Journal of Critical Care 32 (2016) 126–137

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

The effects of chlorhexidine gluconate bathing on health care–associated infection in intensive care units: A meta-analysis

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ARTICLE INFO

Keywords:
Chlorhexidine bathing
Health care–associated infection
Meta-analysis
Risk ratio

ABSTRACT

Purpose: The purpose was to assess the effects of chlorhexidine gluconate (CHG) bathing on health care–associated infections among critically ill patients.
Methods: This meta-analysis evaluated English-language studies from the PubMed, Embase, and Cochrane databases. The Cochrane Collaboration methodology was used to evaluate all publications regarding daily CHG bathing and the risks of acquiring central line–associated bloodstream infection (CLABSI), methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-resistant *Enterococcus* (VRE). Risk ratios (RRs) and the ratio of the log RRs (RRR) were estimated with 95% confidence intervals (CIs).
Results: Eighteen studies were included. Compared with conventional care, the RRs (95% CIs) for CLABSI, MRSA, and VRE with CHG bathing were 0.45 (0.37-0.55), 0.67 (0.59-0.77), and 0.60 (0.42-0.85), respectively (all, $P < .05$). For MRSA acquisition, CHG bathing with concomitant nasal antibiotics provided a lower incidence compared with only CHG bathing (RRR: 0.81, 95% CI: 0.66-0.98, $P = .035$). Greater risk reduction was also observed in studies with prolonged interventions (RRR per 1-month extension: −0.02, $P = .027$).
Conclusions: Daily CHG bathing was associated with reduced risks of acquiring CLABSI, MRSA, and VRE. A prolonged intervention period and concomitant nasal antibiotic use were associated with lower risks of MRSA acquisition.

1. Introduction

Health care–associated infections (HAIs) are associated with clinically significant morbidity and mortality among critically ill patients, and the associated costs may not be reimbursed under some health care insurance plans [1]. In addition, infections with multidrug-resistant organisms are considerably more difficult to treat because of the limited number of effective antimicrobial drugs. However, chlorhexidine gluconate (CHG) is effective against gram-positive and gram-negative organisms, facultative anaerobes, aerobes, and yeasts [2]. Furthermore, the use of CHG for skin antisepsis can prevent the transmission of drug-resistant organisms in intensive care units (ICUs), such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), and central line–associated bloodstream infection (CLABSI) [3]. Therefore, there has been increasing interest in using daily CHG bathing to reduce HAI among critically ill patients. A number of researchers have reported that daily CHG bathing reduced the acquisition of multidrug-resistant bacteria and decreased the frequencies of bloodstream infections and ventilator-associated pneumonia [3–6]. However, more recent studies have reported contradictory findings that do not support the routine use of CHG bathing to reduce HAI among critically ill patients [7].

After quality management for clinical microbiology was introduced during the 1960s [8], many clinical microbiology laboratories developed standardized biochemical methods to test for antimicrobial susceptibility. Among the various guidelines for quality control, the most widely used guidelines were developed by the Clinical Laboratory Standards Institute [9]. The Clinical Laboratory Standards Institute guidelines include quality control and quality assurance considerations for antibiotic susceptibility testing and culture media to ensure the accuracy, reliability, and reproducibility of the various tests. This quality system has enabled researchers to perform high-quality systematic reviews and meta-analyses of microbiological outcomes from different medical centers.

The present study used meta-analysis to investigate the effects of daily CHG bathing on HAI, compared with the effects of conventional care (eg, soap and water bathing), among critically ill patients.

2. Methods

2.1. Literature search

This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for systematic reviews and meta-analyses of randomized controlled trials (RCTs)

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http://dx.doi.org/10.1016/j.jcrc.2015.11.011
0883-9441/

[10]. Two independent reviewers (JM Kim and HY Kim) separately searched the PubMed, Embase, and Cochrane Central Register databases for all eligible English-language studies that were published before May 2, 2015. The MeSH search terms were *chlorhexidine, chlorhexidine and nosocomial infection, chlorhexidine and MRSA, chlorhexidine and VRE, chlorhexidine and CLABSI, intensive care unit, and critical illness*. We also searched for *daily showering or whole body washing with chlorhexidine*, which has the same meaning as *daily chlorhexidine bathing*. Additional studies were identified by hand searching the references of the original studies and review articles that were returned by our search. Authors of potentially relevant studies were contacted for further information if relevant data were not published. Case reports, reviews, and abstracts were excluded. The 2 reviewers (JM Kim and HY Kim) selected all data sets for this study via consensus.

2.2. Eligibility criteria

The included studies were prospective trials and interrupted time series (ITS) trials that compared daily CHG bathing with controls (conventional care). The primary outcome measures were the rates for acquisition of CLABSI, MRSA, and VRE among critically ill adult patients in ICU settings. To be included, each study was required to provide microbiology-based rates for CLABSI, MRSA, and VRE acquisition in the intervention and control arms. The definitions and diagnostic criteria for CLABSI, MRSA, and VRE were based on the Centers for Disease Control and Prevention (CDC) definitions [11] (Table 1). Furthermore, to be included, each study was required to report the findings as the number of acquired HAI cases per 1000 central line-days (for CLABSI) or 1000 patient-days in the ICU (for MRSA and VRE). Therefore, 1 study that reported the primary outcomes as weekly incidence rate ratios was excluded from our analysis [12]. Fig. 1 contains a Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart for the data selection process.

2.3. Quality assessment

The 2 reviewers assessed the articles and investigated the risk of bias for RCTs using the Risk of Bias (RoB) tool from the Cochrane Collaboration. Quasi-experimental studies were evaluated using the Risk of Bias Assessment tool for Nonrandomized Studies (RoBANS) [13]. Review Manager software (RevMan; version 5.3) was used to evaluate the risk of bias in the included studies.

2.4. Statistical analysis

Meta-analyses were performed to calculate pooled risk ratios (RRs) with 95% confidence intervals (CIs). Based on a conservative approach, we used a random-effects model, which produces wider CIs than a fixed-effect model. Heterogeneity was assessed using 2 methods: Cochrane Q test, which indicates significantly heterogeneity at P values of $< .1$, and I^2 statistics, which indicate significant heterogeneity at values of 30% to 50% [14]. Publication bias was evaluated using Egger regression test and a funnel plot. Among the studies of MRSA acquisition, subgroup analyses were performed using a test of interaction [15] to identify the effects of using concomitant nasal antibiotic ointment. In addition, a meta-regression analysis and a cumulative meta-analysis were performed to identify the influence of treatment duration and the change in effect size due to the accumulation of short-term studies. All statistical analyses were performed using Comprehensive Meta-Analysis software (version 2.0; Biostat Inc, Englewood, NJ).

3. Results

3.1. Identifying eligible studies

The database search retrieved 256 records (93 from PubMed, 175 from Embase, and 92 from the Cochrane Library), and 18 studies (124 ICUs) that were published in English between February 2005 and January 2015 were included in the meta-analysis (Fig. 1). Studies were excluded because they were not clinical trials (eg, reviews and comments on previous studies; n = 78), they were studies regarding CHG bathing that did not involve the whole body (n = 40), only the abstract was available (n = 32), the trial did not evaluate adults (n = 24), the trial evaluated other infections (ie, not CLABSI, MRSA, VRE, or blood contamination; n = 21), the trial examined CHG bathing in non-ICU settings (n = 20), CHG bathing was not performed for all patients in the intervention group (n = 12), and the report was not written in English (n = 3). Studies that did not fulfill the selection criteria (n = 3) [16–18], studies with incomplete outcome data (n = 3) [12,19,20], studies with an unknown study period (n = 1) [21], and studies using a gastric agent with CHG bathing and nasal agents (n = 1) [22] were also excluded. Eleven articles were available regarding CLABSI acquisition [4–7,23–29], 7 articles were available regarding MRSA acquisition [3,25,30–34], and 3 articles were available regarding VRE acquisition [3,25,35].

3.2. Characteristics of the included trials

Eighteen trials were included in this study. One large study accounted for more than half of the patient-days in the MRSA analysis [31]. The characteristics of the 6 RCTs [3,7,23,24,31,32] and 12 ITSs [4–6,25–30,33–35] are summarized in Table 2. The outcomes from each study are summarized in Table 3.

3.3. Quality assessment

The 6 RCTs were evaluated using the RoB tool [3,7,23,24,31,32] (Fig. 2). There was no selection bias or attribution bias in the RCTs, although 4 studies had a high risk of performance bias due to the absence of participant and personnel blinding [3,7,24,31]. Two studies

Table 1
Centers for Disease Control and Prevention definitions [11]

HAI	A localized or systemic condition that results from an adverse reaction to the presence of infectious agent(s) or toxin(s) that (1) occurs in a health care setting (eg, a hospital or outpatient clinic), (2) was not present or incubating at the time of admission unless the infection was related to a previous admission in the same setting, and (3) meets the criteria for a specific infection site if the setting is a hospital.
Colonization	Microorganisms are present on skin, on mucous membranes, in open wounds, or in excretions or secretions, but are not causing adverse clinical signs or symptoms; and inflammation that results from a tissue response to injury or stimulation by noninfectious agents, such as chemicals.
CLABSI	A patient with a central venous catheter in place in whom a recognized pathogen is cultured from 1 or more blood cultures and is not related to an infection at another site. Alternatively, *CLABSI* can be defined as a common skin organism being cultured from 2 or more blood cultures that were drawn on separate occasions (within 2 d of each other), and with at least 1 of the following signs or symptoms (that are not due to infection at another site): fever (38°C), chills, or hypotension. *Acquired CLABSI* is defined as signs and symptoms of infection that were not present at the time of admission, with positive blood culture sample being drawn while the patient was housed in the unit or within 48 h of discharge from the unit.
Colonization with MRSA or VRE	The isolation of MRSA or VRE from a biological material in the absence of any infection signs and symptoms.
Infection with MRSA or VRE	The isolation of MRSA or VRE from normally sterile fluids, or isolation from a normally nonsterile biological material, in the presence of infection symptoms.
Acquisition of MRSA or VRE	An initial negative culture at admission and a follow-up culture that reveals the growth of MRSA or VRE from either a surveillance or clinical specimen that was obtained at >48 h after admission to the ICU.

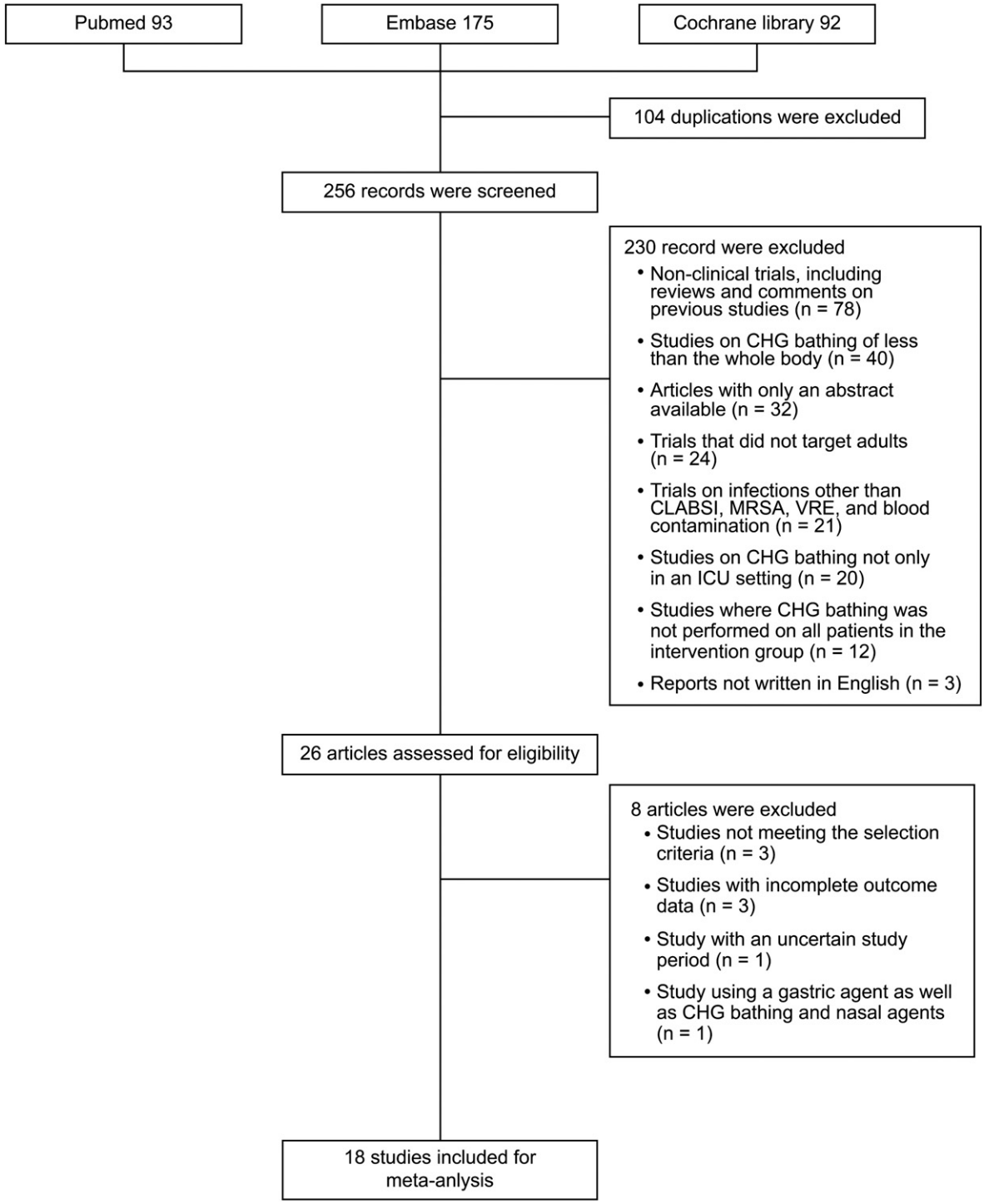

Fig. 1. Flowchart for the study selection process.

used a double-blinded design and had a low risk of performance bias [23,32]. However, these 2 studies were derived from a single study by the same corresponding author, and the second study was a post hoc analysis of the previous RCT [32]. Four studies had no detection bias, as the outcome assessors were blinded [3,23,31,32], and the 2 remaining studies had unclear risks of detection bias [7,24]. Protocols from http://www.clinicaltrials.gov were used to evaluate reporting bias due to selective outcome reporting. One study deviated from the registered protocol, as the registered protocol included microbiological outcomes, although the published report did not include these outcomes [24]. Three studies had other sources of bias [7,24,31]. One study used a reporting method for the infection rate (CLABSI cases per patient-days) that differed from that in other studies (CLABSI cases per central line-days) [7]. Another study included patients in the intervention arm who had significantly longer hospital stays [24], and the third study's intervention arm consisted of patients from bone marrow and transplantation ICUs (which treat more severely ill patients) [31]. The post hoc analysis study had unclear risks for other sources of bias [32].

Twelve studies used a quasi-experimental design, and these studies were evaluated using the RoBANS tool [4–6,25–30,33–35] (Fig. 3). Four studies had a high risk of selection bias, as 3 studies were performed using a retrospective design [6,29,30] and the fourth study did not

recruit consecutive patients [5]. One study had a high risk of confounding bias due to different severities of illness in the control and intervention groups [29], and one study had an unclear risk of confounding bias because the patients' stay durations were unknown [33]. Two studies had a high risk of performance bias due to inappropriate intervention measurement, as 1 study increased the microbiological surveillance during the intervention period [25] and the other study had different surveillance protocols for the included ICUs [34]. The risk of detection bias was unclear in most studies because we could not find any comments regarding blinding of the outcome assessment, although 2 studies did have detection bias [30,35]. The first study used a nonblinded outcome assessment [35], and the infection control nurse in the second study was involved in data collection during the intervention period [30]. There was no attribution bias due to incomplete data. The risk of reporting bias due to selective outcome reporting was difficult to assess in the quasi-experimental studies because the study protocols were not provided by the authors. Thus, we assessed the risk of bias as being low if the outcomes were expressed as indicated in the methods, and all studies were assessed as having a low risk.

3.4. Central line–associated bloodstream infection

The 11 trials regarding CLABSI acquisition included a total of 151,546 central line-days, with 80,920 central line-days in the intervention group and 70,672 central line-days in the control group [3–7,23,24,26–29]. The overall incidence of CLABSI acquisition in the intervention group was 2.00 cases per 1000 central line-days (162/80,920) compared with 4.32 cases per 1000 central line-days (305/70,627) in the control group. A forest plot was used to determine that the RR for CLABSI acquisition in

Table 2
Characteristics of the included studies

Primary author	Publication year	Study design	Setting	Intervention	Control	Duration
Camus C [23].	2005	RCT	ICU-intubated patients	Twice daily baths using 15 mL of a 4% solution of CHG with warm water + 2% intranasal mupirocin 3 times daily	Twice daily baths using soap and water	Apr 1996 to Oct 1998
Vernon MO [35]	2006	ITS	MICU	Daily baths using disposable 2% no-rinse washcloths	Daily baths using 1. Soap and water 2. Nonmedicated cloths	Oct 2002 to Dec 2003
Gould IM [30]	2007	Retro-ITS	SICU/MICU	Daily baths using a 4% solution of CHG with warm water + intranasal anti-MRSA preparations	MRSA screening and contact precautions	Mar 1999 to Apr 2003
Bleasdale SC [24]	2007	RCT	MICU	Daily baths using disposable 2% no-rinse washcloths	Daily baths using soap and water	Jun 2005 to Jun 2006
Climo MW [25]	2009	ITS	Mixed ICUs	Daily baths using a 4-oz bottle of a 4% solution of CHG with warm water in a 6-qt basin, which was followed by rinsing	Daily baths using soap and water	Dec 2004 to Jan 2006
Popovich KJ [26]	2009	ITS	MICU	Daily baths using disposable 2% no-rinse washcloths	Daily baths using soap and water	Sep 2004 to Oct 2006
Popovich KJ [28]	2010	ITS	SICU	Daily baths using disposable 2% no-rinse washcloths	Daily baths using soap and water	Sep 2004 to Oct 2006
Evans HL [6]	2010	Retro-ITS	Trauma ICU	Daily baths using disposable 2% no-rinse washcloths	Daily baths using soap and water	Nov 2006 to Oct 2007
Dixon JM [27]	2010	ITS	SICU	Daily baths using disposable 2% no-rinse washcloths	Daily baths using soap and water	Jan 2007 to Sep 2009
Montecalvo MA [5]	2012	ITS	MICU/SICU/RC	Daily baths using disposable 2% no-rinse washcloths	Daily baths using soap and water or nonmedicated cloths	Apr 2008 to Aug 2010
Climo MW [3]	2013	RCT	Mixed ICUs/BMTU	Daily baths using disposable 2% no-rinse washcloths	Nonmedicated cloths	Aug 2007 to Feb 2009
Huang SS [31]	2013	RCT	Adult ICUs	Daily baths using disposable 2% no-rinse washcloths + intranasal mupirocin twice daily	MRSA screening and isolation	Apr 2010 to Sep 2011
Camus C [32]	2014	RCT[a]	ICU-intubated patients	Twice daily using 15 mL of a 4% solution of CHG with warm water + 2% intranasal mupirocin 3 times daily	Twice daily baths using soap and water	Apr 1996 to Jun 1999
Viray MA [33]	2014	ITS	SICU	Daily baths using a 4-oz bottle of CHG soap with 4 qt of water, which was followed by rinsing	Daily baths using soap and water	Jan 2002 to Dec 2007
Martinez-Resendez MF [4]	2014	ITS	MICU/SICU	Daily baths using disposable 2% no-rinse washcloths and a hand hygiene program	1. Preintervention: daily baths using soap and water 2. Postintervention: daily baths using soap and water + a hand hygiene program	Jan 2012 to Jun 2013
Petlin A [34]	2014	ITS	Mixed ICUs	Daily baths using a 4-oz bottle of a 4% solution of CHG with warm water in a 6-qt basin, which was followed by rinsing	Daily baths using soap and water	Jul 2008 to Apr 2011
Noto MJ [7]	2015	RCT	Mixed ICUs	Daily baths using disposable 2% no-rinse washcloths	Nonmedicated cloths	Jul 2012 to Jul 2013
Entesari-Tatafi D [29]	2015	Retro-ITS	Mixed ICUs	Daily baths using disposable 2% no-rinse washcloths	Conventional care	Jul 2006 to Jun 2014

Retro indicates retrospective; MICU, medical ICU; SICU, surgical ICU; RC, respiratory care; BMTU, bone marrow transplantation unit.
[a] Post hoc analysis of an RCT.

Table 3
Outcomes from the included studies

Primary author	Outcomes	Diagnostic criteria	Conclusion
Camus C [23]	Incidence of CLABSI	CDC definition[a]	No significant difference
Vernon MO [35]	Acquisition of VRE	Culture negative at admission, culture from the perirectal area positive for >3 d after admission	VRE decreased
Gould IM [30]	Acquisition of MRSA	No screening at admission, culture positive from the nares, throat, axillary, and groin regions	MRSA decreased
Bleasdale SC [24]	Incidence of CLABSI	CDC definition[a]	CLABSI decreased
Climo MW [25]	Acquisition of MRSA Acquisition of VRE	Culture negative at admission, culture positive for >48 h after admission: 1. MRSA culture at the nares 2. VRE culture at the perirectal area	MRSA and VRE decreased
Popovich KJ [26]	Incidence of CLABSI	CDC definition[a]	CLABSI decreased
Popovich KJ [28]	Incidence of CLABSI	CDC definition[a]	No significant difference
Evans HL [6]	Incidence of CLABSI	CDC definition[a]	CLABSI decreased
Dixon JM [27]	Incidence of CLABSI	CDC definition[a]	CLABSI decreased
Montecalvo MA [5]	Incidence of CLABSI	CDC definition[a]	CLABSI decreased
Climo MW [3]	1. Incidence of CLABSI 2. Acquisition of MRSA 3. Acquisition of VRE	1. CLABSI: CDC definition[a] Culture negative at admission, culture positive for >48 h after admission: 2. MRSA culture at the nares 3. VRE culture at the perirectal area	CLABSI decreased No significant difference for MRSA or VRE
Huang SS [31]	Acquisition of MRSA	No screening at admission, culture positive at the nares from the 3rd day after admission through the 2nd day after ICU discharge	MRSA decreased
Camus C [32]	Acquisition of MRSA	Culture negative at admission, culture positive at the nares and groin within 48 h after discharge	MRSA decreased
Viray MA [33]	Acquisition of MRSA	Culture negative at admission, culture positive at the nares from >48 h after admission	MRSA decreased
Martinez-Resendez MF [4]	Incidence of CLABSI	CDC definition[a]	No significant difference
Petlin A [34]	Acquisition of MRSA	Culture negative at admission, culture positive at the nares from >48 h after admission	MRSA decreased
Noto MJ [7]	Incidence of CLABSI	CDC definition[a]	No significant difference
Entesari-Tatafi D [29]	Incidence of CLABSI	CDC definition[a]	CLABSI decreased

[a] The CDC definition that is described in Table 1.

the intervention group (vs the control group) was 0.45 (95% CI: 0.37-0.55; $P < .001$) (Fig. 4a).

3.5. Methicillin-resistant Staphylococcus aureus

Seven trials investigated MRSA acquisition (intervention group: 205,959 patient-days; control group: 183,977 patient-days) [3,25,30–34]. The overall MRSA acquisition rate in the intervention group was 3.28 cases per 1000 patient-days (676/205,959) compared with 4.97 cases per 1000 patient-days (914/183,977) in the control group. The RR for MRSA acquisition in the intervention group (vs the control group) was 0.67 (95% CI: 0.59-0.77; $P < .001$) (Fig. 4b).

3.6. Vancomycin-resistant Enterococcus

Three trials investigated VRE acquisition (intervention group: 39,179 patient-days; control group: 39,544 patient-days) [3,25,35]. The overall VRE acquisition rate in the intervention group was 3.00 cases per 1000 patient-days (116/39,179) compared with 4.86 cases per 1000 patient-days (192/39,544) in the control group. The RR for VRE acquisition in the intervention group (vs the control group) was 0.60 (95% CI: 0.42-0.85; $P = .004$) (Fig. 4c).

3.7. Heterogeneity testing

There was substantial heterogeneity in the patients' clinical characteristics from the included studies. Therefore, heterogeneity testing was performed for each analysis. Moderate heterogeneities were observed for the effects of CHG bathing on the acquisition of CLABSI ($I^2 = 49.95\%$, $P = .029$), MRSA ($I^2 = 39.7\%$, $P = .127$), and VRE ($I^2 = 42.59\%$, $P = .175$).

3.8. Subgroup analysis

Subgroup analysis was used to evaluate the effect of concomitant nasal agents. The 7 studies regarding MRSA acquisition were divided into 2 subgroups, with 1 group performing CHG bathing with concomitant nasal antibiotic ointment treatment (eg mupirocin) [30–32] and the other group only performing CHG bathing [3,25,33,34]. The concomitant use of nasal antibiotic ointment was associated with a significantly lower incidence of MRSA acquisition compared with only CHG bathing (ratio of log RR: 0.81, 95% CI: 0.66-0.98, $P = .035$).

3.9. Meta-regression analysis

A meta-regression analysis was performed to explore the possible sources of heterogeneity based on the intervention duration. Two studies regarding CLABSI [5,29] and 1 study regarding MRSA [33] exhibited a >2-month difference in the control and intervention durations. Thus, only 9 studies regarding CLABSI [3,4,6,7,23,24,26–28] and 6 studies regarding MRSA [3,25,30–32,34] were included in the meta-regression. As shown in Fig. 5a, there was no significant correlation between intervention duration and RR reduction for CLABSI ($P = .477$). In contrast, intervention duration was significantly correlated with the RR reduction for MRSA, with a 1-month increase in the intervention duration providing a log RR reduction of 2% ($P = .027$) (Fig. 5b).

3.10. Cumulative meta-analysis

A cumulative meta-analysis (Fig. 6) revealed that the effects of the RR reduction decreased slightly as short-term studies were accumulated. However, the RR reduction remained stable and significant for both CLABSI (RR: 0.45, 95% CI: 0.30-0.68, $P < .001$) and MRSA (RR: 0.64, 95% CI: 0.56-0.74, $P < .001$).

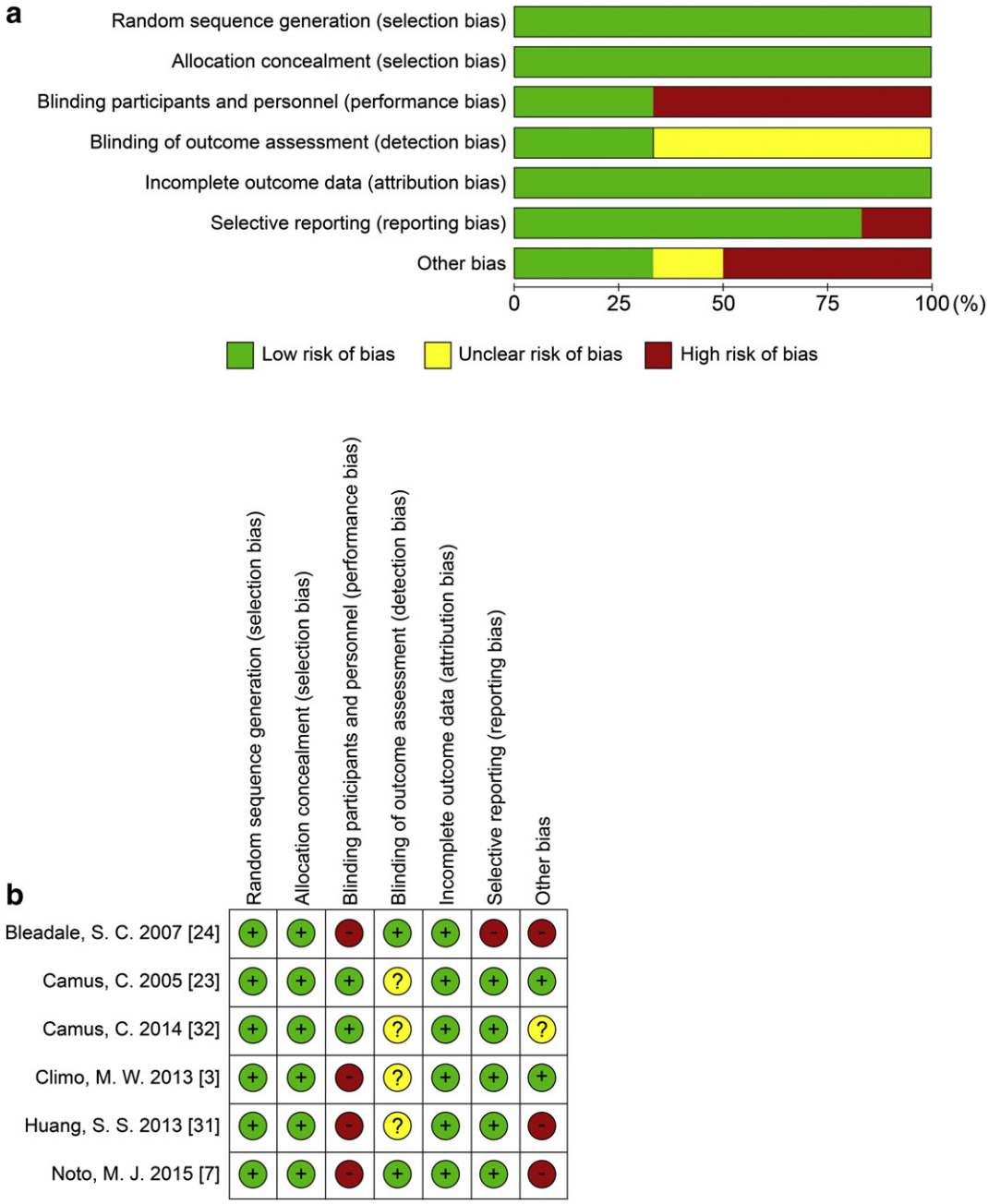

Fig. 2. Risk of bias graph (a) and summary (b) for the randomized controlled trials. "+" indicates a low risk of bias, "−" indicates a high risk of bias, and "?" indicates an unclear risk of bias.

3.11. Publication bias

Funnel plot analysis (Fig. 7) did not indicate that publication bias was likely, and no significant publication bias was found using various comparisons (all, $P > .05$).

4. Discussion

The present meta-analysis revealed that daily CHG bathing reduced the acquisition of CLABSI, MRSA, and VRE among ICU patients compared with the acquisition rates that were observed with conventional care. These results were reported in 18 studies, which included 6 RCTs [3,7,23,24,31,32] and 12 ITSs [4–6,25–30,33–35]. The CLABSI analysis included 11 studies [3–7,23,24,26–29], and the pooled estimated RR was 0.45 (95% CI: 0.37-0.55, $P < .001$). The MRSA analysis included 7 studies [3,21,26–30], and the pooled estimated RR was 0.67 (95% CI: 0.59-0.77, $P < .001$). The VRE analysis included 3 studies [3,25,35], and the RR was 0.60 (95% CI: 0.42-0.85, $P = .004$).

Several systematic reviews and meta-analyses have attempted to evaluate the effect of daily CHG bathing on HAI. Some studies have analyzed ICU settings [36,37], and other studies have analyzed hospital settings [38–40]; these studies reported a tendency toward daily CHG bathing being more effective than conventional care. However, Noto et al [7] recently performed a study that included more than 9000 adult patients from 5 ICUs using a cluster randomized crossover controlled design. Their results indicated that daily CHG bathing did not reduce the incidence of HAI, including CLABSI, compared with conventional care. Thus, the present meta-analysis evaluated all eligible studies (including the study of Noto et al) to account for these conflicting results.

Among previous meta-analyses of the ICU settings, O'Horo et al [36] included 12 studies to evaluate the incidence of bloodstream infection

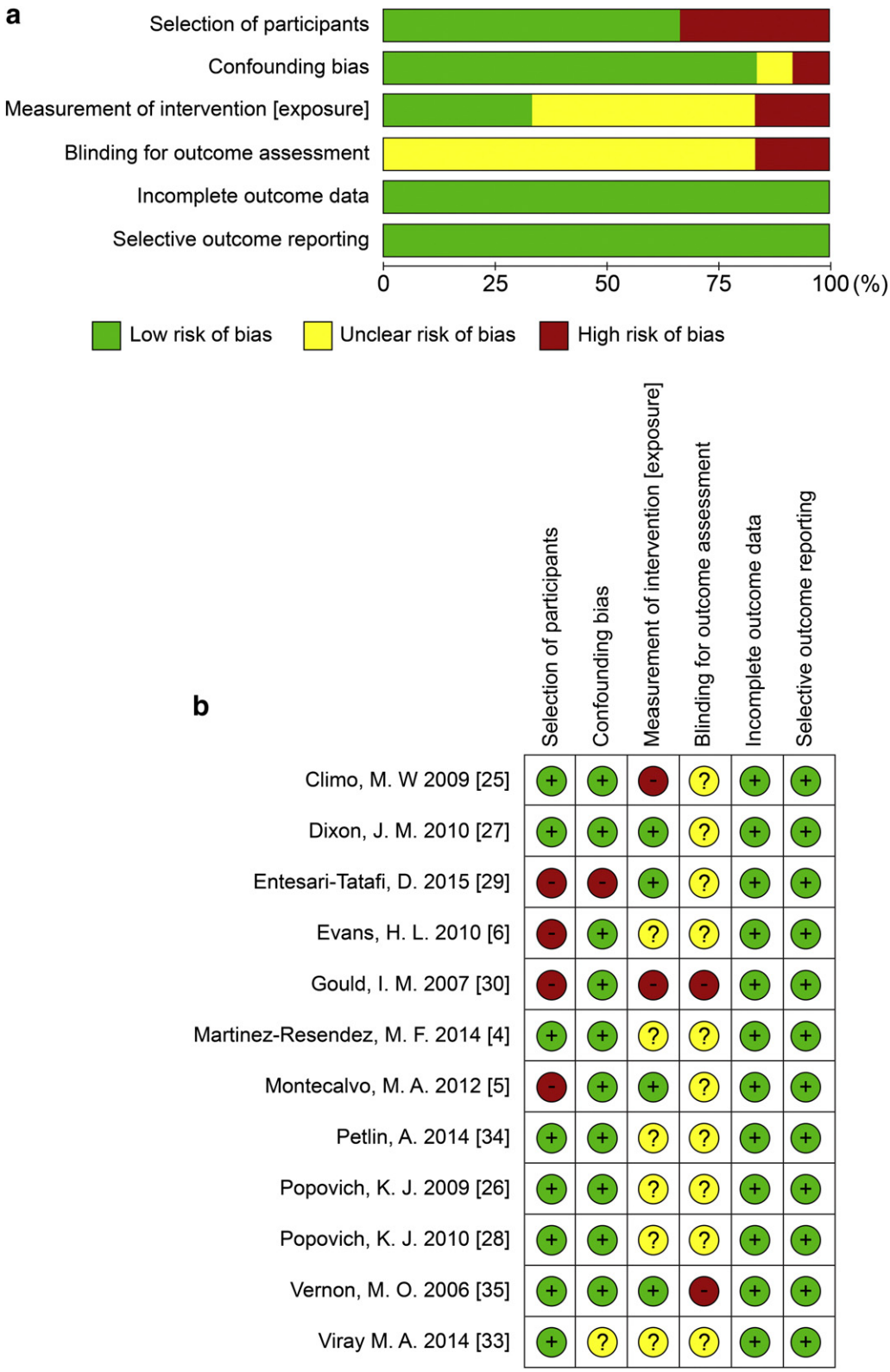

Fig. 3. Risk of bias graph (a) and summary (b) for the interrupted time series trials. "+" indicates a low risk of bias, "−" indicates a high risk of bias, and "?" indicates an unclear risk of bias.

(BSI) and reported a reduced incidence in the daily CHG bathing group compared with that in the conventional care group. However, those results should be interpreted cautiously because O'Horo et al analyzed all BSIs as a single group, which included primary BSI, CLABSI, and BSIs that were caused by specific organisms, such as *Acinetobacter baumannii*, MRSA, or VRE. Therefore, to reduce the outcome variability, we only analyzed BSIs that were associated with a central line. Among the 12 studies that were evaluated by O'Horo et al, we included 7 studies and excluded 5 studies. The 4 studies were excluded because 3 investigated BSIs that were caused by a specific organism [25,30,41], the original data in another could not be evaluated [20], and the remaining study was performed at a long-term acute care hospital where the average stay

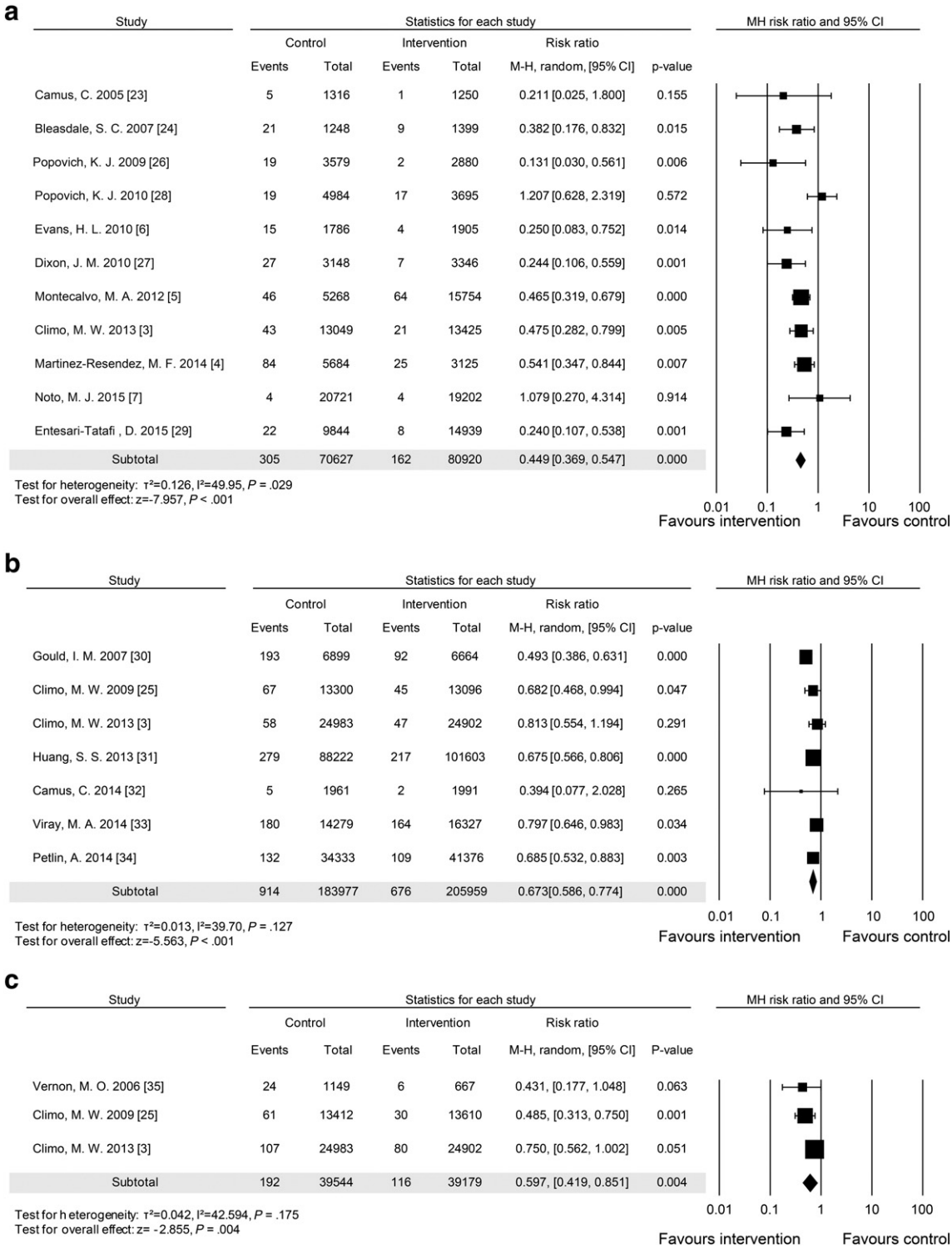

Fig. 4. Forest plot of the RRs and 95% CIs in the intervention (CHG bathing) and control (conventional care) groups using a random-effects model. Total: central line-days in the acquisition of CLABSI (a), patient-days in the acquisition of MRSA (b), and patient-days in the acquisition of VRE (c). Events: number of cases for each outcome. M-H indicates Mantel-Haenszel.

was at least 25 days [42]. In addition to the 7 studies that were evaluated by O'Horo et al, we included 3 other studies regarding CLABSI. Our pooled estimates for the incidence of CLABSI revealed a greater than 50% RR reduction in the daily CHG bathing group compared with the conventional care group.

Derde et al [37] also performed a systematic review to evaluate daily CHG bathing in ICU settings and reported that this method was effective in controlling antimicrobial-resistant bacteria. They also suggested that CHG bathing may be effective in preventing the transmission of BSIs due to MRSA or VRE, although there is no related evidence regarding antibiotic-resistant gram-negative bacteria. The review of Derde et al included 7 studies (2 RCTs and 5 ITSs), and we included 5 of those studies in our analysis, although 2 studies were excluded because 1 study focused on endemic and outbreak MRSA with insufficient data [43] and the other study only used a CHG bathing protocol for MRSA-positive patients [44]. Furthermore, we included 3 studies that were excluded from

the review of Derde et al [6,26,27]. These studies included sufficient data for our analysis, although these studies did not report time-series trend data. Moreover, Derde et al categorized the cases as colonization or infection with MRSA or VRE, although the infection cases only involved bacteremia and did not include other infections such as pneumonia and gastroenteritis [23,25,28,30,44]. Therefore, we evaluated cases of "acquisition" rather than distinguishing between colonization and infection. In the present study, the pooled RR reductions for MRSA or VRE acquisition were approximately 33% and 40%, respectively, in the daily CHG bathing group compared with the conventional care group.

Given the conflicting results that were reported by Noto et al [7], other researchers have addressed various limitations regarding the study's design. First, the study did not involve blinding regarding the bathing regimen, and adherence to care practices was not monitored. Second, the median ICU stay was relatively short (intervention group: 2.56 days, control group: 2.39 days) compared with those in other studies. This may explain why the HAI rates of Noto et al were lower than those in previous studies [45,46]. Based on these issues, we questioned the accuracy of their data given that they expressed the all-infection rate as cases per patient-days. In contrast, most studies report the incidences of CLABSI and ventilator-associated pneumonia as cases per central line-days and cases per ventilator-days, respectively. Thus, the reported CLABSI incidences (intervention group: 0.21, control group: 0.19) of Noto et al are much lower than the incidences from the crossover nonblinded cluster RCT of Climo et al [3] (intervention group: 3.30, control group: 1.55). Therefore, to increase the robustness of our meta-analyses, we performed sensitivity analyses by removing individual studies and observed that the inclusion or exclusion of the study of Noto et al did not noticeably affect the estimates from our meta-analysis.

Many previous studies have investigated the effects of nasal mupirocin on MRSA acquisition. Although its efficacy is considered controversial because of increasing resistance rates [47,48], some systematic reviews have reported that it is effective for preventing nasal colonization [49,50]. Therefore, we performed subgroup analysis by dividing the 7 eligible MRSA studies into studies that performed CHG bathing with concomitant nasal antibiotic treatment [30–32] and studies that performed only CHG bathing [3,25,33,34]. The results of that analysis revealed that the log RR for concomitant nasal agents was 19% lower than that for only CHG bathing (95% CI: 0.66-0.98, $P = .035$).

Among the studies that were eligible for the present meta-analysis, a few studies reported time-series trend data to evaluate the effect of daily CHG bathing according to the intervention duration [25–28,30,33]. Some studies reported that the change in the infection slope tended to decrease as the intervention duration increased [25,26], although other studies reported nonspecific changes [27,28,30,33]. One previous meta-analysis investigated the changes in the CLABSI rate at 3, 6, 12, and 24 months using time regression analyses [51] and reported that the change in the infection rate slope trended toward a reduction, although there was no significant difference. We suggest that these findings are attributable to the infection control protocol development for each institution, as each health care system has a dedicated team that is responsible for developing a protocol and that undergoes intense and repeated training. Given that our meta-analysis revealed evidence of moderate heterogeneity (CLABSI, $I^2 = 49.68\%$; MRSA, $I^2 = 39.70\%$), we performed a meta-regression analysis of the CLABSI and MRSA groups to evaluate the change in effect according to the intervention duration. For this analysis, we hypothesized that longer CHG bathing interventions would provide better efficacies in preventing HAI. Therefore, we selected studies with similar control and intervention durations (a <2-month difference) and

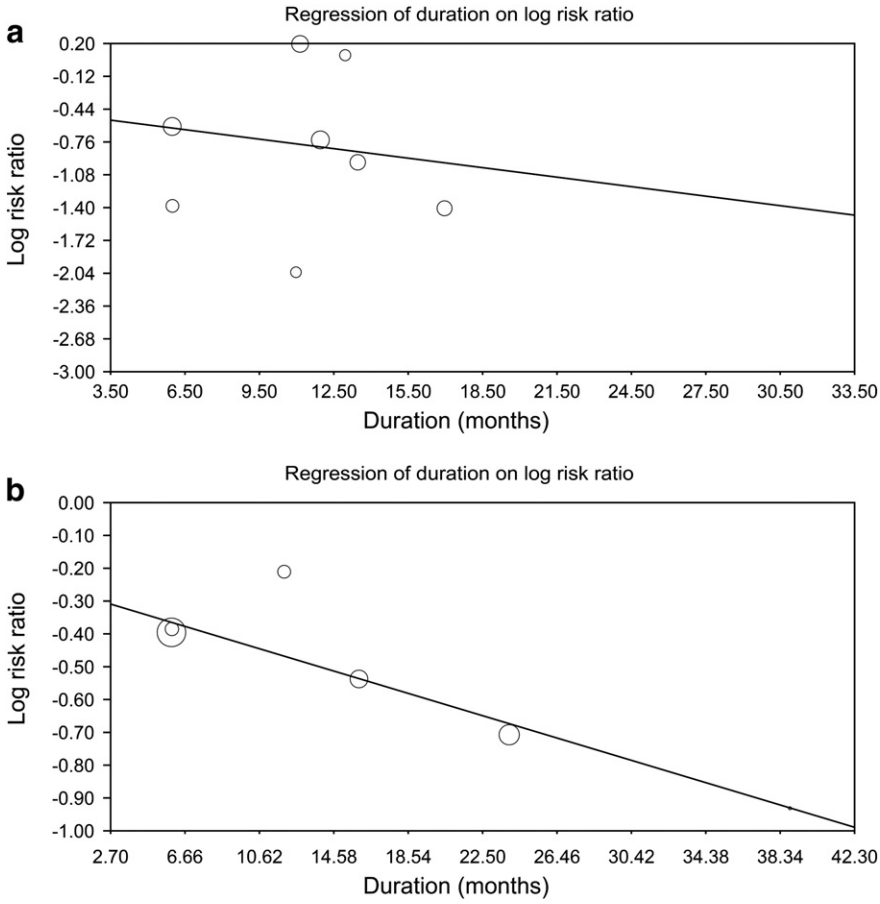

Fig. 5. Meta-regression of the intervention duration in months as a predictor of acquisition. The slope trend for the log RR was −0.03 ($P = .48$) per 1-month period in the acquisition of CLABSI (a) and −0.02 ($P = .027$) per 1-month period in the acquisition of MRSA (b).

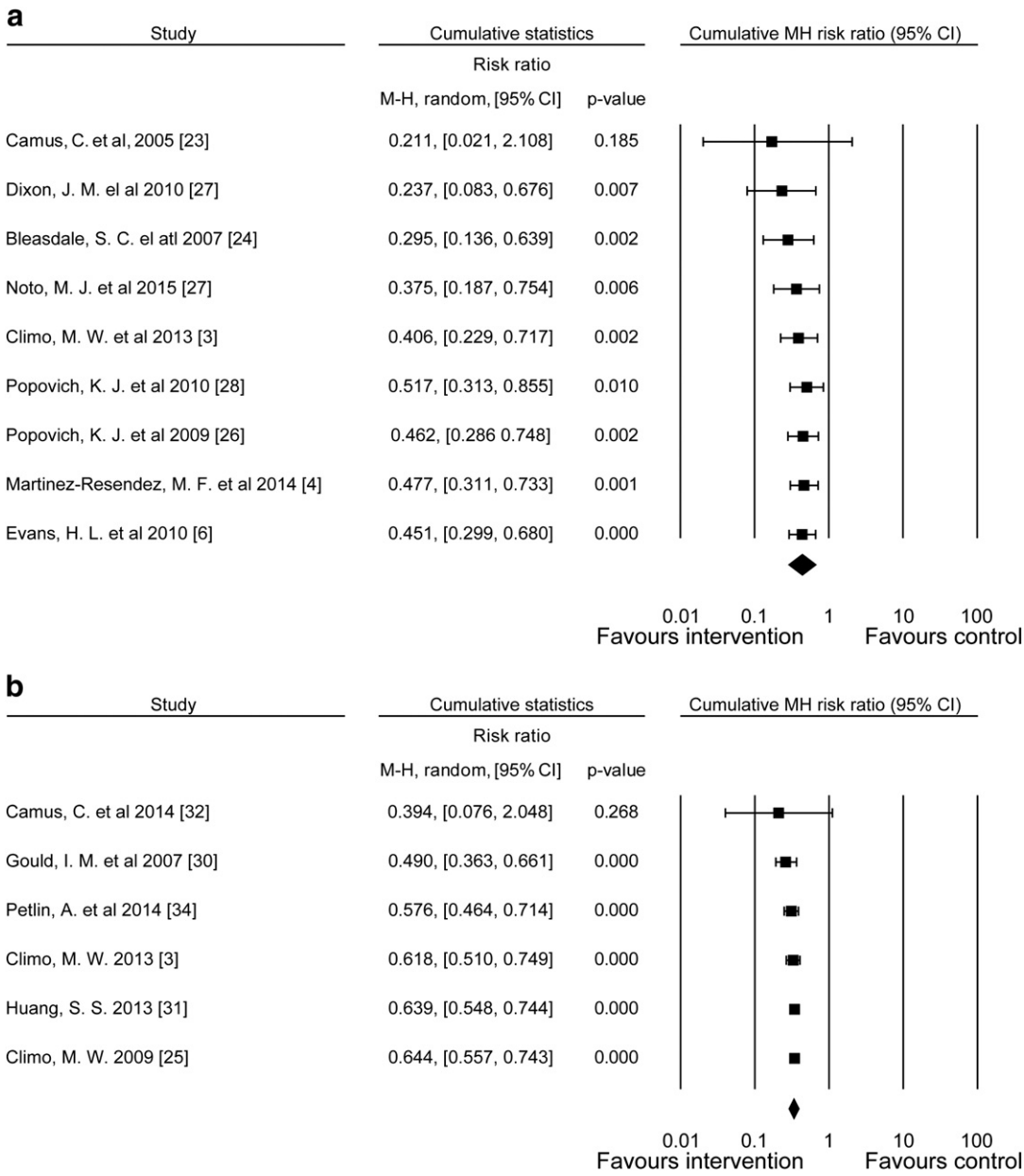

Fig. 6. A cumulative meta-analysis with RRs and 95% CIs for the acquisition of CLABSI (a) and MRSA (b). The overall cumulative RRs were 0.451 ($P < .001$) (a) and 0.644 ($P < .001$) (b).

arranged these studies according to the length of their intervention. In the MRSA group, the log RR was significantly correlated with the intervention duration (a 2% reduction per 1-month increase, 95% CI: −0.03 to 0.001, $P = .027$), although there was no significant correlation in the CLABSI group (a 3% reduction per 1-month increase, 95% CI: −0.12 to 0.05, $P = .477$) (Fig. 5). Therefore, we suggest that intervention duration exerted a greater protective effect on MRSA acquisition compared with CLABSI acquisition. Similarly, previous studies have reported that CHG bathing reduced the frequencies of environmental contamination and patient skin contamination [35] and that contamination in health care settings (eg, health workers' hands and equipment) is a major source of MRSA transmission [33]. In contrast, antiseptic practices at the central line insertion play a prominent role in CLABSI acquisition [52]. Furthermore, we performed a cumulative meta-analysis and found that the RR reduction remained stable despite the accumulation of relatively short-term studies, which confirms that CHG provides robust efficacy in preventing CLABSI and MRSA acquisition even during relatively short periods (Fig. 6).

Other recent reports have described lower CLABSI, MRSA, and VRE infection rates in the US and Ireland [52–54]. Thus, we performed a meta-regression analysis to evaluate whether the recent studies exerted a greater effect on the RR reduction. However, we did not find any significant correlation (CLABSI: $P = .826$; MRSA: $P = .149$). Therefore, we suggest that the recent infection rate reductions were related to other factors (eg, patient, medical, and health care delivery factors) and not only to the effects of daily CHG bathing [53,55–57].

There are several limitations in the present study. First, two thirds of the included studies were nonrandomized studies, which generally used an ITS design. Although we evaluated the risk of bias, there is a high likelihood that potential confounders were not reported or adjusted for in those studies. Second, multiple heterogeneities were observed in the intervention choices and surveillance methods. For example, most included studies used disposable 2% no-rinse CHG washcloths [3–7,24,26–29,31,35], although 6 studies used a 4% CHG liquid solution with warm water and rinsing [23,25,30,32–34]. Among these 6 studies, only 3 studies reported the exact proportions of 4% CHG and water

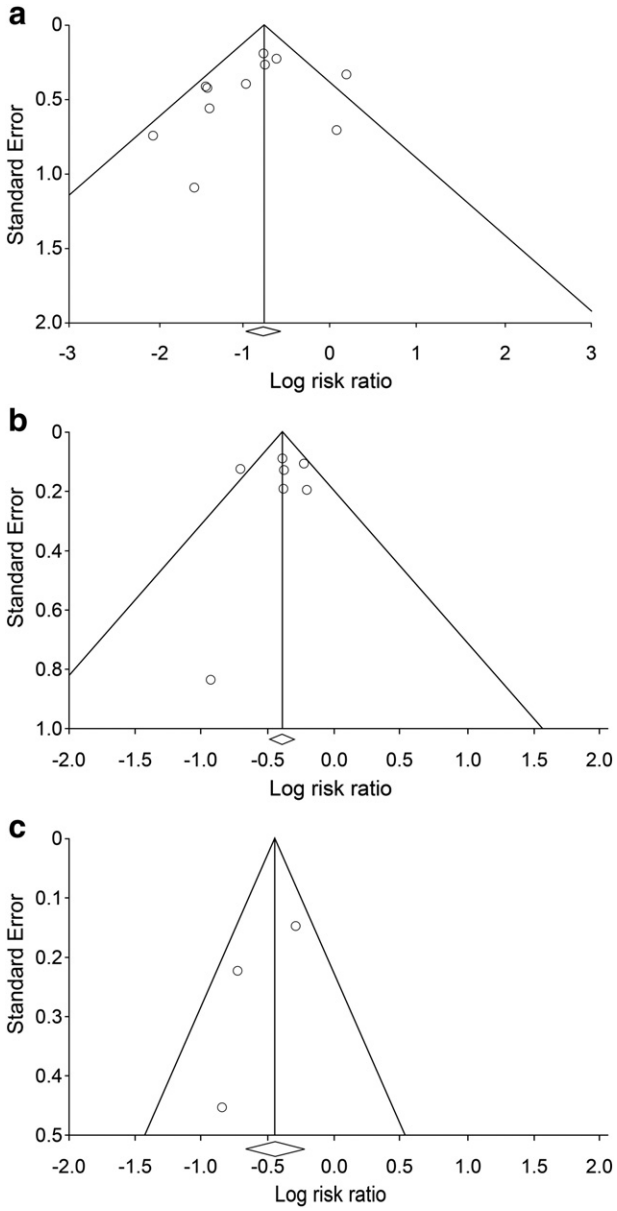

Fig. 7. A funnel plot for the standard error using the log RR for the acquisition of CLABSI (a), MRSA (b), and VRE (c). The results revealed no publication bias, as all *P* values were < .05 (a: .28, b: .78, c: .40).

[25,33,34], and the other 3 studies did not report these proportions [23,30,32]. Furthermore, Camus et al [23,32] bathed their patients twice per day, whereas the other studies' patients were only bathed once per day. Moreover, most studies regarding MRSA and VRE performed active surveillance at admission, every week, and at discharge. However, 2 studies did not perform screening at admission for the control group [30] or the intervention group [31]. In addition, although MRSA detection was performed at the nares in all studies, 2 studies performed MRSA detection in additional areas, such as the throat, axilla, or groin [30,32]. These differences may be relevant and may have affected our findings. Third, in the meta-analysis of the MRSA group, one study exhibited an overwhelming effect size in the patient-days outcome [31], which accounted for 88,222 of the 171,936 patient-days (51.3%) in the control group and 101,603 of the 195,816 patient-days (51.8%) in the intervention group. Therefore, although we did not detect any publication bias (the funnel plot indicated bilateral symmetry and the Egger test *P* value was .40), it is possible that the results from that study exerted a substantially greater effect on the results from our meta-analysis.

In conclusion, the findings from the present meta-analysis suggest that daily CHG bathing decreased the acquisition of CLABSI, MRSA, and VRE among patients in ICU settings. Furthermore, the effects of CHG bathing on MRSA acquisition were enhanced by the concomitant use of nasal antibiotic ointments and by prolonged intervention durations. Although the included studies had multiple heterogeneities in their intervention and surveillance methods, these changes were only associated with a low to medium risk of bias. Nevertheless, well-designed and adequately powered prospective clinical trials are needed to confirm our findings.

5. Compliance with ethical standards

Conflicts of interest: The authors declare that they have no conflicts of interest.

Ethical approval: No formal ethical approval is needed for this type of study.

Acknowledgments

The authors thank Dong-Su Jang, MFA (Medical Illustrator, Medical Research Support Section, Yonsei University College of Medicine, Seoul, Korea), for his help with the illustrations.

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