

Chlorhexidine-based body washing for colonization and infection of methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus*: an updated meta-analysis

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Background: The effects of chlorhexidine-based body washing (CHW) on health care-associated infections have been reported in numerous studies, while their findings remain conflicting. This study aims to update the evidence for the effects of CHW on the risk of colonization or infection with hospital-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE).

Methods: Two independent authors searched PubMed, Embase, and Cochrane Library from inception through February 2018. We selected all observational studies or clinical trials for the effect of CHW on the risk of colonization and infection with hospital-acquired MRSA or VRE. Random-effects models were applied to calculate summary incidence rate ratios (IRRs) for the related associations.

Results: Of 140 records identified, we obtained data from 17 relevant articles for meta-analysis. Compared with patients without antiseptic bathing, patients with CHW had a significantly lower risk of MRSA colonization (IRR 0.61, 95% CI 0.48–0.77) and VRE colonization (IRR 0.58, 95% CI 0.42–0.80). Similarly, we also noted that patients with CHW had a significantly lower risk of MRSA infection (IRR 0.65, 95% CI 0.52–0.81). However, no significantly lower risk of VRE infection (IRR 0.61, 95% CI 0.30–1.25) was noted in patients with CHW. Sensitivity analyses or trim-and-fill method confirmed the robustness of the findings.

Conclusion: Current evidence supports that patients with CHW had a significantly lower risk of MRSA or VRE colonization and a lower risk of MRSA infection. More evidence should be accumulated to reinforce these findings, especially on the effect of CHW on the risk of VRE infection.

Keywords: chlorhexidine, methicillin-resistant *Staphylococcus aureus*, MRSA, vancomycin-resistant *Enterococcus*, VRE, bathing, meta-analysis

Introduction

Over the past few decades, methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE) have become two of the commonest causes of health care-associated infections (HAIs), occurring mostly among individuals with diagnosed health care-associated status such as hospitalization, surgical interventions (eg, central venous catheters), and dialysis. It is estimated that more than 100,000 HAIs occur in USA annually.¹ These two kinds of infections frequently lead to increased length of hospital stay, patient morbidity and mortality, and substantial cost burden to the health care system.²

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Chlorhexidine gluconate (CHG) has a broad-spectrum antibacterial activity, especially for Gram-positive bacteria such as MRSA and VRE. It has been reported that CHG can reduce the overall bioburden of multidrug-resistant Gram-positive organisms, thus reducing the incidence of HAIs and transmissions.^{3,4} Several epidemiological studies showed that daily use of CHG could reduce the rate of MRSA or VRE acquisition and bloodstream infections associated with these organisms^{5–8} in the intensive care units (ICUs) and general medicine units.⁹ However, several other studies have reported neutral findings that do not support using daily CHG bathing.^{10,11} There is also a lack of randomized clinical trials to provide direct evidence for the effect of CHG bathing on the risk of MRSA and VRE colonization or infection. With these dubious results, we aimed to reevaluate the existing uncertain evidence regarding this issue by updating the systematic review and meta-analysis of all published data.

Methods

Literature search

This meta-analysis was conducted under the guidance of a 27-item checklist of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). We searched PubMed, Embase, and the Cochrane Library on February 1, 2018. The following words were searched as keywords and text words: (shower* OR bath* OR wash* OR cleans*) AND (chlorhexidine OR chlorohex* OR eludril* OR corsodyl* OR Periochip* OR CHX OR nolvasan* OR sebidin* OR tubulicid* OR Cervitec* OR Chlorzoin* OR hibitane*) AND (“methicillin-resistan* OR meticillin-resistan* OR MRSA OR EMRSA OR MDRO” OR “vancomycin resistant enterococc* OR VRE”). We did not restrict language or publication type. Gray literature including abstracts was also included. The bibliographies of relevant articles were manually searched for additional references that may have been missed in the database searches. The search strategies for the three databases are given in the “[Supplementary materials](#)”.

Study selection and eligibility criteria

Eligible studies were included if they satisfied the following inclusion criteria: 1) studies investigating the associations between the use of chlorhexidine-based body washing (CHW) and the risk of colonization or infection with hospital-acquired MRSA or VRE; 2) cluster-randomized trial, before-and-after study, quasi-experimental study, interrupted time series study, and sequential group single-arm clinical trial were applied as study designs; and 3) studies or trials reported incidence rate ratios (IRRs) and their 95% CIs or related data for the

calculation of their IRRs. Studies were excluded if they did not satisfy the inclusion criteria. Two investigators (G.X. and Z.C.) independently conducted literature search and selection. We selected the largest studies with the most comprehensive data or analyses when overlapping studies were included.

Data extraction

Data extraction was carried out by two investigators (G.X. and Z.C.), independently using a Microsoft excel spreadsheet (2010 professional edition; Microsoft Corporation, Redmond, WA, USA). The extracted data were then cross-checked and determined by a senior investigator (X.L.). Data extracted included first author, publication year, study design, patient selection, study setting, major intervention, and control intervention. The corresponding authors of original studies were consulted for missing information if necessary.

Study bias assessment

Two authors (G.X. and Z.C.) independently assessed study bias using the Cochrane Risk of Bias Tool. The study was scored as low, unclear, or high risk of bias for randomized controlled trials based on random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete data, selective reporting, and others.¹² For nonrandomized studies, we used the Newcastle–Ottawa Scale (NOS) to assess the methodological bias, encompassing participant selection, comparability, and outcome assessment.¹³ A total of nine stars were assigned for each study with a score of ≥ 6 representing high quality.

Statistical analyses

IRR was set as the effect size measure. The summary effect size was pooled using a random-effects model because we considered that the different patients included in different regions during different periods with different study designs were very likely to have substantial heterogeneity. The Q test was applied to assess the existence of heterogeneity and I^2 statistic to quantify the percentage of between-study heterogeneity, with a value being < 0.10 considered as statistically significant.¹⁴ Funnel plot, Begg’s test, and Egger’s test were used to judge for publication bias.^{15,16} Furthermore, we also used the Duvall and Tweedle trim-and-fill model to adjust risk estimates,¹⁷ which imputes effect sizes until the error distribution closely approximates normality; such a procedure provides a more unbiased estimate of the effect size than does the observed estimate. All meta-analyses were conducted and figures were generated using Stata version 12.0 (StataCorp LP, College Station, TX, USA).

Results

Literature search

The database literature search yielded a total of 146 citations, and after removal of duplicates, 132 individual citations remained. After screening by title or abstract, 31 articles were identified for full text review. Finally, a total of 17 articles met the inclusion criteria. A manual reference search of included articles yielded no additional article that met inclusion criteria (Figure 1). Four articles identified in the original search were excluded because the data were insufficient for meta-analysis. We contacted the corresponding authors to request the original data; however, none of the primary data were available for meta-analysis.

Seventeen individual articles (four cluster-randomized trials, four quasi-experimental studies, three before-after interventional studies and six nonrandomized controlled trials or observational studies) were included in this systematic review and meta-analysis.^{5,9-11,18-30} In total, 467,484 participants were

analyzed, of whom 247,605 received intervention with CHW and 219,879 were not exposed to CHW intervention. Eight studies reported data from ICUs, and the others provided data from patients in mixed departments. Ten studies were conducted in multicentered institutions, and seven studies were carried out on single hospital sites. Details of the included studies are presented in Table 1. Generally, most of the nonrandomized trials had a low risk of bias with the NOS score ranging from 7 to 9, while most of the randomized trials have a high risk of bias, especially in the aspects of blinding method of participants and outcome assessment (refer the “[Supplementary materials](#)”).

Results of meta-analyses and publication bias assessment CHW and MRSA colonization

Nine studies investigated the association between CHW and MRSA colonization, which included 438 events in the

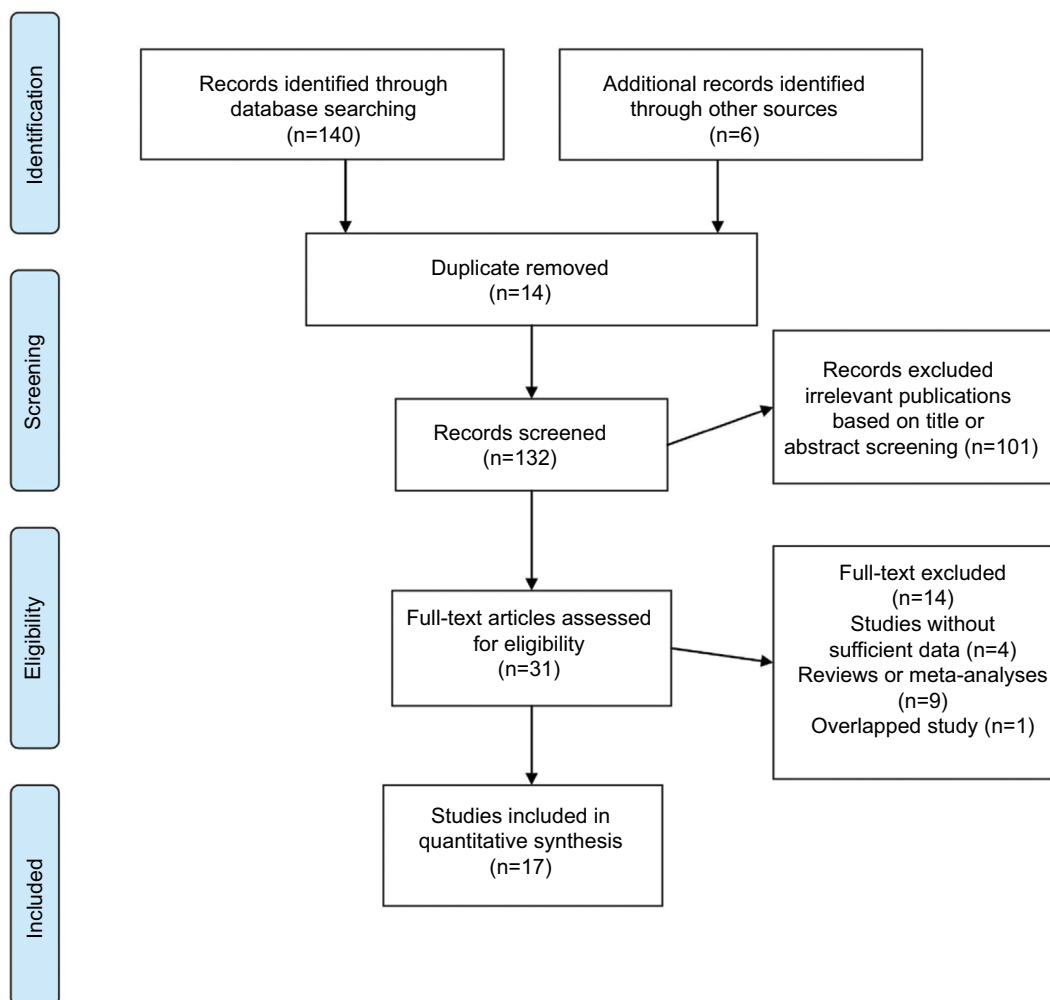


Figure 1 Flow diagram of articles selected for inclusion in the meta-analysis.

Table 1 Characteristics of the included studies

Study	Year	Study design	Patient selection	Study setting	Major intervention	Control intervention	Outcome measures
Lowe et al ¹⁸	2017	Prospective crossover study	Patients from four inpatient medical units (25 beds each) from May 1, 2014 to August 10, 2015	Four medical inpatient units in an urban, academic Canadian hospital	Daily CHW over a 7-month period, including a 1-month wash-in phase	Daily bathing with nonmedicated soap and water	Rates of hospital-associated MRSA and VRE colonization or infection
Amirov et al ¹⁹	2017	Cluster-randomized, open-label, controlled trial	Chronic care patients	Three hospital units	Daily CHW	Daily nonantiseptic bathing	MRSA incidence
Kim et al ²⁰	2016	Interrupted time series study	Patients admitted to the ICU for >48 hours	A 829-bed tertiary care hospital in Hallym University Sacred Heart Hospital	16-month CHW between August 2013 and November 2014	14-month without bathing with chlorhexidine between June 2012 and July 2013	Rates for MRSA acquisition
Millar et al ²¹	2015	Three-group, field-based, cluster-randomized trial	US Army soldiers 17 to 42 years of age, ethnically diverse, and in generally good physical condition	A US army soldier hospital	CHW with a wash cloth after using their personal soap during an additional once-weekly shower	Standard, enhanced standard body wash without using chlorhexidine	MRSA skin and soft-tissue infections' colonization prevalence
Colling et al ²²	2015	Multicenter, retrospective, controlled study	Patients undergoing hip and knee arthroplasties at two affiliated hospitals in the Fairview Hospital System between January 2010 and June 2012	An 874-bed hospital and a community hospital	Having preoperative CHG shower or bath policy in place	Having no antiseptic shower or bath	Rate of <i>S. aureus</i> and MRSA surgical site infections
Climo et al ⁵	2013	A multicenter, cluster-randomized, nonblinded crossover trial	Patients in nine ICUs and bone marrow transplantation units in six hospitals	Nine ICUs and bone marrow transplantation units in six hospitals in USA	CHW-impregnated washcloths for a 6-month period, exchanged for the alternate product during the subsequent 6 months	Bathing with non-antimicrobial washcloths for a 6-month period, exchanged for the alternate product during the subsequent 6 months	The incidence rates of acquisition of hospital-acquired BSIs and acquisition of multidrug-resistant organisms
Huang et al ²³	2013	Three-group, cluster-randomized trial	Patients in adult ICUs in Hospital Corporation of America hospitals	45 hospitals in 16 states with a total of 74 adult ICUs	Bathing with 2% CHG washcloths	Bathing without 2% CHG washcloths	MRSA BSI
Bass et al ¹¹	2013	Before-and-after study	Hematology/oncology patients at the Alfred Hospital	A 34-bed major tertiary teaching hospital in Melbourne, Australia	Bathing with 2% CHG-impregnated washcloths	Bathing with routine soap and water	Incidence rate of VRE colonization

Montecalvo et al ²⁴	2012	Prospective, three-phase, multiple-hospital, non-randomized trial	Patients from a tertiary care hospital and four community hospitals in Westchester County, New York	A medical ICU and the respiratory care unit of a tertiary care hospital and the medical-surgical ICUs of 4 community hospitals	Intervention phase: patients were bathed with 2% CHG cloths, with the number of baths administered and skin tolerability assessed Postintervention phase: CHG bathing was continued but without oversight by research personnel	Preintervention phase: patients were bathed with soap and water or nonmedicated bathing cloths	Hospital-acquired CVC-associated BSI rates
Kassakian et al ⁹	2011	Quasi-experimental study	Patients at four general medicine units, with a total of 94 beds, at a 719-bed academic tertiary care facility in Providence, RI	Four general medicine units at a 719-bed academic tertiary care facility in Providence, RI	Daily bathing with chlorhexidine-impregnated cloths	Daily bathing with soap and water	Incidence of MRSA and VRE HAIs
Evans et al ²⁶	2010	Retrospective before-and-after study design	Severely injured patients in a 413-bed level I trauma center that serves patients from four states	A 12-bed ICU in a level I trauma center	Daily chlorhexidine bathing during the 6-month intervention	Bathed without chlorhexidine prior to the intervention	HAIs and the rate of isolation of multidrug-resistant organisms
Fraser et al ²⁵	2010	Retrospective quasi-experimental study	Patients in the medical ICU	An 18-bed medical ICU at a tertiary care center in Cleveland, Ohio	Daily CHG baths	Daily body wash without CHG	The incidence of hospital-acquired BSI, the incidence of ventilator-associated pneumonia
Popovich et al ¹⁰	2010	Quasi-experimental, pre-post study	Patients in the 30-bed surgical ICU at Rush University Medical Center, a 720-bed tertiary care teaching hospital in Chicago	A medical ICU at Rush University Medical Center and a tertiary care teaching hospital in Chicago	Substituted skin cleansing with no rinse, 2% CHG-impregnated cloths	Soap and water bathing	ICU-acquired CLABSI; blood culture contamination and other ICU-acquired nosocomial infection
Climo et al ²⁸	2009	Multicenter, before-after interventional study	Patients from six ICUs at four academic centers	Six ICUs at four major tertiary care referral hospitals in USA	Daily bathing with a chlorhexidine-containing solution	Soap and water bathing	Incidence of MRSA and VRE colonization and BSI
Popovich et al ²⁷	2009	Quasi-experimental, pre-post study	Patients in the 21-bed medical ICU at Rush University Medical Center, a 720-bed tertiary care teaching hospital in Chicago	A medical ICU at Rush University Medical Center and a tertiary care teaching hospital in Chicago	Substituted skin cleansing with no rinse, 2% CHG-impregnated cloths	Skin cleansing with soap and water	Medical ICU-acquired CVC-associated BSI, blood culture contamination, and other medical ICU-acquired nosocomial infection
Ridenour et al ²⁹	2007	Interrupted time series study	Patients in a 427-bed tertiary care Veterans Affairs hospital	A medical-coronary ICU	Chlorhexidine bathing	Bathing without chlorhexidine	The incidence of MRSA colonization and infection
Vernon et al ³⁰	2006	Prospective, sequential group, single-arm clinical trial	Patients in a 21-bed medical ICU at a 720-bed hospital in Chicago	A medical ICU at a 720-bed hospital in Chicago	Bath with 2% CHG washcloths	Soap and water bathing	Incidence of VRE acquisition

Abbreviations: BSI, bloodstream infections; CHG, chlorhexidine; CHW, chlorhexidine-based body washing; CLABSI, central line-associated bloodstream infections; CVC, central venous catheter; HAIs, health care-associated infections; ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus*; S. aureus; *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus*.

intervention group and 660 events in the control group among 322,053 participants. Meta-analysis showed that the summary IRR was 0.61 (95% CI 0.48–0.77, $I^2=60.9\%$, $P<0.001$ for heterogeneity; Figure 2A). There was no evidence of publication bias using the Begg's ($P=0.917$) or Egger's test ($P=0.817$). The results did not change after using the trim-and-fill method when no missing studies were added (Table 2).

CHW and MRSA infection

Ten studies investigated the association between CHW and MRSA infection, which included 137 events in the intervention group and 193 events in the control group among 370,422 participants. Summary estimates showed that the pooled IRR was 0.65 (95% CI 0.52–0.81, $I^2=0\%$, $P=0.723$ for heterogeneity; Figure 2B). There was no evidence of

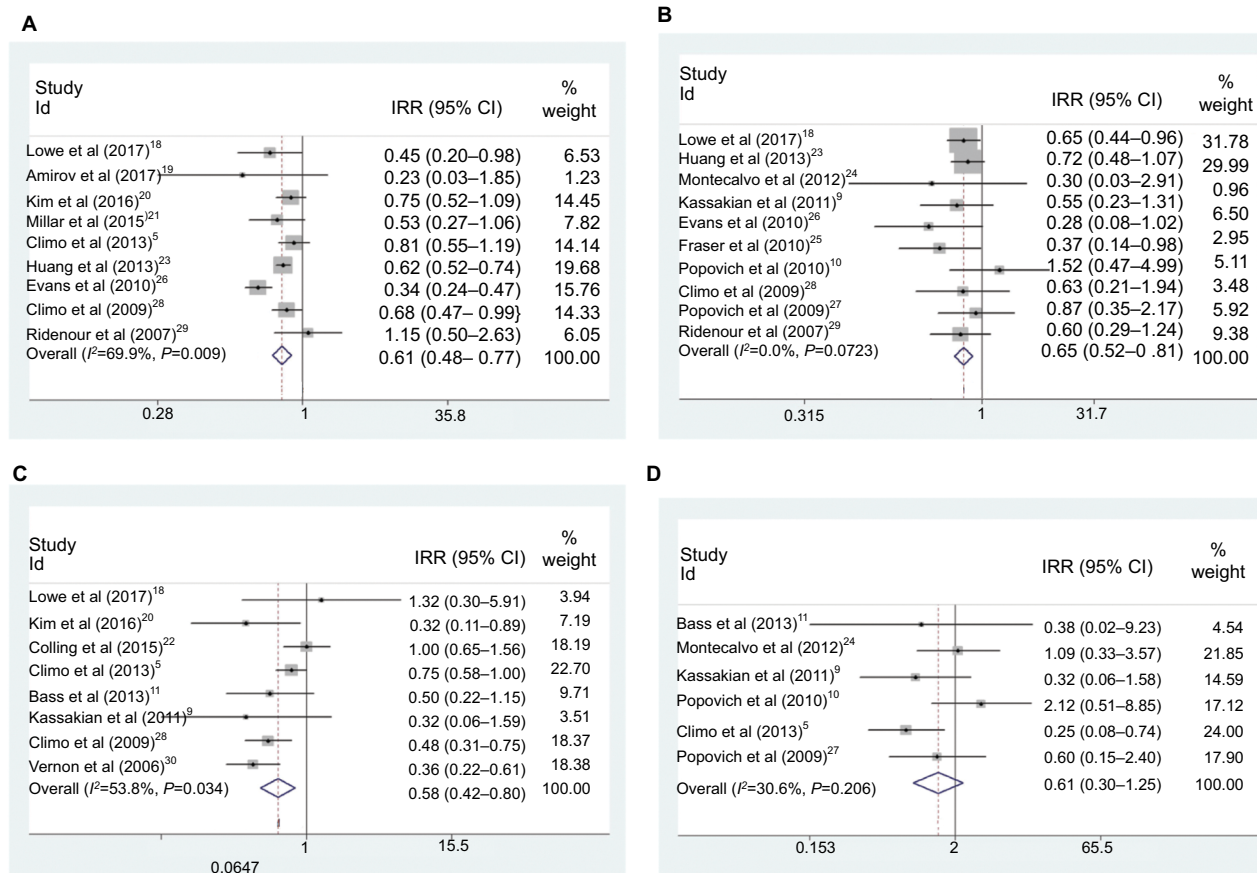


Figure 2 Forest plots comparing the effects of CHW on the risk of (A) MRSA colonization, (B) MRSA infection, (C) VRE colonization, and (D) VRE infection with those of the routine intervention.

Note: Weights are from random-effects analysis.

Abbreviations: CHW, chlorhexidine-based body washing; IRR, incidence rate ratio; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus*.

Table 2 Results of meta-analysis for the effects of CHW on the risk of MRSA colonization or infection and VRE colonization or infection; analyses of the publication bias with different models

Variable	No of studies	IRR (95% CI)	P	I^2 , P_{het}
CHW and MRSA colonization	9	0.61 (0.48–0.77)	<0.001	60.9, 0.009
CHW and MRSA infection	10	0.65 (0.52–0.81)	<0.001	0.0, 0.723
CHW and VRE colonization	8	0.58 (0.42–0.80)	0.001	53.8, 0.034
CHW and VRE infection	6	0.61 (0.30–1.25)	0.176	30.6, 0.206
Publication bias	Begg's P-value	Egger's P-value	T&F (Fill), IRR (95% CI)	
CHW and MRSA colonization	0.917	0.817	0.61 (0.48–0.77)	
CHW and MRSA infection	0.592	0.896	0.65 (0.52–0.81)	
CHW and VRE colonization	1.000	0.617	0.58 (0.42–0.80)	
CHW and VRE infection	0.707	0.983	0.61 (0.30–1.25)	

Notes: Fill, number of studies added by trim-and-fill method; het, heterogeneity; T&F, result of trimmed and filled analysis, using assumption of random effects.

Abbreviations: CHW, chlorhexidine-based body washing; het, heterogeneity; IRR, incidence rate ratio; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus*.

publication bias using the Begg's test ($P=0.592$) or Egger's test ($P=0.896$). The results did not change after using the trim-and-fill method when no missing studies were added (Table 2).

CHW and VRE colonization

Eight studies investigated the association between CHW and VRE colonization, which involved 195 events in the intervention group and 296 events in the control group among 201,556 participants. Meta-analysis showed that the pooled IRR was 0.58 (95% CI 0.42–0.80, $I^2=53.8\%$, $P=0.034$ for heterogeneity; Figure 2C). There was no evidence of publication bias using the Begg's test ($P=1.000$) or Egger's test ($P=0.617$). The results did not change after using the trim-and-fill method when no missing studies were added (Table 2).

CHW and VRE infection

Six studies investigated the association between CHW and VRE infection, which included 20 events in the intervention group and 37 events in the control group among 153,965 participants. Summary estimates showed that the pooled IRR was 0.61 (95% CI 0.30–1.25, $I^2=30.6\%$, $P=0.206$ for heterogeneity; Figure 2D). There was no evidence of publication bias using the Begg's test ($P=0.707$) or Egger's test ($P=0.983$). The results did not change after using the trim-and-fill method when no missing studies were added (Table 2).

Sensitivity analyses

Sensitivity analyses by excluding one study at a time from each analysis indicated that all the four meta-analysis results seemed to be robust to the influence of individual studies (Figure 3). The results were also not substantially altered when combining studies with the same study design (data not shown).

Discussion

In this meta-analysis of nonrandomized controlled studies, moderate to strong decreases in the risk of IRR of MRSA colonization, VRE colonization, and MRSA infection for individuals with CHW were observed. Although the result for VRE infection was not significant in the meta-analysis, the association appeared to have similar trend with MRSA infection.

Our findings are consistent with five previous meta-analyses of CHW and risk of HAIs^{31–35} but included a much larger sample size, more focused analyses on the two HAIs including MRSA and VRE, sensitivity and trim-and-fill method analyses, and analyses of incidence rate ratios. To our knowledge, this is the largest meta-analysis to comprehensively summarize results for the relationship between CHW and MRSA and VRE infections, not just focused on ICU patients. The null association for VRE infection might be because of the few studies involved in this outcome subset with a limited sample size, which should be further investigated.

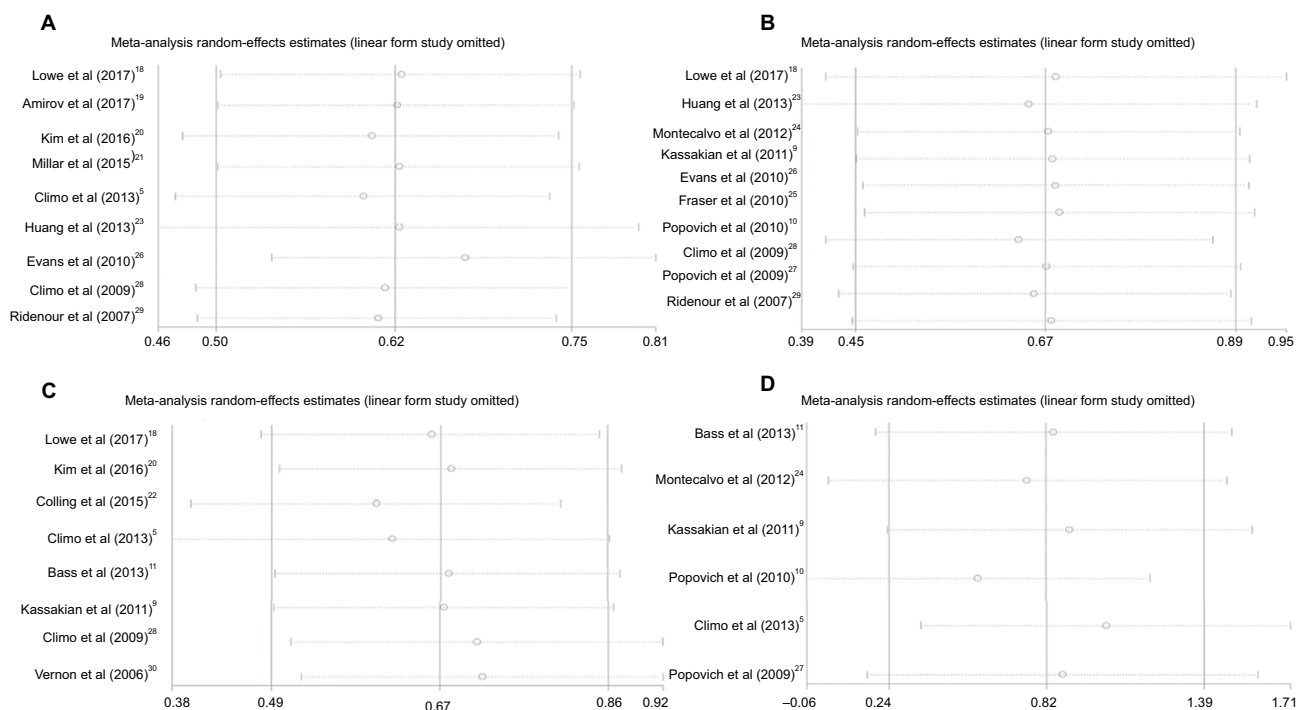


Figure 3 Sensitivity analyses for the effects of CHW on the risk of (A) MRSA colonization, (B) MRSA infection, (C) VRE colonization, (D) VRE infection. **Abbreviations:** CHW, chlorhexidine-based body washing; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus*.

This meta-analysis has several strengths. First, it is strengthened by applying a comprehensive search strategy, making literature screening and eligibility criteria rigorous, and reporting the findings transparently. Second, the three major databases were thoroughly searched without language or publication date limits, making the risk of missing publications less possible, which could minimize publication bias. Third, at least two authors selected studies and cross-checked and identified the final included studies. In order to perform the meta-analysis more objectively and minimize the selection bias to the greatest extent, all the authors jointly developed a data abstract form through discussion.

There are some limitations for this meta-analysis. First, most of the studies have difference in study design such as cluster-randomized trials, quasi-experimental studies, and before–after interventional studies, which is one source of inter-study heterogeneity. In fact, most of the studies were observational and retrospective, with some having limited capacity for adjustment, and thus were at a high risk of selection bias and residual confounding. Second, since there were a small number of studies in each outcome subset, we had to interpret the results with caution, although no evidence of publication bias in the analysis of all four outcome subsets was noted. Third, heterogeneity was rather high in two of the four analyses ($I^2 > 50\%$), but this appeared to partly attribute to differences in the size of the risk estimates between studies rather than a lack of association. Fourth, study patients had wide variation in baseline features, and were from different kinds of units such as ICUs,^{5,10,20,23,25,27,28,30} general medicine units, tertiary care hospital units,^{24,29} and inpatient medical units,¹⁹ potentially leading to significant heterogeneity in outcomes, which limited the capacity for pooled analyses.

Conclusion

Current evidence to some extent supports the hypothesis that patients with application of CHW had significantly lower MRSA colonization and infection, as well as VRE colonization. More evidence should be accumulated to reinforce these findings, especially on the effect of CHW on VRE infection.

Disclosure

The authors report no conflicts of interest in this work.

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