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Review

Oral hygiene care for critically ill children to prevent ventilator-associated pneumonia: a systematic review and meta-analysis

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SUMMARY

There is limited evidence on the effectiveness of oral hygiene care as part of the care bundle for preventing ventilator-associated pneumonia (VAP), particularly in children. The aim of this study was to assess whether the use of anti-infective agents in oral care can reduce the incidence of VAP in critically ill children. The systematic review and meta-analysis were conducted following PRISMA guidelines and registered with PROSPERO (CRD 42024508886). A systematic search of PubMed, CENTRAL, and Igaku Chuo Zasshi was performed in May 2024. Randomized controlled trials that evaluated oral hygiene interventions in critically ill children (≤18 years old) on mechanical ventilation for at least 48 h were included. Data were extracted independently by two reviewers, and the risk of bias was assessed. Meta-analysis was performed using a random-effects model. Five studies were included in the meta-analysis. The incidence of VAP, mortality, intensive care unit (ICU) stay duration, and mechanical ventilation duration were assessed. Oral hygiene procedures using antiseptics showed no significant difference in preventing VAP in critically ill children (risk ratio (RR) 0.95, 95% confidence interval (CI) 0.72–1.25). Similarly, there were no significant differences in mortality, ICU stay duration, or mechanical ventilation duration (RR 0.94, 95% CI 0.67–1.33; RR 2.02, 95% CI -0.87 to 4.91; and mean difference −1.01, 95% CI -2.35 to 0.33, respectively). This study found no evidence supporting the prevention of VAP through oral care in critically ill paediatric patients, although the evidence quality was low.

Introduction

Ventilator-associated pneumonia (VAP) is a common healthcare-associated infection in intubated children, accounting for 12–38% of paediatric intensive care units (PICUs) [1–3]. Studies have indicated that VAP is linked to a prolonged duration of mechanical ventilation, extended PICU stay, higher hospital costs, and increased mortality in children [4,5].

VAP can be caused by several factors, including prolonged ventilator use, bacterial invasion through endotracheal tubes, aspiration, and contaminated circuits [6]. To prevent VAP, ventilator care bundles have been introduced [7]. Oral hygiene

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care is generally included as part of these care bundles [7]. However, the most effective oral hygiene intervention, particularly for children, remains unclear. Some studies have demonstrated the effectiveness of oral hygiene procedures using antiseptic agents in adults [8—10], while others have shown no significant benefit from this approach [11,12]. In children, evidence supporting the use of antiseptic agents in oral hygiene care for preventing VAP is scarce.

We conducted a systematic review and meta-analysis to evaluate the effectiveness of oral antiseptic solutions as part of ventilator care bundles in preventing VAP in intubated children within hospital settings.

Methods

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The study was registered in PROSPERO (CRD 42024508886).

Information sources and search strategy

We conducted a comprehensive literature search of MEDLINE (Ovid), Cochrane CENTRAL, and Igaku Chuo Zasshi from their inception to 20th May 2024. The search combined Medical Subject Headings (MeSH) terms such as "Oral Hygiene" and "Pneumonia, Ventilator-Associated", and free-text keywords related to oral hygiene interventions (e.g., "oral decontamination") and VAP in paediatric populations. Filters were applied to include only studies involving children or adolescents (≤18 years old) and randomized or quasi-randomized controlled trials.

The complete search strategies for each database are summarized in the Supplementary material.

Eligibility criteria

Inclusion criteria

We included randomized controlled trials (RCTs) that assessed the effectiveness of oral hygiene procedures on the incidence of VAP in paediatric patients (≤18 years old) requiring mechanical ventilation for at least 48 h in a hospital setting. Eligible interventions involved oral hygiene practices such as mouthwash, toothpaste, gels, sprays, or liquids, using antiseptic agents including chlorhexidine (CHX), povidone-iodine, sodium bicarbonate, or saline. Comparators included no oral care, placebo, or usual care without antiseptic oral hygiene.

Studies were included if they reported at least one of the following outcomes: (1) primary outcome — incidence of VAP; (2) secondary outcomes — mortality (ICU or 30-day), duration of ICU stay, duration of mechanical ventilation, and adverse effects related to oral hygiene procedures.

Exclusion criteria

We excluded studies involving adults only (>18 years old), as well as non-randomized studies, quasi-experimental designs without control groups, or observational studies. Additionally, unpublished studies, conference abstracts lacking full-text data, and articles not peer-reviewed were excluded. Studies not published in English or Japanese were excluded. Finally, studies were excluded if the intervention did not involve oral hygiene or antiseptic oral care.

Selection of studies and date extraction

In the first screening, two independent reviewers, blinded to each other's decisions, reviewed the titles and abstracts of the studies to select articles meeting the inclusion criteria. If there was disagreement, a third reviewer's opinion was considered. In the second screening, three independent reviewers examined the full texts of all studies included from the first screening and excluded articles based on the exclusion criteria. Disagreements were resolved through discussion.

Two reviewers independently extracted data from each included study using standardized extraction forms. We extracted the following information: authors, year of publication, countries of study, funding, languages of publication, study duration, study design; participant details (total number, setting, age, sex, country); diagnostic criteria for VAP; details of intervention and control procedures; incidence of VAP or other respiratory diseases; mortality, duration of mechanical ventilation, duration of ICU stay, systemic antibiotic use, and any adverse outcomes related to the interventions.

Risk of bias assessment

The Cochrane Risk of Bias Tool for Randomized Trials (RoB 2) was used to assess the risk of bias in the included studies. At least two authors evaluated the risk of bias for each study. The risk was categorized as low (adequate measures), high (inadequate measures), or some concern. Disagreements were resolved through discussion.

Statistical analysis

Statistical analysis was performed using the Cochrane Collaboration's RevMan Web tool with a random-effects model to account for variability across studies. Risk ratios (RRs) with 95% confidence intervals (CIs) were calculated for binary outcomes, while mean differences (MDs) with 95% CIs were used for continuous outcomes.

Statistical heterogeneity was assessed using the χ^2 test, visual inspection of forest plots, and quantified using the I^2 statistic, with values ≥50% indicating substantial heterogeneity. To evaluate the potential for publication bias, funnel plots were generated for the primary outcome.

A sensitivity analysis was also performed by excluding studies with a high risk of bias to assess the robustness of the findings.

Subgroup analysis

Subgroup analyses were planned in order to explore potential sources of heterogeneity in treatment effects.

Analyses were stratified by: (1) clinical setting — studies conducted in neonatal intensive care units (NICUs) vs PICUs, to reflect differences in patient characteristics and care practices; (2) age group — children younger than one year of age vs those aged one year and older, as previous studies have indicated that the VAP incidence is higher among children younger than one year old [13,14]; (3) onset timing of VAP — early-onset VAP (diagnosed within the first four days of mechanical

ventilation) vs late-onset VAP (diagnosed after four days), based on potential variations in microbial aetiology and intervention effectiveness.

Assessment of the certainty of the evidence

The certainty of evidence was assessed based on the overall risk of bias, directness of the evidence, consistency of the results, precision of estimates, and risk of publication bias. The certainty was categorized into four levels: high, medium, low, or very low.

Results

Study selection

A total of 69 articles were identified from the electronic databases, of which 56 were excluded after the first screening. Thirteen articles were reviewed in full and assessed for eligibility. After a second screening, eight articles were excluded. Finally, five articles that met all the inclusion criteria were included in the review (Figure 1) [13–17].

Characteristics of included studies

Table I summarizes the key characteristics of the included studies including participants, clinical settings, intervention and control procedures in each study. Four of the five studies were conducted in PICUs [13–17]. Among these, three used 0.12% CHX as the oral antiseptic [13–15], and one used 1.0% CHX [16]. One of PICU studies exclusively included children who had undergone cardiac surgery for congenital heart disease [13]. The remaining study, conducted in an NICU, used antiseptic solution containing lactoperoxidase, lysozyme, and lactoferrin [17]. Additional details of each study are provided in Supplementary Table S1.

Risk of bias assessment

The risk of bias assessment for the reviewed studies is presented in Supplementary Figure S1. One study had a low risk of bias [14], one had a moderate risk [13], and three had serious or critical risks [15–17].

Primary outcome

- Incidence of VAP (Figure 2)

In this meta-analysis of five studies (three with a high risk of bias, one with an unclear risk of bias, and one with a low risk of bias), oral hygiene procedures with antiseptics showed no evidence of preventing VAP in critically ill children (RR 0.95, 95% CI 0.72–1.25, 521 participants). Funnel plots indicated symmetry (Supplementary Figure S2). Heterogeneity was not significant (P=0.82, $I^2 = 0\%$).

Secondary outcome

- Mortality (Figure 3)

Mortality did not differ between the intervention and control groups, with minimal heterogeneity (RR 0.94, 95% CI 0.67–1.33, P=0.51, $I^2 = 0\%$).

- Duration of ICU stay (Figure 4)

The duration of ICU stay was reported in four studies (397 participants). The meta-analysis showed no evidence of a difference between the intervention and placebo/usual care

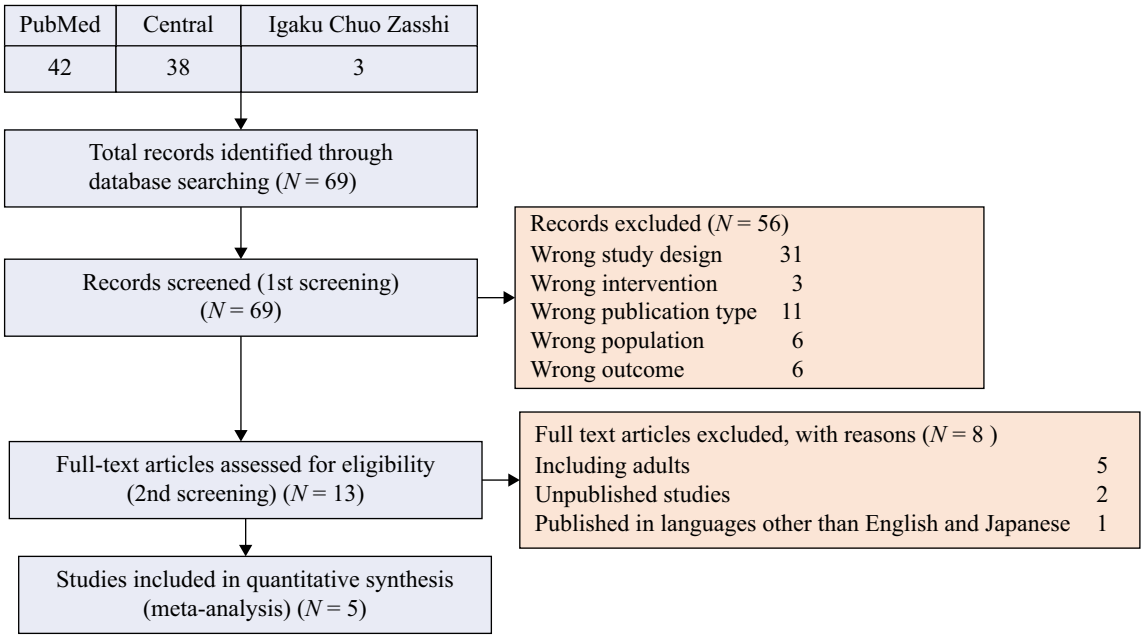

Figure 1. Flow chart of the study selection process. A total of 69 articles were identified through the electronic databases. After the first screening, 56 were excluded. The remaining 13 articles underwent full-text review for eligibility. Following a second screening, eight articles were excluded, leaving five articles that met all the inclusion criteria and were included in the review.

Table I
Summary of characteristics of included studies

Study	Country	Study design	Sample size	Population and age range	Setting	Intervention	Comparison	Implementation interval
Jácomo 2011 [13]	Brazil	RCT	160	Children with congenital heart disease undergoing cardiac surgery aged 0 months to 18 years	PICU	0.12% chlorhexidine rinse solution	Sterile water	Twice a day
Karakaya 2021 [14]	Turkey	RCT	138	Children aged 1 month to 18 years	PICU	0.12% chlorhexidine rinse solution	0.9% NaCl	Every 4 h
Kusahara 2012 [15]	Brazil	RCT	96	Children aged 1 month or older	PIUC	0.12% chlorhexidine gel	Placebo gel	Twice a day
Sebastian 2012 [16]	India	RCT	86	Children aged 3 months to 15 years	PICU	1% chlorhexidine gel	Placebo gel	Every 8 h
Stefanescu 2013 [17]	USA	RCT	41	Newborn: gestational age ≤28 weeks	NICU	Oral care with Biotene OralBalance® gel containing enzymes (lactoperoxidase, lysozyme, lactoferrin)	Sterile water	Every 4 h

NICU, neonatal intensive care unit; PICU, paediatric intensive care unit; RCT, randomized control trial.

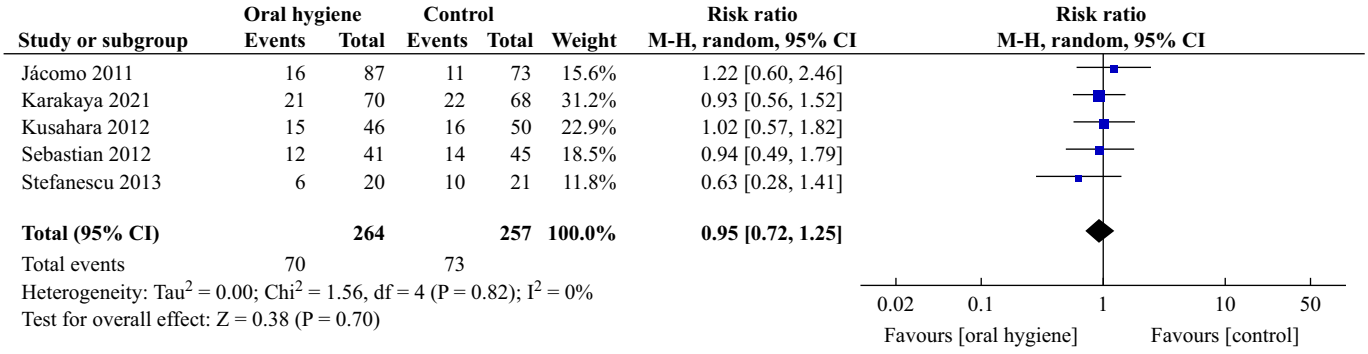

Figure 2. Forest plot comparing the incidence of ventilator-associated pneumonia (VAP) between intervention and control groups. Oral hygiene care procedures using antiseptics show no significant difference in preventing VAP in critically ill children (risk ratio 0.95, 95% confidence interval (CI) 0.72–1.25).

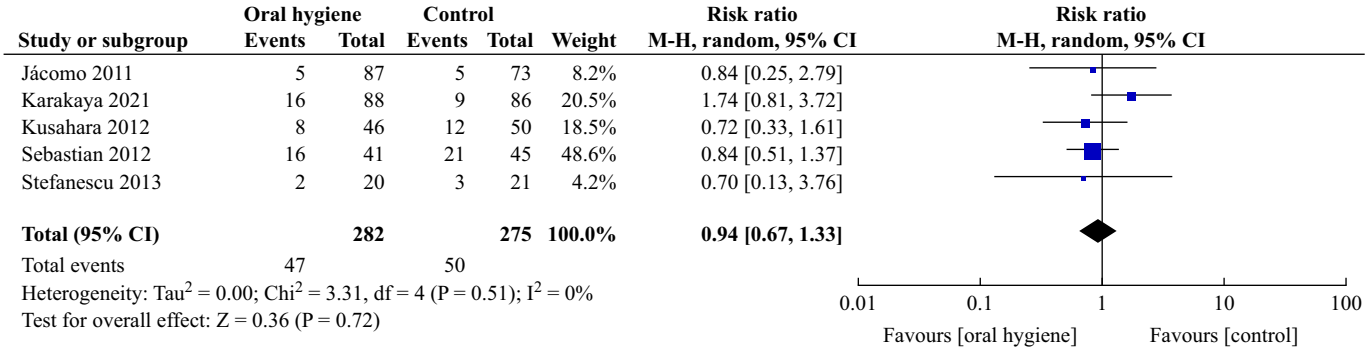

Figure 3. Forest plot of comparing mortality between intervention and control groups. Oral hygiene care procedures with antiseptics show no significant difference in mortality of critically ill children (risk ratio 0.94, 95% confidence interval (CI) 0.67–1.33).

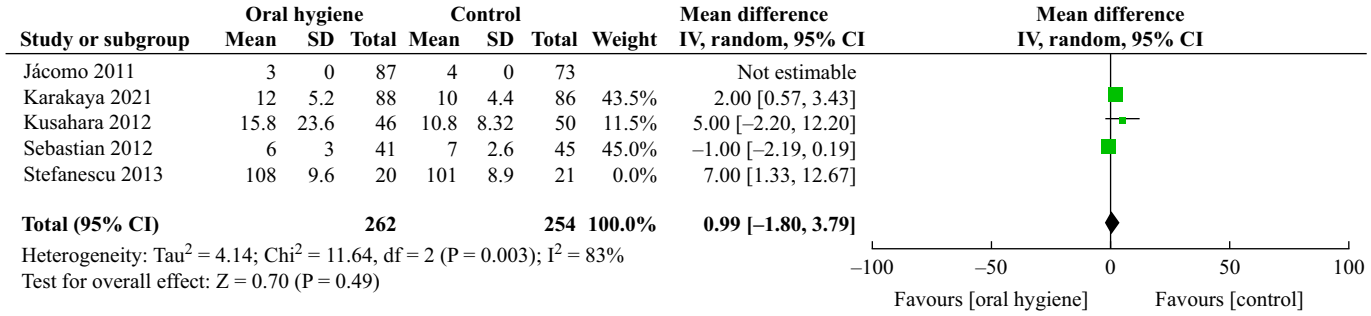

Figure 4. Forest plot of comparing duration of intensive care unit between intervention and control groups. Oral hygiene care procedures with antiseptics show no significant difference in the duration of intensive care unit (ICU) stay of critically ill children (risk ratio (RR) 2.02, 95% confidence interval (CI) -0.87 to 4.91). SD, standard deviation.

groups (MD 2.02, 95% CI -0.87 to 4.91). Heterogeneity among studies was significant (P=0.0008, I^2 = 82%).

- Duration of mechanical ventilation (Figure 5)

The duration of mechanical ventilation was reported in three studies (356 participants) and showed no evidence of a difference between the intervention and control groups (MD -1.01, 95% CI -2.35 to 0.33). Heterogeneity between studies was insignificant (P=0.71, I^2 = 0%).

- Adverse effects of the interventions

All included studies in this meta-analysis reported no serious adverse events.

Sensitivity analysis

For the primary outcome, a sensitivity analysis was performed by excluding three studies with a high risk of bias [15–17]. The result remained consistent with the main analysis (RR 1.02, 95% CI 0.68–1.52, 298 participants vs RR 0.95, 95% CI 0.72–1.25, 521 participants) (Supplementary Figure S3).

Subgroup analysis

Clinical setting

- PICU settings and incidence of VAP (Supplementary Figure S4)

In this meta-analysis, four studies conducted in PICUs showed no evidence of a difference between the intervention and control groups (RR 1.00, 95% CI 0.74–1.34).

- NICU settings and incidence of VAP (Supplementary Figure S5)

In this meta-analysis, only one study conducted in an NICU showed no evidence of a difference between the intervention and control groups, although there was a trend toward lower incidence of VAP in intervention group (RR 0.63, 95% CI 0.28–1.41) [17].

Age-based group

- Incidence of VAP among children under one year of age (Supplementary Figure S6)

In this meta-analysis, only one study conducted subgroup analysis stratified by age [13]. We combined its result with another included study conducted in a NICU where all participants were under one year of age [17]. The result indicated no significant difference in the VAP incidence between the intervention and control groups (RR 1.11, 95% CI 0.64–1.92).

- Incidence of VAP among children aged one year and older (Supplementary Figure S7)

Only one study provided stratified data for children aged one year and older. The result also showed no significant difference in the VAP incidence between the intervention and

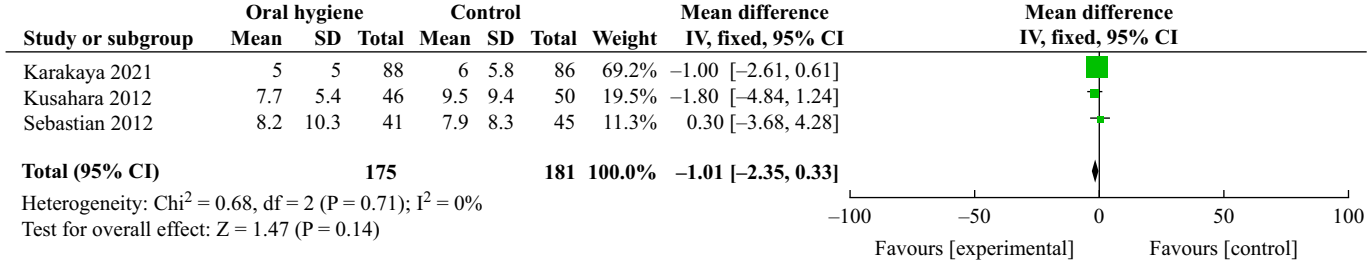

Figure 5. Forest plot of comparing duration of mechanical ventilation between intervention and control groups. Oral hygiene care procedures with antiseptics show no significant difference in the duration of mechanical ventilation of critically ill children (mean difference -1.01, 95% confidence interval (CI) -2.35 to 0.33). SD, standard deviation.

control groups in this age subgroup, although there was a trend toward lower incidence of VAP in intervention group (RR 0.41, 95% CI 0.08—2.11) [13].

Onset timing of VAP

- Efficacy of oral hygiene care in preventing early onset VAP (Supplementary Figure S8)

Two studies compared the efficacy of oral hygiene care in preventing early onset VAP and showed no evidence of a difference between the intervention and control groups (RR 0.98, 95% CI 0.54—1.76).

- Efficacy of oral hygiene care in preventing late-onset VAP (Supplementary Figure S9)

Two studies compared the efficacy of oral hygiene care in preventing late-onset VAP and showed no evidence of a difference between the intervention and control groups (RR 0.96, 95% CI 0.53—1.74).

The certainty of the evidence and summary of findings

Table II presents a summary of the main outcomes, including incidence of VAP, mortality, duration of ICU stay, and mechanical ventilation. The certainty of the evidence for all outcomes was rated as very low, primarily due to concerns about risk of bias, imprecision, and indirectness.

Discussion

Our meta-analysis found no significant differences between the oral care with antiseptic groups and the control groups regarding the reduction of VAP, mortality, duration of ICU stay, duration of ventilator days, or the spectrum of organisms detected in patients with VAP, although the certainty of the evidence was very low. In addition, a sensitivity analysis was conducted for the reduction of VAP, which confirmed the stability of our finding.

Oral hygiene care is a key component of most VAP care bundles, and it is crucial to emphasize its role in VAP prevention. However, evidence on the most effective oral hygiene practices for critically ill children remains limited. In adults, the Centers for Disease Control and Prevention recommends oral hygiene with 0.12% CHX in the perioperative period of cardiac surgery, though no routine recommendation exists for its use in preventing nosocomial pneumonia in critically ill patients [18]. Despite this, evidence on the effectiveness of oral hygiene care with CHX is inconclusive. A meta-analysis of adults found that oral hygiene with CHX reduced the incidence of VAP, though it had no impact on the duration of ventilator days, ICU stay, or mortality [19]. However, another meta-analysis failed to demonstrate that oral hygiene with CHX reduced the incidence of VAP [20]. The effects of oral hygiene, particularly in children, are still not well understood.

Several factors may explain why our meta-analysis did not show the effectiveness of oral antiseptics in preventing VAP [19]. One reason may be that the relative contribution of these factors to the development of VAP is less significant in children than in adults. VAP is caused by multiple factors, including oral condition [21]. Generally, adults have a higher risk of periodontal disease, which is linked to bacterial infections and plaque accumulation, whereas children are typically less prone to periodontal disease [22]. In adults, some studies have suggested that poor oral hygiene and a poor oral microbial environment contribute to the development of VAP [23,24]. Children's oral environments differ from those of adults, and

Table II
The certainty of the evidence — summary of findings

	The illustrative risk (95% CI)		Relative effects (95% CI)	The number of participants (studies)	Certainty of the evidence (GRADE)
	Assumed risk control group	Corresponding risk intervention group			
Incidence of ventilator-associated pneumonia	267 per 1000	262 per 1000 (192—334)	0.95 (0.72—1.25)	521 (5 studies)	Very low ROB -2 Indirectness of evidence -1 Imprecision -2
Mortality	182 per 1000	167 per 1000 (112—222)	0.94 (0.67—1.33)	557 (5 studies)	Very low ROB -1 Imprecision -2
Duration of ICU stay	The mean duration of ICU stay in the control groups ranged from 7 to 101 days	The mean duration of ICU stay in the intervention groups was 2.02 days longer (-0.87 to 4.91)		397 (4 studies)	Very low ROB -2 Inconsistency of results -1 Indirectness of evidence -1 Imprecision -2
Duration of mechanical ventilation	The mean duration of ventilation in the control groups ranged from 6 to 8 days	The mean duration of ventilation in the intervention groups was 1.01 days fewer (-2.35 to 0.33)		356 (3 studies)	Very low ROB -2 Indirectness of evidence -1 Imprecision -2

Assumed risk was based on the median event rate in the control groups of the included studies. The corresponding risk (and its 95% confidence interval (CI)) is based on the assumed risk in the intervention group and the relative effect of the intervention (and its 95% CI). ICU, intensive care unit.

the effectiveness of oral care in preventing VAP in children may therefore be limited [25].

Another possibility is that the concentration of antiseptics used for oral hygiene care was insufficient, or the frequency of oral hygiene was inadequate [26]. Some studies in this meta-analysis compared the spectrum of organisms causing VAP between the intervention and control groups and found no significant differences [14,16]. These findings suggest that the interventions did not significantly alter the oral environment. CHX, one of the most common antiseptics used in oral hygiene care, was used in four of the five studies included in this meta-analysis. However, the optimal concentration of CHX remains unknown. Although 0.12—0.2% CHX are typically recommended [27], one study reported that low concentrations of CHX were ineffective in decontaminating Gram-negative pathogens frequently detected in VAP patients [28]. In adult populations, some RCTs have demonstrated the effectiveness of 2% CHX for VAP prevention [29,30]. In this meta-analysis, one study used 1% CHX, which is a relatively high concentration for paediatric patients, but did not observe a preventive effect. While higher concentration of CHX may be effective, their safety profile in paediatric patients remains uncertain and warrants further investigation. Additionally, evidence on the optimal frequency of oral care is limited. In the included studies, frequency ranged from two to six times per day, but no clear association with outcomes was found.

Lastly, there is a possibility that oral CHX decontamination does not reduce the incidence of VAP, as reported by a recent meta-analysis [20]. CHX resistance has been observed in other interventions, such as decolonization of patients colonized with antimicrobial-resistant organisms [31]. This may partly explain why the reduction in VAP with a CHX-based oral hygiene regimen was not statistically significant.

Regarding secondary outcomes, the intervention group showed a trend toward a shorter duration of mechanical ventilation but a slightly longer ICU stay compared with the control group, although neither difference reached statistical significance. Conceptually, ICU stay and mechanical ventilation duration are related, however, our findings indicated distinct results for each outcome with no strong correlation. This discrepancy may be attributed to the variability of ICU practices and patient-management strategies across studies. Additionally, the widespread use of non-invasive respiratory support devices could have influenced the relation between ICU stay and mechanical ventilation duration [32].

This study has some limitations. First, as mentioned, we did not examine the concentration or frequency of antiseptics. Significant effects may only become apparent when specific dosing methods or concentrations are evaluated. However, the number of available studies was insufficient for such an analysis. Second, owing to insufficient data, we were unable to perform a meta-analysis on certain aspects of the disease. For instance, the effects of oral decontamination should ideally have been evaluated separately for early- and late-onset VAP, but there were too few studies to perform such an analysis. Moreover, setting-based and age-based subgroup analyses for the incidence of VAP could not be performed sufficiently due to the lack of available data, although it had been considered. In the available data, trends toward lower incidence of VAP were observed in NICU populations and among children aged one year and older, however, these trends were insignificant and were each based on a single study. Whereas some studies indicated no significant differences in the incidence of VAP by age [15,16], others suggested that the incidence of VAP may differ significantly between children under one year old and those older than one year [13,33]. Several factors may contribute to the potential differences in VAP incidence, notably the large differences in the oral environment among newborns, infants and older children [14,34,35]. The differences in oral conditions could also influence the effectiveness of oral hygiene care in prevention of VAP. Thus, further studies specifically considering age-related oral environmental differences are needed to clarify the effective oral hygiene care for critically ill children. Third, this meta-analysis was limited to studies published in Japanese or English, meaning there could be relevant data in studies published in other languages.

In conclusion, this study found no evidence to support the prevention of VAP through oral care with antiseptics in paediatric patients. However, the quality of the available evidence was low, and therefore, further high-quality RCTs are needed.

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Author contributions

H.O.: Conceptualization, methodology, formal analysis, investigation, visualization, data curation, writing-original draft, writing — review and editing. M.F.: Conceptualization, methodology, validation, investigation, writing-original draft, writing — review and editing, project administration, and supervision. S.N.: Conceptualization, methodology, validation, and data curation. K.T.: Conceptualization, writing — review and editing and supervision. M.S.: Conceptualization, writing — review and editing, and supervision.

Conflict of interest statement

The authors have no conflicts of interest to disclose.

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Appendix A. Supplementary data

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