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Review

Does copper treatment of commonly touched surfaces reduce healthcare-acquired infections? A systematic review and meta-analysis

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S U M M A R Y

Background: Healthcare-acquired infections (HAIs) cause substantial morbidity and mortality. Copper appears to have strong antimicrobial properties under laboratory conditions.
Aim: To examine the potential effect of copper treatment of commonly touched surfaces in healthcare facilities.
Methods: Controlled trials comparing the effect of copper-treated surfaces (furniture or bed linens) in hospital rooms compared with standard rooms on HAIs were included in this systematic review. Two reviewers independently screened retrieved articles, extracted data, and assessed the risk of bias of included studies. The primary outcome was the occurrence of HAIs.
Findings: In total, 638 records were screened, and seven studies comprising 12,362 patients were included. All included studies were judged to be at high risk of bias in two or more of the seven domains. All seven studies reported the effect of various copper-treated surfaces on HAIs. Overall, this review found low-quality evidence of potential clinical importance that copper-treated hard surfaces and/or bed linens and clothes reduced HAIs by 27% (risk ratio 0.73, 95% confidence interval 0.57–0.94; $I^2 = 44\%$, P=0.01).
Conclusion: Given the clinical and economic costs of HAIs, the potentially protective effect of copper treatment appears to be important. The current evidence is insufficient to make a strong positive recommendation. However, it would appear worthwhile and urgent to conduct larger publicly funded clinical trials into the impact of copper treatment.

Introduction

Healthcare-acquired infections (HAIs) are infections acquired directly or indirectly by patients while receiving health care. HAIs are a major cause of preventable harm, result in substantial morbidity, prolong hospitalization, increase the

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cost of healthcare delivery, and contribute to mortality [1,2]. Despite current efforts aiming to prevent and control HAIs, recent estimates suggest that they remain among the most prevalent and preventable challenges to patient safety worldwide [3,4].

One strategy to control HAIs is to reduce the transmission of fomite pathogens that can occur if common objects such as door handles, stair banisters, table surfaces, utensils or taps are contaminated [5]. Cleaning shared surfaces is one proposed preventive mechanism, but would require frequent and extensive cleaning.

Copper appears to have strong bactericidal and viricidal properties, and substantially reduces the duration of pathogen viability on surfaces from days to 30–60 min under laboratory conditions [6]. The inactivation property of copper has been demonstrated for both norovirus and coronavirus species with inactivation occurring in less than 60 min [6]. Inactivation also occurs on copper alloys, and the activity appears to be directly proportional to the percentage of copper present in the alloy. This property has led researchers to examine the potential for copper plating common surfaces to reduce HAIs with multi-drug-resistant bacteria as well as viruses, with attempts made to copper plate common shared surfaces in hospital wards [7]. These include surfaces such as bedrails, door handles and table surfaces, as well as soft textiles such as bed linen, patient gowns and towels.

If treatment of commonly touched surfaces in hospital rooms with copper/copper alloys could reduce HAIs, the impact could be substantial in both health and economic terms [8]. Therefore, this review aimed to examine the potential for copper plating common shared surfaces in hospitals. The aim was to identify all controlled trials that had compared copper-treated surfaces in hospital rooms or items with standard rooms or items.

Methods

This review aimed to find, appraise and synthesize eligible studies that have compared the effect of copper-treated hospital room surfaces with standard room surfaces on HAIs. This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, and the review protocol was developed prospectively [9].

Eligibility criteria

Participants

Studies of patients of any age and with any condition in acute and long-term care settings [including intensive care units (ICUs), rehabilitation centres and aged care facilities] were included in this review.

Interventions

Studies that evaluated interventions involving copper (or copper alloy)-treated rooms or objects in patient care rooms/spaces were included in this review. The intervention was expanded to include studies that evaluated copper-treated soft textiles such as bed linens, clothes and gowns as sufficient data were available.

Comparators

Studies with any comparator were included in this review, as long as the comparator did not involve the use of copper or copper alloy surfaces.

Outcomes

The primary outcome was the incidence of HAIs (e.g. bacterial or viral infections, not colonizations) in patients. The secondary outcomes were the incidence of death and any skin reactions in patients, and any HAIs (bacterial or viral) in hospital staff and visitors. Studies that only reported the rate of colonization (not infection) were excluded from this review.

Study design

Randomized and pseudo-randomized (e.g. alternate allocation) controlled trials were included in this review.

Search strategies to identify studies

Database search strings

PubMed, Cochrane CENTRAL and Embase were searched from inception to 25th March 2020. A search string was designed in PubMed that included the following concepts: copper AND infections AND healthcare facility AND controlled trial. The PubMed search string was translated using the Polyglot Search Translator [10] and run in the other two databases (Appendix 1, see online supplementary material).

Restriction on publication type

No restrictions by language or publication date were imposed. Publications that were published in full were included in this review. In addition, publications available as abstract only (e.g. conference abstracts) were included if they had a clinical trial registry record, or other public report, with the additional information required for inclusion. Publications available as abstract only (e.g. conference abstracts) with no additional information available were excluded from this review.

Other searches

On 26th March 2020, a backwards (cited) and forwards (citing) citation analysis was conducted in Scopus on the studies identified by the database searches. These were screened against the inclusion criteria. Clinical trial registries were searched on 25th March 2020 via Cochrane CENTRAL, which includes the World Health Organization International Clinical Trials Registry Platform and clinicaltrials.gov.

Study selection and screening

Two authors (LA, OB) independently screened the titles and abstracts against the inclusion criteria. One author (JC) retrieved the full-texts, and two authors (LA, OB) screened the full-texts for inclusion. Any disagreements were resolved by discussion or by reference to a third author (PG). The selection process was recorded in sufficient detail to complete a PRISMA flow diagram (Figure 1) and a list of excluded full-text articles with reasons for exclusions (see Appendix 2, see online supplementary material).

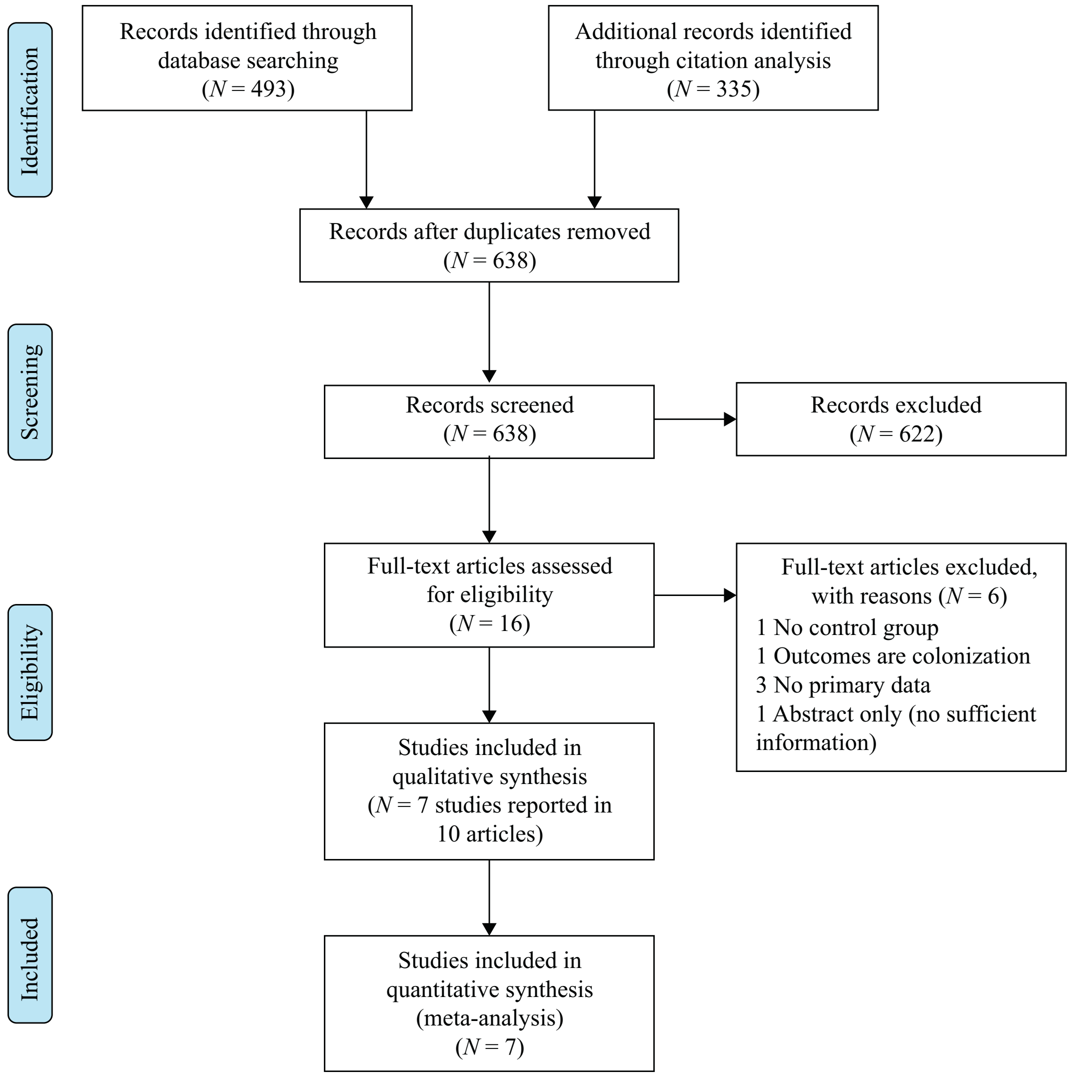


Figure 1. PRISMA flow diagram of included articles.

Data extraction

A data extraction form was used for study characteristics and outcome data, which was piloted on two studies in the review. Two authors (LA, OB) extracted the following data from the included studies:

- methods: study authors, location, study design, duration of study, duration of follow-up;
- participants: number, age (mean or median; range), gender, diagnosis or infection type at admission, ward or room type of admission (e.g. ICU, acute care, long-term care);
- interventions and comparators: type of copper coating (e.g. percentage of copper in the alloy), type of surfaces covered by copper/copper alloy (e.g. bed controls, tables, etc.), type of comparator, average duration of stay in the room; and
- outcomes: incidence of HAIs (e.g. bacterial or viral infections) in patients (primary outcome) or hospital staff/visitors (secondary outcome), and number of deaths (secondary outcome) and skin reactions (secondary outcome).

Assessment of risk of bias in included studies (assessment of quality of studies)

Two review authors (LA, OB) independently assessed the risk of bias for each included study using Risk of Bias Tool 1, as outlined in the Cochrane Handbook [11]. All disagreements were resolved by discussion or by referring to a third author (PG). The following domains were assessed:

- random sequence generation;
- allocation concealment;
- blinding of participants and personnel;
- blinding of outcome assessment;
- incomplete outcome data;
- selective outcome reporting; and
- other bias (focusing on potential biases due to funding or conflict of interests).

Each potential source of bias was graded as low, high or unclear, and each judgement was supported by a quote from the relevant trial.

Table I
Characteristics of included studies ($N=7$)

Study ID, year and location	Study type and duration	Participants, setting	Intervention	Control	Primary outcomes[a] (as reported in original studies)
Salgado 2013 (USA) [18]	Double-blind randomized controlled trial, 11 months	614 adult ICU patients (60.4 years)	*Copper-treated surfaces* Copper plating of bed rails, overbed tables, IV poles and arms of the visitor's chair (nurses' call button, computer mouse, bezel of touchscreen monitor, and palm rest of laptop differed depending on the hospital)	Regular ICU	Incidence rate of HAI and/or MRSA or VRE colonization. HAIs were determined using NHSN definitions (i.e. infections on and after third day of admission)
Rivero 2014 (Chile) [17]	Controlled trial, 13 months	440 adult ICU patients (51 years)	*Copper-treated surfaces* C11000 copper alloy (99% copper) equivalent to approximately 80% of the areas most touched by patients (four bed rails, patient's table and two IV poles)	Regular ICU	HAIs, associated mortality, cost of antimicrobials
von Dessauer 2016 (Chile) [21]	Non-randomized, unmasked, controlled clinical trial, 12 months	65 PICU patients (1 year)	*Copper-treated surfaces* Copper plating of bed rails, bed rail levers, IV poles, sink handles and the nurses' workstation	Regular PICU	Diagnosis of an HAI event associated with patient stay within the PICU or PIMCU. HAIs were determined by standard definitions used by the National Surveillance System of the Ministry of Health of Chile (i.e. infections on and after third day of admission)
Zerbib 2020 (France) [22]	Controlled trial, 16 months	556 nursing home residents (85.4 years)	*Copper-treated surfaces* Copper alloy (containing 90% copper) treatment of 438 door handles, 322 m of handrails and 10 grab bars	Regular nursing home setting	Rates of infection during outbreak (five cases in 4 days)
Marcus 2017 (Israel) [14]	Double-blind, controlled crossover trial, 7 months (2 x 3 months, separated by a 1-month washout period)	112 ventilator-dependent patients in a long-term care facility (69.8 vs 71.3 years)	*Copper-treated textiles* Copper-oxide-impregnated linen and hospital patients' clothes and towels	Regular ICU	ATIEs, fever-days, days of antibiotic treatment, and antibiotic defined daily dose per 1000 hospitalization-days. This review used ATIEs as an indirect indication for HAIs
Marik 2020 (USA) [15]	Prospective, cluster, crossover, randomized control trial, 11 months (2 x 5 months separated by 2 weeks of washout)	1282 adult ICU patients (60 years)	*Copper-treated textiles* Copper-oxide-treated linens (top sheets, fitted sheets, pillowcases, under pads, wash cloths, towels and patient gowns)	Regular ICU	HCAIs were determined using NHSN definitions (i.e. infections on and after third day of admission)

Sifri 2016 (USA) [20]	Quasi-experimental study with a control group, 10 months	9961 adult acute care patients (58.5 vs 60.5 years)	*Combined copper-treated textiles and surfaces* 16% copper-oxide-impregnated composite countertops (sinks, vanities, desks, computer stations, soiled utility rooms, nurses' workstations) and moulded surfaces (overbed tray tables, bedrails), and copper-impregnated woven linens (patient gowns, bedding, washcloths, towels, bath blankets, thermal blankets)	Regular ICU	Incidence rate of hospital-onset infections (*Clostidioides difficile* or MDROs). HAIs were determined using NHSN definitions (i.e. infections on and after third day of admission)

ICU, intensive care unit; HAI, healthcare-acquired infection; MRSA, meticillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant enterococci; PICU, paediatric ICU; PIMCU, intermediate paediatric care unit; HCAI, healthcare-associated infection; MDRO, multi-drug-resistant organism; NHSN, National Healthcare Safety Network; IV, intravenous; ATIE, antibiotic treatment initiation event.

[a] As reported by the authors of included studies; however, only the outcomes proposed in the Methods were extracted (e.g. if authors reported both colonization and HAIs, only HAIs were extracted and reported, as per the proposed methods).

Measurement of effect and data synthesis

Risk ratios or rate ratios (RR) were used for dichotomous outcomes – risk ratios for results reporting the number of patients with an event, and rate ratios for the results reporting the number of events alone. Meta-analyses were only undertaken when meaningful (when at least two studies or comparisons reported the same outcome); a random effects model was used in anticipation of considerable heterogeneity. Review Manger 5 was used to calculate the intervention effect.

Assessment of heterogeneity and reporting biases

Both clinical and methodological heterogeneity were considered among the included studies (i.e. differences between included studies in terms of population, intervention, comparison, outcomes and study designs). This assessment of clinical and methodological heterogeneity was supplemented with information regarding statistical heterogeneity, assessed using Chi-squared test (a significance level of $P<0.10$ was considered to indicate significant heterogeneity) in conjunction with the I^2 statistic ($I^2 \geq 75\%$ indicates considerable heterogeneity) [12]. As fewer than 10 trials had been included, a funnel plot was not created.

Dealing with missing data

Investigators or study sponsors were contacted to provide missing data.

Subgroup and sensitivity analyses

The intention was to perform a subgroup analysis by type of infection/patient and a sensitivity analysis by including vs excluding studies at high risk of bias; however, these analyses were not undertaken due to the low number of studies included in this review.

Results

In total, 638 titles and abstracts, and 16 full-text articles were screened for inclusion in this review. After exclusion of six articles, 10 articles pertaining to seven studies were included [13–22]. In addition, five relevant clinical trial registries (two for studies already identified and included, and three for studies that have not been published) were included. Figure 1 shows the PRISMA flow diagram of studies. Excluded full-text articles are presented in Appendix 2 (see online supplementary material) with reasons for exclusion.

Characteristics of included studies

Seven controlled studies, which enrolled a total of 12,362 participants, were included in this review [14,15,17,18,20–22]. Included studies had been conducted in the last decade in the USA (N=3 [15,18,20]), Chile (N=2 [17,21]), France (N=1 [22]) and Israel (N=1 [14]). Three of the studies were set in adult ICUs [15,18,20], one in a paediatric ICU [21], one in an aged care facility [22], one on an acute care ward [17] and one in a long-term care facility for ventilator-

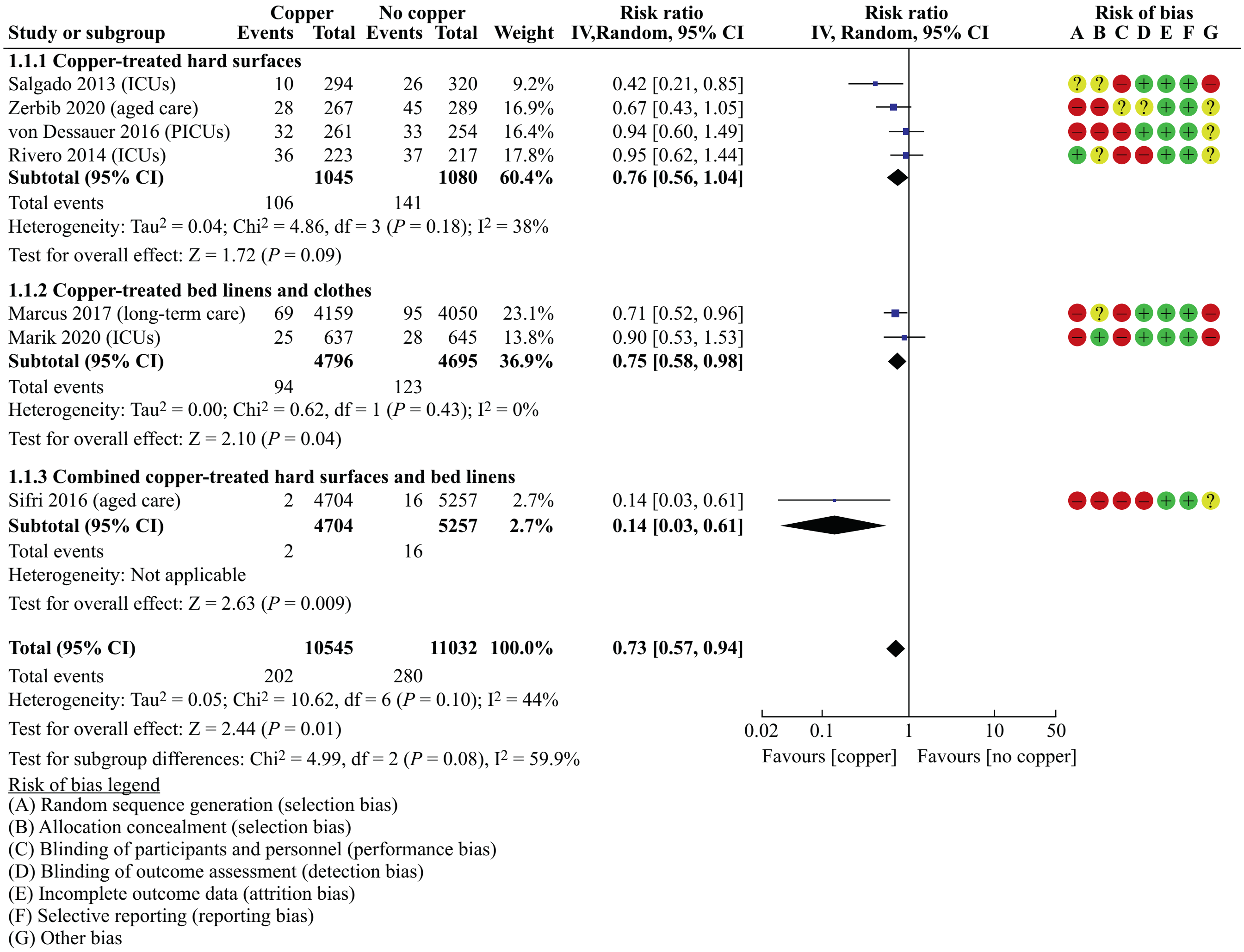


Figure 2. Forest plot of healthcare-acquired infections (HAIs) for copper-treated surfaces vs no copper. ICUs, intensive care units; PICUs, paediatric ICUs; CI, confidence interval. Marcus 2017 data refer to antibiotic treatment initiation events rather than HAIs, and are reported as the number of events per hospitalization-day.

dependent patients [14]. The duration of the studies ranged from 7 to 16 months.

Four of the included studies evaluated the effect of copper plating commonly touched hard surfaces such as bed rails and tables, intravenous poles, door handles and taps on HAIs [17,18,21,22]. Two studies evaluated copper-treated linens (bedding, patient gowns and towels) [14,15] and one study included both hard surfaces and linens [20]. All included studies reported the effect of copper on HAIs in patients (i.e. primary outcome); none of the included studies reported the effect of copper on hospital staff or visitors (i.e. secondary outcome) (see Table I).

Risk-of-bias assessment (quality of studies)

All seven included studies were judged to be at high risk of bias in two or more domains. Of the seven studies, five were judged to be at high or unclear risk for selection bias (either random sequence generation or allocation concealment). All seven studies were judged to be at high or unclear risk for blinding of participants or personnel and conflict of interest (recorded as 'other risk of bias'). All seven studies were judged to be at low risk for attrition bias (i.e. incomplete outcome data) and reporting bias (i.e. selective reporting).

Effects of copper-treated surfaces

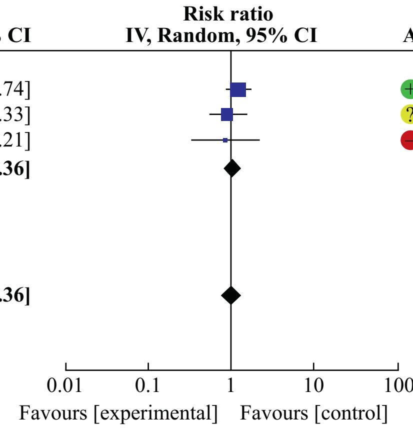
Healthcare-acquired infections

All seven included studies reported the effect of copper-treated surfaces on HAIs. Overall, copper-treated hard surfaces and/or bed linens and clothes were found to reduce HAIs by 27% [RR 0.73; 95% confidence interval (CI) 0.57—0.94] (Figure 2).

Copper-treated hard surfaces (four studies). Four studies (2125 participants) that evaluated the effect of copper-treated hard surfaces on HAIs were identified [17,18,21,22]. There was no significant reduction in HAIs among participants hospitalized in facilities with copper-treated surfaces compared with no copper (RR 0.76, 95% CI 0.56—1.04; I^2=38%).

Copper-treated bed linens and clothes (two studies). Two studies (276 participants) that evaluated the effect of copper-

Study or subgroup	Copper Events	Copper Total	No copper Events	No copper Total	Weight	Risk ratio IV, Random, 95% CI	Risk of bias A	B	C	D	E	F	G
1.2.1 Copper-treated hard surfaces													
Rivero 2014 (ICUs)	57	223	45	217	51.1%	1.23 [0.87, 1.74]	+	?	−	−	+	+	?
Salgado 2013 (ICUs)	42	294	50	320	42.0%	0.91 [0.63, 1.33]	?	?	−	+	+	+	−
Von Dessauer 2016 (PICUs)	8	261	9	254	6.9%	0.87 [0.34, 2.21]	−	−	−	+	+	+	?
Subtotal (95% CI)		**778**		**791**	**100.0%**	**1.06 [0.83, 1.36]**							
Total events	107		104										
Heterogeneity: Tau² = 0.00; Chi² = 1.51, df = 2 (*P* = 0.47); I² = 0%													
Test for overall effect: Z = 0.47 (*P* = 0.64)													
Total (95% CI)		**778**		**791**	**100.0%**	**1.06 [0.83, 1.36]**							
Total events	107		104										
Heterogeneity: Tau² = 0.00; Chi² = 1.51, df = 2 (*P* = 0.47); I² = 0%													
Test for overall effect: Z = 0.47 (*P* = 0.64)													
Test for subgroup differences: Not applicable													



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 3. Forest plot of mortality for copper-treated surfaces vs no copper. ICUs, intensive care units; PICUs, paediatric ICUs; CI, confidence interval.

treated bed linens and clothes on HAIs were identified [14,15]. A significant 25% relative reduction in HAIs among participants hospitalized in facilities with copper-treated bed linens and clothes was observed compared with no copper (RR 0.75, 95% CI 0.58–0.98; I^2=0%).

Combined copper-treated hard surfaces and bed linens and clothes (one study). A single study of 9961 participants evaluated the combined effect of both copper-treated hard surfaces and bed linens and clothes on HAIs [20]. A significant 86% relative reduction in HAIs was observed among participants hospitalized in facilities with copper-treated surfaces compared with no copper (RR 0.14, 95% CI 0.03–0.61).

Mortality

Of the seven included studies, three (1569 participants) reported the effect of copper-treated hard surfaces on mortality [17,18,21]. There was no significant difference in mortality between participants hospitalized in facilities treated with copper compared with no copper (RR 1.06, 95% CI 0.83–1.36) (Figure 3).

Skin reactions

Of the seven included studies, two reported data on skin reactions [20,21]. von Dessauer *et al.* did not observe any adverse events (i.e. skin or other allergic reactions) among any participants in either group [21]. Sifri *et al.* reported that 10 (of 4707) patients hospitalized in copper-treated rooms developed skin rashes (nine were evaluated by a dermatologist and attributed to alternative aetiology, one was discharged before evaluation) [20].

Heterogeneity in included studies

Both clinical and methodological heterogeneity between included studies were noted. For example, differences were found in how included studies defined and measured the primary outcome (i.e. HAIs). For instance, although six of the seven included studies measured HAIs directly (i.e. infection not just colonization), the randomized controlled trial of 112 ventilator-dependent patients in a long-term care facility did not measure HAIs, and instead measured antibiotic initiation events as an indicator for HAIs [14]. Further, four of the seven included studies determined HAIs following comparable definitions: three used the National Healthcare Safety Network definitions [15,18,20] and one used the National Surveillance System of the Ministry of Health of Chile (i.e. infections on and after the third day of admission) [21]. The remaining three studies did not report clearly how they defined HAIs. Despite these differences, the quantified Q and I^2 statistics did not identify substantial statistical heterogeneity; the I^2 statistics of all meta-analyses of all outcomes ranged between 0% and 44% (all not significant, P>0.10).

Discussion

The literature search identified seven controlled trials which, when combined, suggest that copper plating of surfaces or the use of copper in textiles may have some effect in reducing HAIs. The combined studies suggest a modest but potentially important effect.

There are several limitations to these findings. First, many of the studies were poorly reported, preventing a clear appraisal of the methods. Second, even when reporting was clear, the research methods often involved flaws in the study design which may have introduced bias. Third, studies reported HAIs caused by different organisms, most of them bacterial (e.g. *Pseudomonas* spp., meticillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci) but also viral (e.g. norovirus and adenovirus), and different body system affected (e.g. respiratory, bloodstream, urinary). Fourth, although substantial statistical heterogeneity (i.e. evaluated using Q test and I^2 statistics) was not identified, observed clinical and methodological heterogeneity between the studies limits the authors' certainty in the effect estimates and poses interpretive challenges. Finally, the small total number of infections meant that the CIs around effects were wide, indicating considerable uncertainty in the size of any effect. The poor quality of reporting and methods, and small sizes of the studies downgrades the overall quality of the evidence, rating it — in GRADE terms — as low-quality evidence but of potential clinical importance. In addition to these problems, many of the investigator teams had a conflict of interests with companies involved with the use of copper.

There was one difference between the protocol and the review. Initially, the intention was to include only studies of copper-plated hard surfaces, such as furniture. However, as several studies assessed the impact of treating textiles (clothing and/or bed linens) with copper, the inclusion criteria were broadened. This resulted in the inclusion of two studies on copper-treated clothing/linen alone [14,15] and one study that assessed the impact of copper treatment of both furniture and textiles [20].

To the authors' knowledge, the only previous systematic review on this subject was published in 2017 by Cochrane Australia for Australia's National Health and Medical Research Council. This found two of the studies [18,21] included in the present review, and concluded that 'With only two non-randomised trials, both with uncertain results, it is not possible to draw conclusions from this evidence'. The three trials that have been performed since then, plus two studies that were not identified in the 2017 review, have strengthened the body of evidence, but not sufficiently to be able to make strong recommendations.

Finding effective and sustainable ways to reduce the transmission of pathogens is important for all epidemics, but is particularly urgent in the current coronavirus disease 2019 (COVID-19) pandemic [23]. Although the exact relative importance of different modes of transmission is currently unknown, there appear to be three main avenues: direct aerosol, contact with fomites, and, the most controversial, airborne transmission [24]. Reducing the incidence of infections will require addressing all modes of transmission. While social distancing is widely promoted, it may not completely prevent fomite transmission if common objects such as door handles, stair banisters, table surfaces, utensils or taps are contaminated [5]. Therefore, the present findings may also be relevant to the current COVID-19 pandemic.

Given the clinical and economic costs of HAIs, the potential effect of copper treatment appears to be important. The current evidence is insufficient to make a strong positive recommendation. However, it would appear worthwhile and urgent to conduct larger publicly funded clinical trials into the impact of copper treatment. If such studies were to be funded, it would also be important to collect additional data, such as the separation of bacterial and viral infections, and measuring outcomes for healthcare workers, particularly for viral infections.

Conflict of interest statement
None declared.

Funding sources
None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhin.2020.09.005.

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