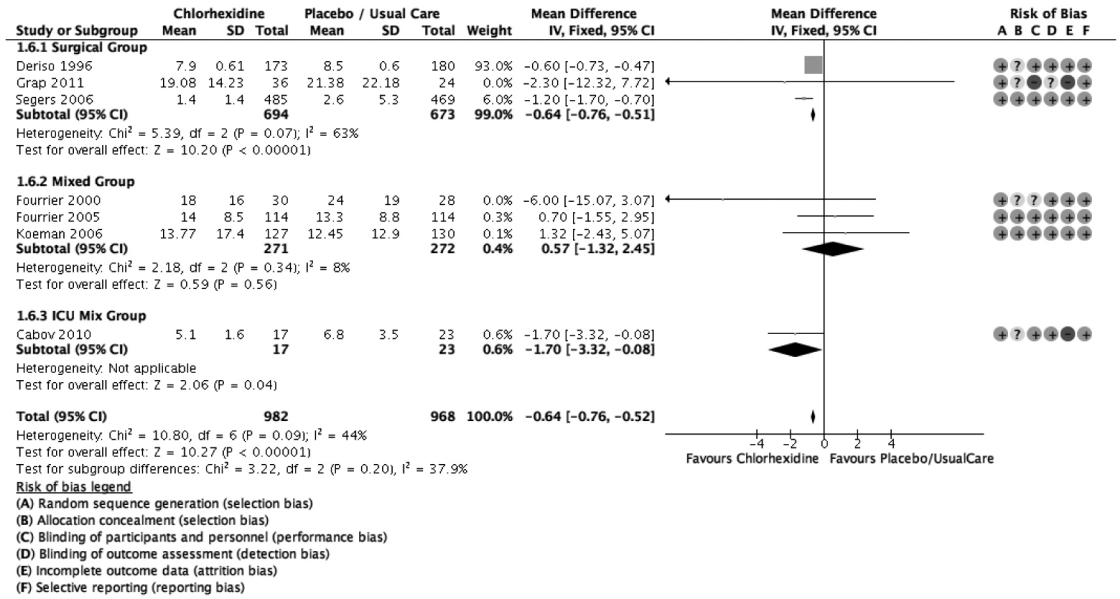

Figure 7. Chlorhexidine vs Placebo / Usual Care : ICU Days

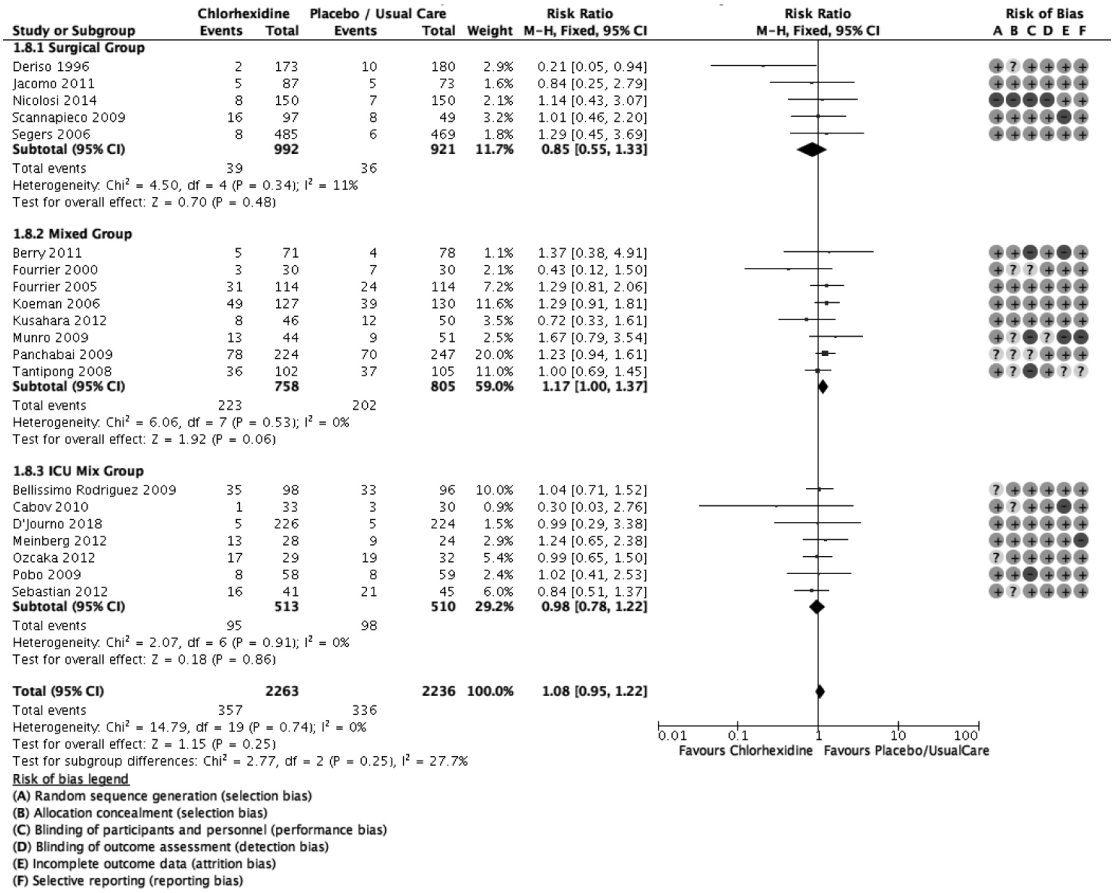

Figure 8. Chlorhexidine vs Placebo / Usual Care : Mortality

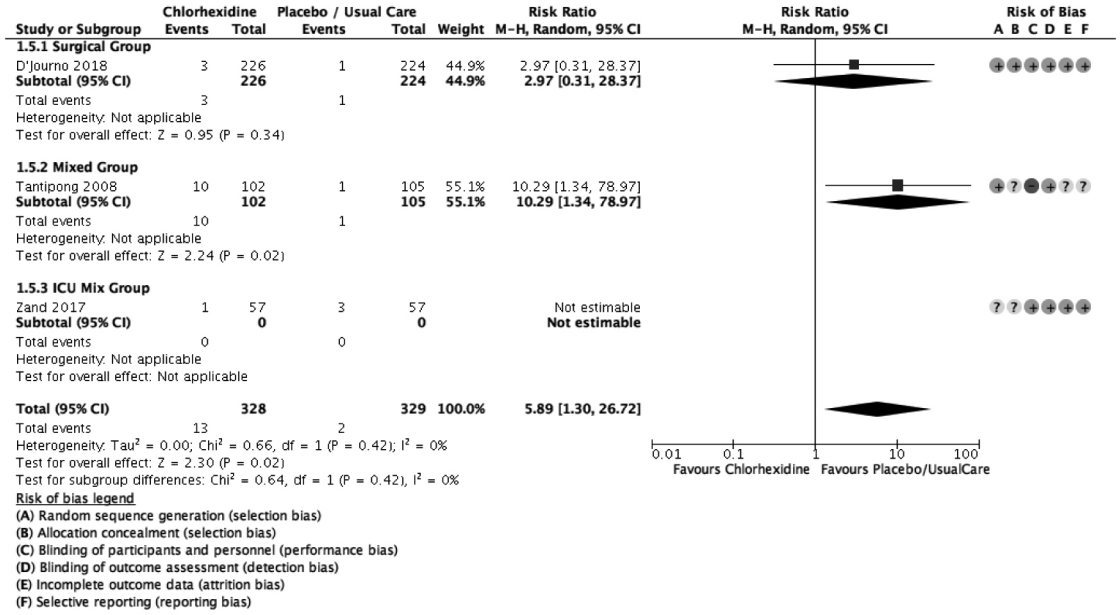

Figure 9. Chlorhexidine vs Placebo/Usual Care : Adverse Events

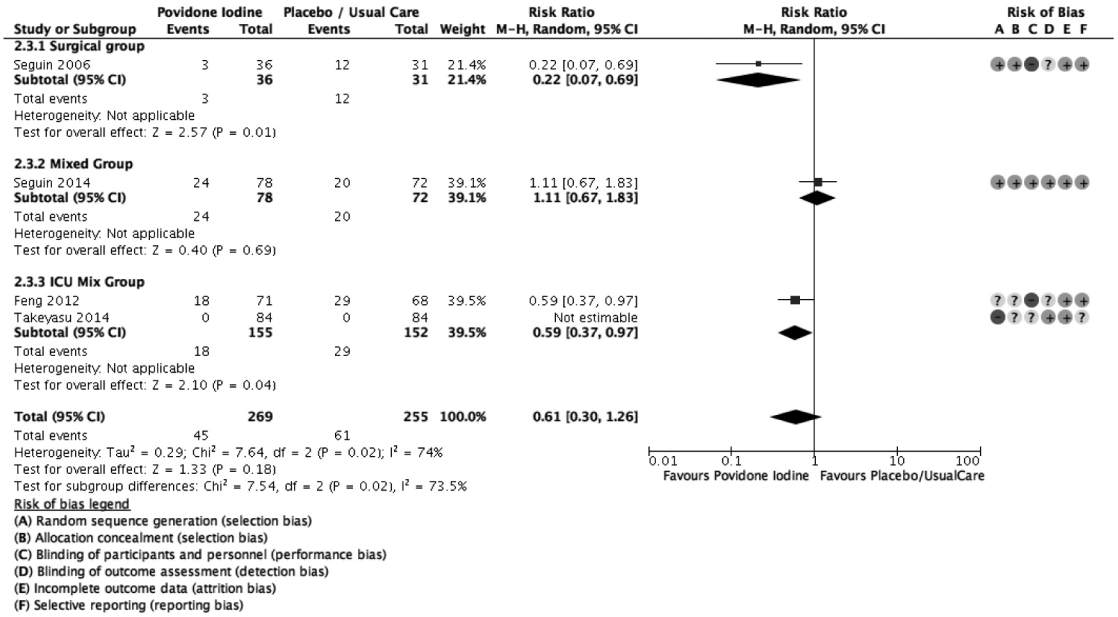

Figure 10. Povidone iodine vs Placebo/Usual Care : Ventilator-associated Pneumonia

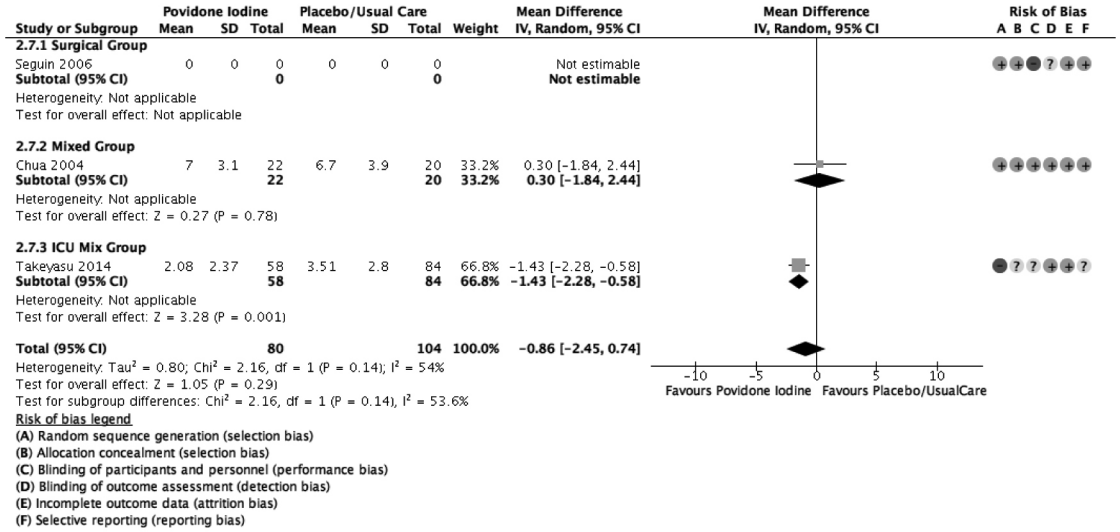

Figure 11. Povidone iodine vs Placebo/Usual Care : Ventilator Days

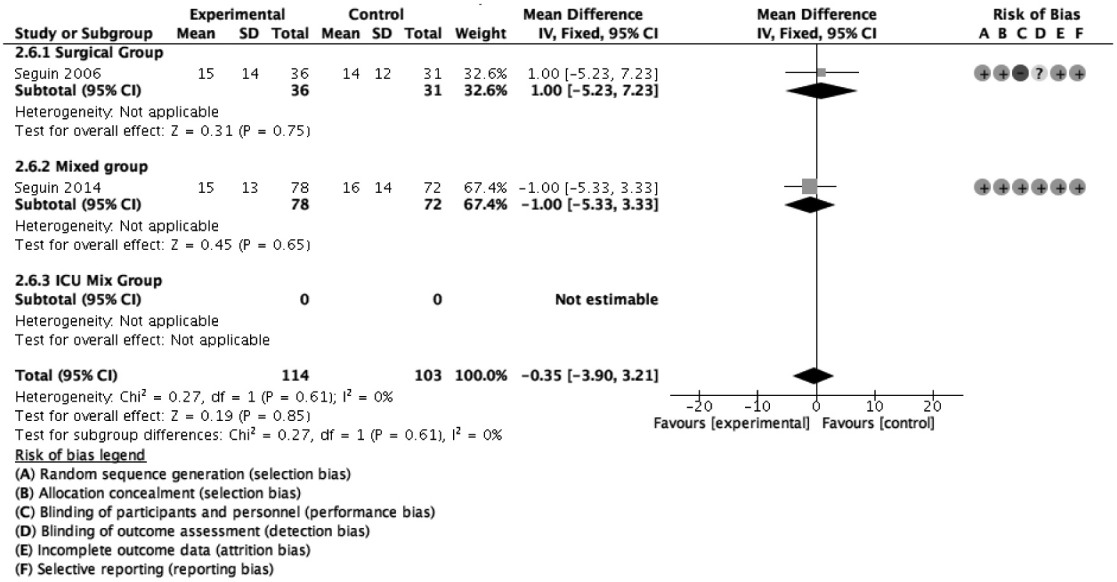

Figure 12. Povidone iodine vs Placebo/Usual Care : ICU Days

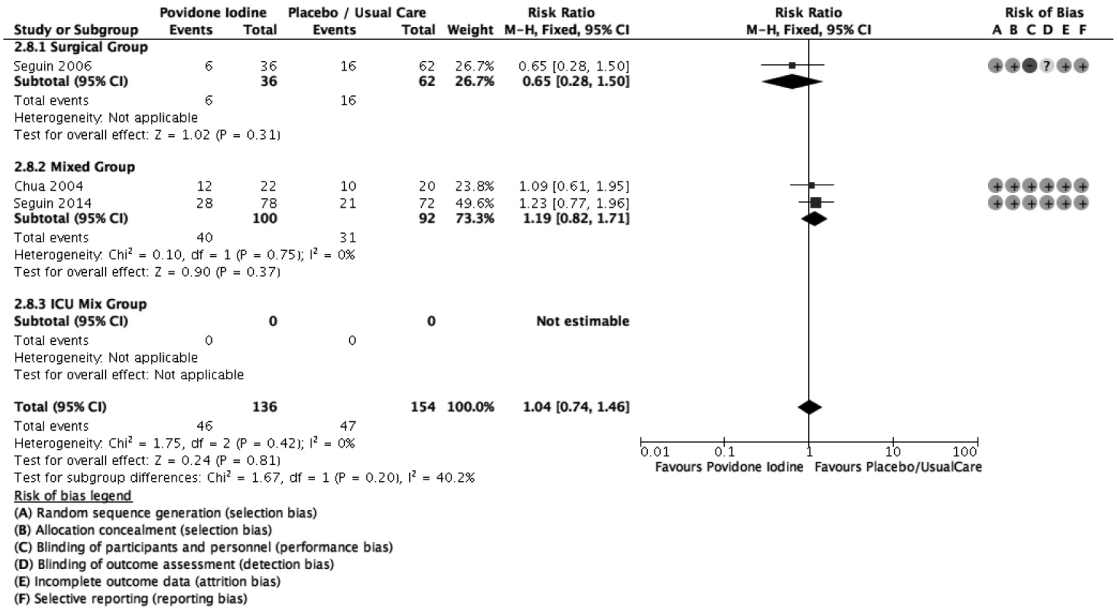

Figure 13. Povidone iodine vs Placebo / Usual Care : Mortality

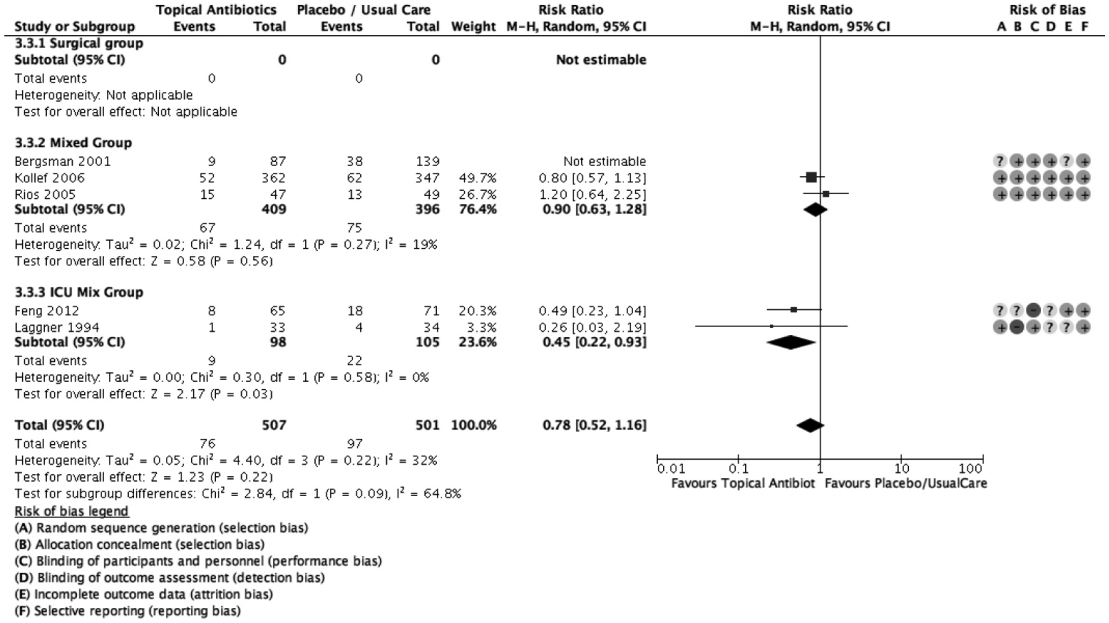

Figure 14. Topical antibiotics vs Placebo/ Usual Care : Ventilator-associated pneumonia

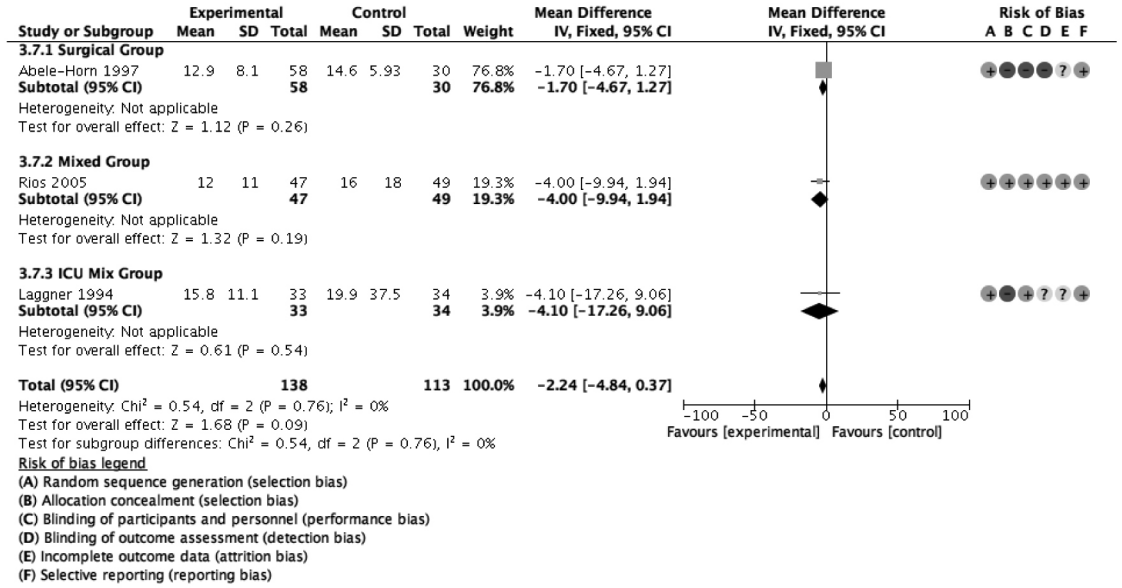

Figure 15. Topical antibiotics vs Placebo / Usual Care : Ventilator Days

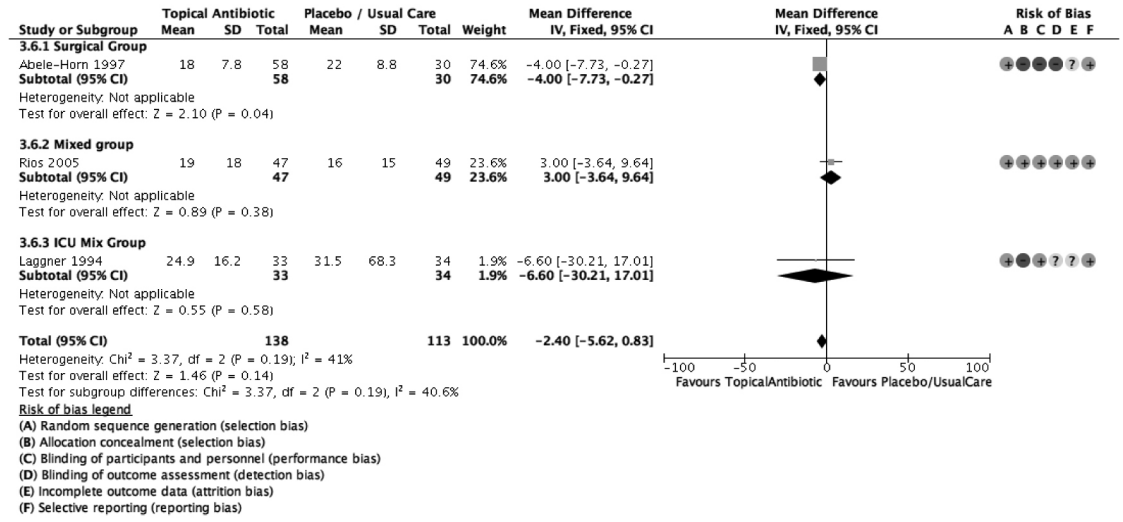

Figure 16. Topical antibiotics vs Placebo/Usual Care : ICU Days

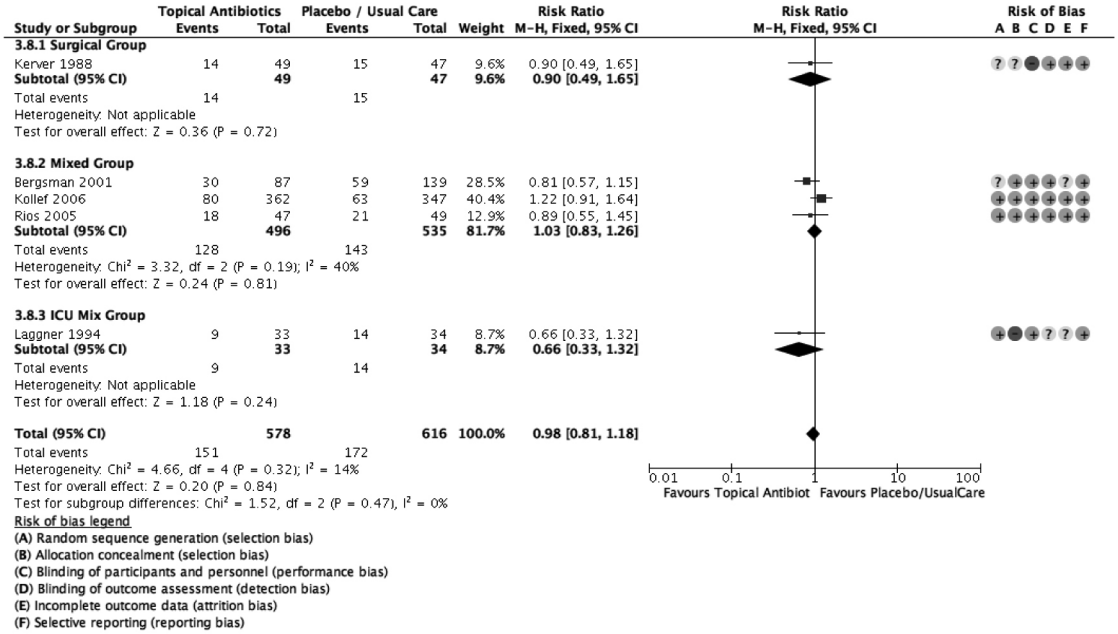

Figure 17. Topical antibiotics vs Placebo / Usual Care : Mortality

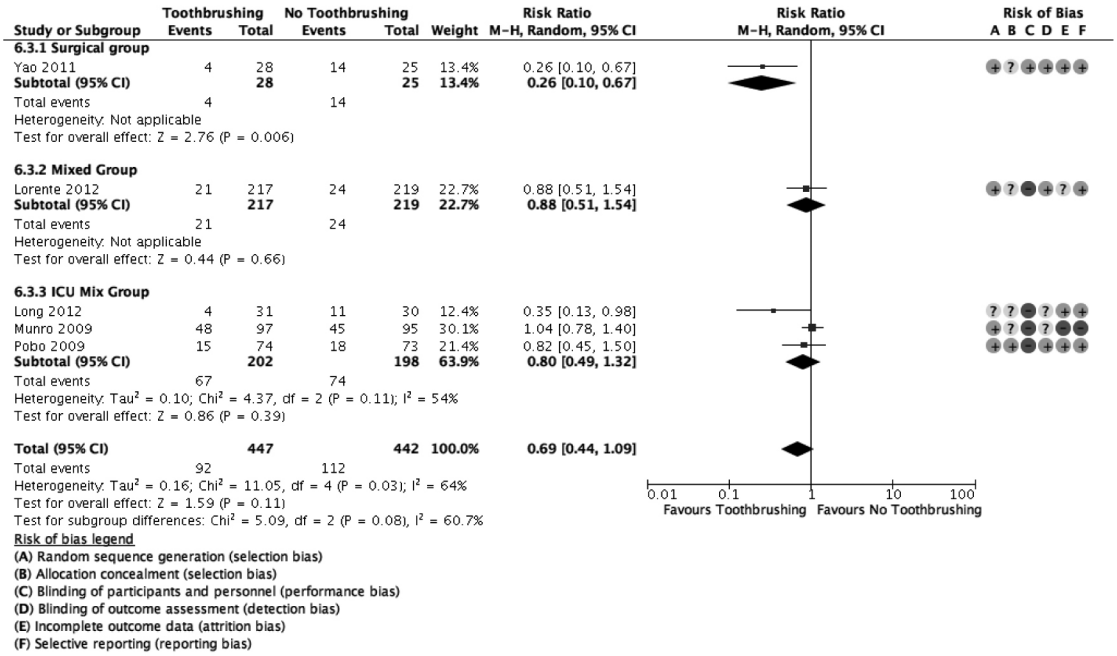

Figure 19. Toothbrushing vs No Toothbrushing : Ventilator-associated pneumonia

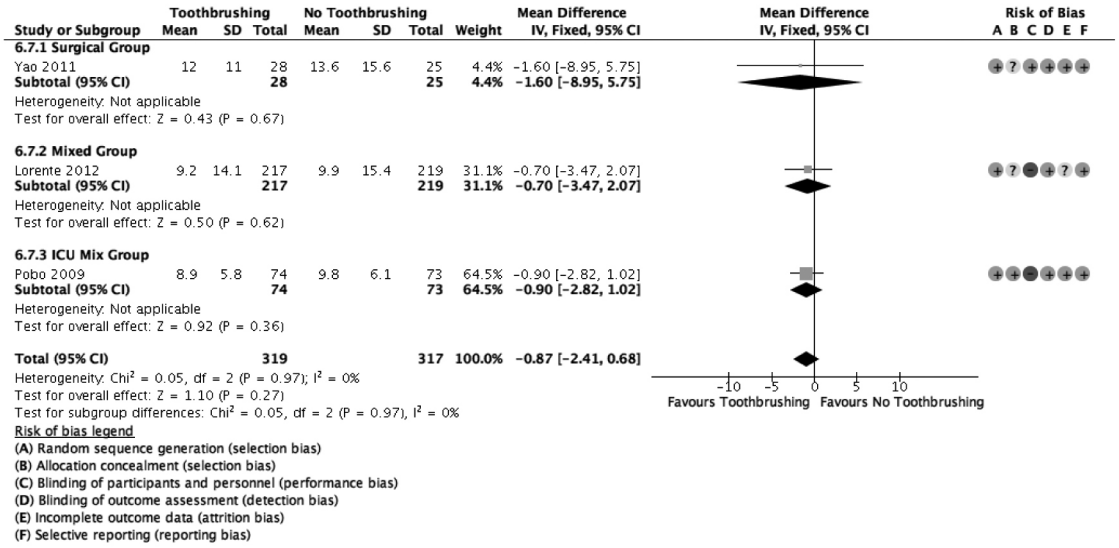

Figure 20. Toothbrushing vs No Toothbrushing : Ventilator Days

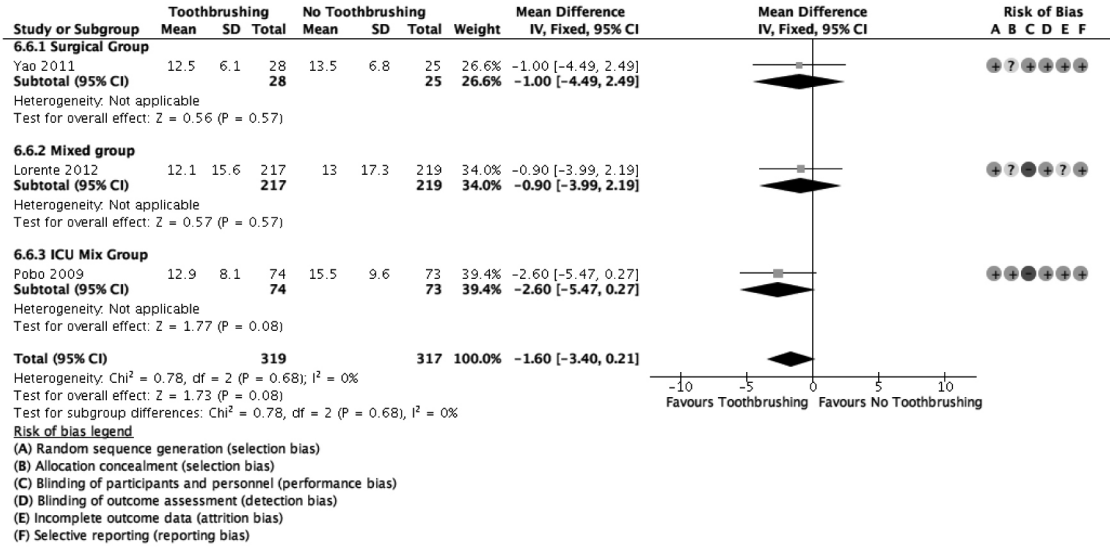

Figure 21. Toothbrushing vs No Toothbrushing : ICU Days

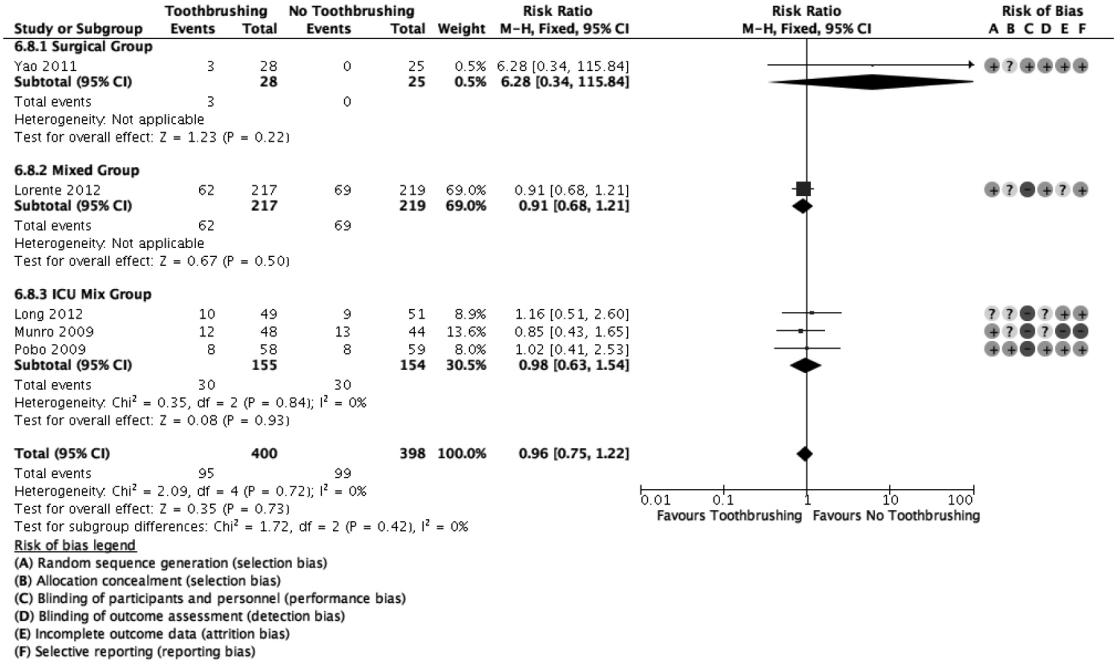

Figure 21. Toothbrushing vs No Toothbrushing : Mortality

Appendix 3. Evaluations of other agents, one agent versus another, or dosing and frequency comparisons.

A. Essential Oil-based Mouthwash

One study compared essential oils-based mouthwash and placebo or standard/usual care, with 133 patients receiving essential and 127 receiving placebo.[1]

The 3-armed trial compared Listerine mouthwash with sodium bicarbonate mouthwash and sterile water among critically ill patients. No significant differences in ventilator-associated pneumonia rates (4.7% vs 4.4%, RR 1.07, 95%CI 0.41, 2.78), ventilator days, ICU stay, adverse event rates, or systemic antibiotic use were observed across all treatment groups.[1] The methodological quality of this study was poor due to high risk of bias in several domains including lack of blinding, high attrition rate, and possible selective reporting.

One randomized trial compared chlorhexidine and phenolic mixture (Listerine) among patients who underwent aortocoronary bypass.[2] Incidence of nosocomial pneumonia did not differ significantly between the two groups (4/279 vs 9/291, p = 0.21), nor did the incidence of positive culture growth (52/270 vs 44/291, p =0.19). Mortality rates were also similar between the two groups (6/270 vs 3/291). Colony culture studies showed more growth in the chlorhexidine group than in the Listerine group (19.26% vs 15.12%) although the difference was not statistically significant (p=0.19).

All other available information on essential oils-based mouthwash was limited to normal healthy patients or on patients with dental conditions.

B. Oral Probiotics

One study compared oral probiotics bacterium Lactobacillus planterum 299 and toothbrushing followed by chlorhexidine swab among mechanically ventilated patients with 69 patients receiving oral probiotics and 68 receiving toothbrushing followed by chlorhexidine swab.[3] The methodological quality of the study was satisfactory, with three out of five domains at low risk for bias specifically allocation concealment, blinding of outcome assessment, and selective reporting. No difference was found between the two groups in terms of ventilator days, length of stay in the ICU, and in-hospital mortality rates.

C. Other Agents

Three trials studied the use of other agents other than the ones previously mentioned. One study compared the use of 0.12% chlorhexidine combined with sodium bicarbonate mouthwash and sterile water, with 33 receiving the combination mouthwash and 43 receiving sterile water.[4] Another trial compared the use of sodium bicarbonate mouthwash and sterile water, with 138 receiving sodium bicarbonate mouthwash and 127 receiving sterile water.[1] One trial compared an antibiotic mouthwash containing 500mg neomycin and 500mg erythromycin and placebo[5], with 7 patients receiving antibiotic mouthwash and 5 receiving placebo. The methodological quality of these studies was generally poor due to high risk of performance bias and attrition bias.

D. One Agent vs Another

Three trials compared one agent and another agent head to head. One three-armed trial compared the use of 0.5% alpha-bisabolol mouthwash, 0.12% chlorhexidine with 0.5% alpha-bisabolol mouthwash and 0.12% chlorhexidine 6, with 11 receiving 0.5% alpha-bisabolol only, 10 receiving 0.5% alpha-bisabolol and 0.12% chlorhexidine mouthwash combination, and 9 receiving 0.12% chlorhexidine alone. Another trial compared the use of 0.12% chlorhexidine rinse and a solution of a phenolic mixture[2], with 270 patients receiving chlorhexidine and 291 patients receiving phenolic mixture. One trial compared 1% cetrimide solution and 0.9% sodium chloride[7], with 30 receiving 1% cetrimide and 30 receiving 0.9% sodium chloride. The methodological quality of these studies was mixed.

There is limited trial evidence directly comparing one agent with another. Only two trials were identified,

one comparing chlorhexidine and phenolic mixture / essential oils[2] and another comparing chlorhexidine and hexetidine.[8] No clear difference was established in the effectiveness of the different agents.

D. Dosing and Frequency Comparison

The present study compared the use of chlorhexidine at different doses, with 57 receiving 0.2% chlorhexidine and 57 receiving 2% chlorhexidine.[9] The incidence of VAP was significantly higher in the group which received 0.2 % chlorhexidine (13/57 or 22.8% v 3/57 or 5.3%, p value=0.007). One three-armed trial compared chlorhexidine at different frequencies (once a day and twice a day) with usual care.[10] Both frequencies reported similar incidences of VAP (7/47 or 14.98% vs 7/50 or 14%).

References

1. Berry AM. A comparison of Listerine and sodium bicarbonate oral cleansing solutions on dental plaque colonisation and incidence of ventilator associated pneumonia in mechanically ventilated patienst: a randomised control trial. Int Crit Care Nurs 2013; 29(5): 275-81.

2. Houston S, Hougland P, Anderson JJ, LaRocco M, Kennedy V, Gentry LO. Effectiveness of 0.12% chlorhexidine gluconate oral rinse in reducing prevalence of nosocomial pneumonia in patients undergoing heart surgery. Am J Crit Care 2002 Nov;11(6):567-70. PMID: 12425407

3. Klarin B, Adolfsson A, Torstensson A, Larsson A. Can probiotics be an alternative to chlorhexidine for oral care in the mechanically ventilated patient? A multicentre, prospective, randomised controlled open trial. Crit Care. 2018 Oct 28;22(1):272. doi: 10.1186/s13054-018-2209-4. PMID: 30368249; PMCID: PMC6204275.

4. Berry AM, Davidson PM, Masters J, Rolls K, Ollerton R. Effects of three approaches to standardized oral hygiene to reduce bacterial colonization and ventilator associated pneumonia in mechanically ventilated patients: A randomised control trial. Int J Nurs Studies 2011;48(6):681-8

5. Jones TR, Kaulbach H, Nichter L, Edlich RF, Cantrell RW. Efficacy of an antibiotic mouthwash in contaminated head and neck surgery. Am J Surg 1989; 158(4): 324-7. doi:10.1016/0002-9610(89)90126-8

6. Amora-Silva BF, Ribeiro SC, Vieira CL, et al. Clinical efficacy of new α-bisabolol mouthwashes in postoperative complications of maxillofacial surgeries: a randomized, controlled, triple-blind clinical trial. Clin Oral Investig 2019; 23(2): 577-84. doi:10.1007/s00784-018-2464-4

7. Kosutic D, Uglesic V, Perkovic D, Persic Z, Solman L, Lupi-Ferandin S, Knezevic P, Sokler K, Knezevic G. Preoperative antiseptics in clean/contaminated maxillofacial and oral surgery: prospective randomized study. Int J Oral Maxillofac Surg 2009; 38(2): 160-5. doi: 10.1016/j.ijom.2008.11.023. Epub 2009 Jan 22. PMID: 19167188

8. Zouka M, Soultati I, Hari H, Pourzitaki C, Paroutsidou G, Thomaidou E, et al. Oral dental hygiene and ventilator associated pneumonia prevention in an ICU setting: Comparison between two methods (preliminary data of a randomised prospective study). Int Care Med 2010; 36: S103.

9. Zand F, Zahed L, Mansouri P, Dehghanrad F, Bahrani M, Ghorbani M. The effects of oral rinse with 0.2% and 2% chlorhexidine on oropharyngeal colonization and ventilator associated pneumonia in adults' intensive care units. J Crit Care 2017; 40: 318-22. doi: 10.1016/j.jcrc.2017.02.029. Epub 2017 Mar 1. PMID: 28320561.

10. Scannapieco FA, Yu J, Raghavendran K, et al. A randomized trial of chlorhexidine gluconate on oral bacterial pathogens in mechanically ventilated patients. Crit Care 2009; 13(4): 1-12. doi:10.1186/cc7967