REVIEW ARTICLE

The role of copper surfaces in reducing the incidence of healthcare-associated infections: A systematic review and meta-analysis

Ignacio Pineda, MD, MSc, M.P.H,[1] **Richard Hubbard**, PhD,[2] **Francisca Rodríguez**, MSc[3]

[1] *Comite de Industrias Inteligentes, Corporación de Fomento de la Producción, Moneda 921, 8320250, Santiago, Chile. 600 586 8000*
[2] *Division of Epidemiology and Public Health, University of Nottingham, Nottingham NG5 1PB, United Kingdom*
[3] *Facultad de Medicina, Universidad San Sebastián, Lota 2465, Santiago 7510157, Chile*

Corresponding Author:
Ignacio Pineda
600 586 8000
nachopinedav@gmail.com
Fax: 780-342 0316

ABSTRACT

Background: Healthcare-associated infections are a major public health problem, with an important clinical and economic burden on health systems worldwide. In-vitro and in-vivo studies have shown that copper has the potential to kill microorganisms on contact. It has been described as the "contact killer". Despite this, the preventive role of antimicrobial copper on the reduction of healthcare-associated infections is not clear yet.

Aims & Objectives: To assess the role of copper surfaces on the reduction of healthcare-associated infections.

Methods: A systematic review of the literature with a meta-analysis. The search was carried out in five electronic databases, grey literature and reference list of included studies. Two researchers independently screened and judged the quality of the included studies. The GRADE approach was used to assess the quality of the body of evidence.

Results: Fourteen studies met the inclusion criteria. Overall, the introduction of antimicrobial copper alloys surfaces in high-touch surfaces reduced the incidence of healthcare-associated infections by around a quarter (IRR 0.74, 95% CI 0.56 to 0.97; $p = 0.03$; low quality of the evidence). Additionally, the probability of achieving the recommended concentration of less than 250 colony forming units/100cm^2 was 2.73 times higher in copper surfaces than in regular surfaces (RR 2.73, 95% CI 1.83 to 4.07; $p < 0.00001$; moderate quality of the evidence). No significant difference was observed in the mortality rate.

Conclusion: This systematic review and meta-analyses suggest that the introduction of antimicrobial copper alloys in replacement of high-touch surfaces may have a positive effect on the incidence rate of HAIs. Larger clinical trials will be needed to show an impact on mortality.

KEY WORDS:

Healthcare-associated infections, copper, cross infections, antimicrobial surfaces

INTRODUCTION

Despite current worldwide efforts, the incidence of healthcare-associated infections (HAIs) is still a significant public health problem. The prevalence of HAIs varies worldwide, with incidence in Europe at 7.1% (1), in the United Kingdom at 9%, and in the United States at 4.5% in the year 2011 (2).

In ICUs in high-income countries, nearly 30% of patients are affected by at least one episode of HAIs, significantly increasing their morbidity, length of stay, readmission rate and mortality (3, 4).

In the last decade, the contribution of the contamination of metallic or plastic surfaces in hospitals to the acquisition of HAIs has been extensively described in the literature (5-9). Most common hospital-acquired pathogens have the ability to survive on surfaces for months, and be a continuous source of transmission (10).

To prevent this phenomenon, regular cleaning and disinfection are needed. However, multiple studies reported that existing hospital-cleaning techniques alone are not sufficient to restrain the growth of microorganism for prolonged periods of time (11-13).

In response to this situation, the utilization of antimicrobial surfaces to reduce the bacterial load in the patient environment has been proposed due to their potential to inactivate the microorganisms on contact (14).

The use of a relatively cheap technology, copper, seems like an opportunity to address this problem, because of its intrinsic broad-spectrum antimicrobial activity (15-17). A series of trials have been conducted to measure the effectiveness of copper surfaces in reducing HIAs, but no good-quality systematic review has been carried out to answer this question. We performed a systematic review of the literature with a meta-analysis, to evaluate the association between the use copper surfaces and incidence of the healthcare-associated infections (HAIs).

MATERIALS AND METHODS

Type of studies and interventions

Randomized control trials (RCTs), including cluster-RCTs, observational studies, and economic evaluations were included.

We included the studies comparing antimicrobial copper versus regular surfaces in patients' environments where surface cleaning/disinfection methods otherwise remained unchanged. In ambiguous cases, study designs were discussed and consensus reached.

Outcome measures

The recommended threshold of CFU/100cm2 is max. 250 CFU/100cm^2. The outcome measured for this review is the probability of copper surfaces achieving this threshold vs. regular surfaces. Consequently, the primary outcomes used in the review were incidence rate of healthcare-associated infections (HAIs), and the probability of achieving the recommended threshold of colony forming units/100cm^2, as well as adverse events related with the utilization of antimicrobial copper.

A secondary outcome was all-cause deaths among hospitalized patients, total reduction of microbial burden and cost-effectiveness.

Literature search

We identified studies between 1 January 2000 to 30 April 2016 by searching MEDLINE, EMBASE, LILACS, Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL Plus with Full Text (EBSCO) and Epistemonikos.

Search of grey literature was performed in the following databases: TRoPHI (The Trials Register for Promoting Health Interventions); Grey Literature Report (*http://www.greylit.org/library/search*); and NHS reports.

Data extraction

Two people (IP) and (RH) independently screened titles and abstracts of all identified articles to assess the eligibility for inclusion. Decision of inclusion of articles was reached by simple consensus. A third researcher (FR) resolved possible disagreement between the two reviewers.

The following data were extracted for each eligible study: type of study, participants and setting, types of intervention, comparison and outcomes measures, and results. Additional information was extracted when appropriate: funding sources, conflicts of interest, key conclusions, and references to other relevant studies.

Quality assessment

IP and FR independently assessed the risk of bias using the Cochrane risk of bias assessment tool for RCTs, classifying it as high, unclear or low (18). The risk of bias in non-randomized controlled studies was assessed using the ROBINS-I tool (Risk Of Bias In Non-randomized Studies of Interventions) (19).

The GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach was used to assess the quality of evidence. The Review Manager software (20) was used to import data to GRADEpro GDT (21) to create the Summary of findings tables. The quality of evidence was downgraded or upgraded after the assessment of the following domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias for the body of evidence that contributed to the report of an outcome.

Finally, the reviewer classified the quality of the body of evidence for each outcome following the guidelines recommended in the handbook published by the GRADE Working Group: the quality of evidence was classified as High, Moderate, Low or Very Low (22).

Measures of treatment effect

Studies were qualitatively assessed by the reviewers to determine whether to include them in a pooled meta-analysis. Authors stratified studies according to the outcome report for the meta-analysis and calculated rate ratio for difference in rates, risk ratio (RR) for dichotomous outcomes and when possible, hazard ratio (HR) for mortality outcomes.

The data was analyzed using Review Manager 5.3 (RevMan) (20) and results presented with 95% confidence intervals.

For rate outcomes, the incidence rates of different studies were pooled using the generic inverse variance with random effects.

For those trials where data on person-time at risk was not reported, we estimated the total person-time follow up in order to calculate the rate ratio.

RESULTS

The electronic search of databases generated a total of 1,961 potentially eligible results. After eliminating duplicates and screening by title and abstract, 110 articles were assessed full-text for eligibility. A total of 14 articles (13 full-text articles and one poster presentation) were included in the analysis. The PRISMA flow diagram with the results of the search is shown in Figure 1.

Description of studies

We included fourteen trials published between 2010 and 2016. Four studies were randomized clinical trials (23-26), one crossover study (27), eight non-randomized controlled studies (28-35), and one was an uncontrolled before/after study (36).

Twelve trials used antimicrobial copper alloys surfaces as intervention (23, 24, 26-35). One study used biocidal copper-oxide impregnated linens (36) and another study compared 50 regular pens used by ICUs nurses to 50 copper-containing pens (25). All institutions maintained their regular cleaning and disinfecting procedures in both arms during the trials. Four clinical trials measured the incidence rate of healthcare-associated infection as the primary outcome (23, 24, 42, 36), five of the studies reported the total amount of surfaces that achieved the optimal threshold of colony forming units/100cm^2 in both arms of the trial (25, 31-34), 10 studies measured the effectiveness of antimicrobial copper in reducing the total microbial burden (25-27, 29-35), three studies reported the mortality rate (23, 24, 42) and only one study reported adverse events (42). Description of all the included articles is presented in Appendix A.

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FIGURE 1: PRISMA flow diagram

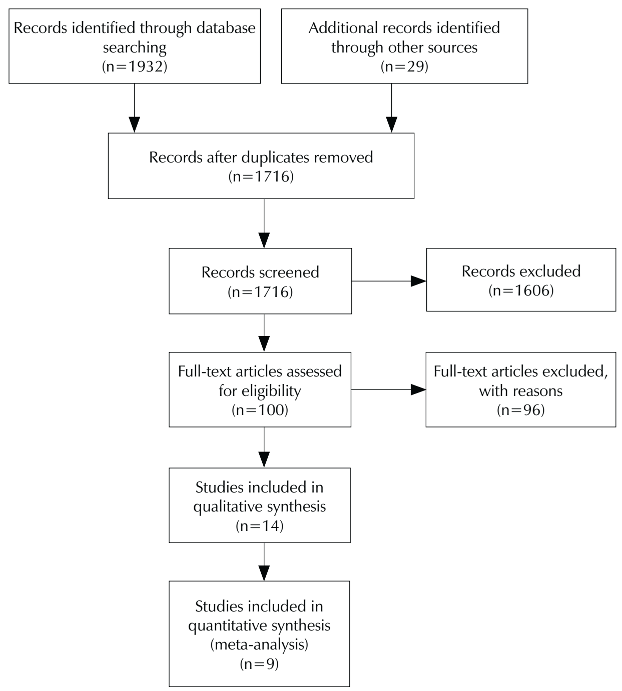


FIGURE 2: Risk of bias summary: review of authors' judgments about each risk of bias item for each included study

Risk of bias

Figure 2 shows the risk of bias summary for RCT and for one non-randomized trial with low risk of bias in the assessment with ROBINS-I tool.

Sequence generation and allocation concealment

One of the four randomized clinical trials, reported an adequate method for generating allocation sequence and allocation concealment (25). Two of them described the allocation sequence as random but did not present further details (23, 24). The allocation concealment was not evaluated in the before/after study (36). Eight studies were non randomized- controlled studies (28-35) and one was a crossover (27).

Blinding

We recognized that blinding of participants is not possible in trials using antimicrobial copper surfaces, as copper is a metal with a distinct colour and odour. Outcome evaluators could be blinded, so that was assessed. Only one study reported blinding of the outcome evaluators (28).

Incomplete outcome data

One study reported the exclusion of patients after randomization, but did not include them in the final analysis (23). Two of the studies reported a protocol deviation regarding the exposure to copper (mainly because of misplaced objects and patient movement). This lead to patients originally allocated in the intervention group to spend some hospitalization days in the control rooms and vice versa. An intention-to- treat analysis was carried out in both studies (23, 28).

Quality of non-randomized controlled studies

Eight studies were nonrandomized-controlled studies. The intervention was not blinded for hospital staff in any study. Among these eight studies, it is not clear if the outcome assessors were blinded to the intervention. Reasonable controls were used in all trials, and confounding was analyzed before the start of the trials. The surfaces included in the study were selected before the onset of the studies, and not based off the characteristics observed after the start of the intervention. The intervention groups were clearly defined in all studies. Two studies reported the introduction of the copper surfaces at least three months prior the start of the trial period (27, 29).

No major deviations from the intended intervention were observed in any trial. One study reported missing data in both intervention and control arms. Although the authors provided the reasons, loss of data was not evenly distributed between the intervention and control groups (17% vs. 11%, respectively) (31). Overall, four studies were judged as low risk of bias in all domains (28, 32-34), one study as moderate risk of bias (30), and three as serious risk of bias (29, 31, 35), including the before/after study (36).

HAI incidence

Only four studies (23, 24, 28, 36) reported the incidence rate of HAIs in both arms. Of these four, one was excluded from the meta-analysis because of the different type of intervention (copper-impregnated linen yarn) and different study design (36).

Overall, the introduction of antimicrobial copper alloys surfaces in high-touch surfaces reduced the incidence of HAIs by around a quarter (IRR 0.74, 95% CI 0.56 to 0.97; $p = 0.03$; three trials; 1569 participants; moderate quality of the evidence).

FIGURE 3: Forest plot of comparison: Antimicrobial copper surfaces in ICUs rooms vs. regular surfaces, Outcome Incidence of healthcare-associated infections: rate ratios

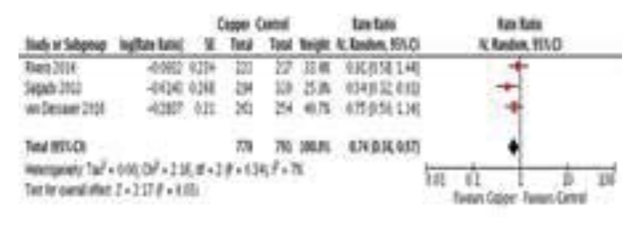
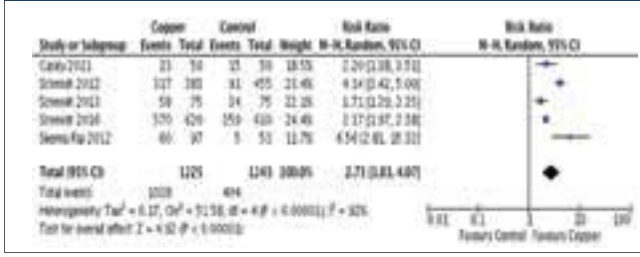


FIGURE 4: Forest plot of comparison: Antimicrobial copper surfaces vs. regular surfaces, Outcome Surfaces achieving minimum benchmark (<250 CFU/100 cm2): risk ratio



All of the studies measure the hand-washing rate in both groups to determine if any difference was present between groups. No difference was observed. To prevent the introduction of bias, cleaning staff were unaware of the study protocols or outcomes. The analysis is shown in Figure 3.

CFU threshold

Five studies reported the total of objects that achieved the recommended threshold (29, 31-34). All of them were included in the meta-analysis. Overall, the probability of achieving the recommended concentration of less than 250 CFU/100cm^2 was 2.73 times higher in copper surfaces than in regular surfaces (RR 2.73, 95% CI 1.83 to 4.07; p <0.00001; five trials; 2486 surfaces; moderate quality of the evidence). The analysis is presented in Figure 4.

Mortality rate

Three studies (23, 24, 28) reported the total number of participant's deceased in both arms and only one of them reported the HAIs-related mortality rate, founding no difference between both groups (IRR 1.17, 95% CI 0.3 to 4.36; p = 0.81) (24).

Total microbial burden reduction

Nine studies reported the total MB reduction as the main outcome. These studies could not be pooled due to methodological variability and missing data (26, 27, 29-35). All the studies reported a significant total microbial burden reduction between copper alloy surfaces and control surfaces. The percentage of reduction varies across the studies, from 37% to 100%. All of the studies were carried out in a clinical setting, with similar sample recollection between groups. The studies generally took samples in the morning, before the first cleaning and in the afternoon, after visiting hours. This was to detect any statistical difference between morning samples and night samples. Difference in hand-washing rates, room temperature, and humidity were assessed in the studies, reporting no significant difference between groups. Results for each study are presented in Table 1.

DISCUSSION

This systematic review and meta-analysis have demonstrated a reduction of about a quarter in the incidence rate of HAIs in patients hospitalized in rooms using antimicrobial copper surfaces. Also, the results presented here demonstrated that copper surfaces had an increased probability of achieving the recommended threshold of colony forming units/100cm2 than plastic/stainless steel surfaces, providing consistency in the findings

There were virtually no data available on mortality as an outcome. Due to the high number of participants needed to determine a significant difference between the two groups, it seems impractical that researchers choose mortality rate as a primary outcome in this kind of studies.

The studies included in this review were carried out in different settings: from ICUs rooms (both adult and pediatric) to a rural clinic in South Africa. Based on these results, it is clear that irrespective of the clinical setting, copper surfaces is associated with achieving the cleaning threshold of CFU/100cm^2 and reduction of total microbial burden. Furthermore, there may a benefit of introducing copper surfaces for reducing the rate of HAIs in ICUs rooms.

Based on the studies included, and in previous studies (37, 38) there were no adverse effects associated with copper alloys surfaces.

All of the studies were carried out in high-income countries, except from one. Therefore, it is unclear what would be the real impact from copper on HAI rates in low and middle-income levels (LMICs). As stated before, these countries present a higher rate of HAIs than HICs, so it is possible that the introduction of copper have a bigger benefit in those countries that the one presented here.

The follow-up duration in all included studies was relatively short (12 months the longest). It is unclear if the reduction of the incidence of HAIs would be the same after this period of time, or if the efficacy of copper surfaces would suffer damage and deteriorate from chemical cleaning and disinfection.

Based on the studies included in this review, it is clear that the use of antimicrobial copper cannot replace regular cleaning/disinfection. No study attempted replacing this process with copper. All of them added the antimicrobial copper to regular cleaning. Therefore, we are unclear what is the effectiveness of copper as an isolated intervention in reducing the rate of HAIs.

In terms of cost of the intervention, no proper economic evaluation was identified in the systematic review of the literature. A conference poster, presented by Taylor et al. of the University of York, used an economic model to answer this question (39). The cost of replacing six high-touch surfaces in 20 ICU beds with

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TABLE 1: Total microbial burden reduction: Copper surfaces vs. regular surfaces

Study	Intervention	Sample Size	Colony Forming Units/100 cm² Mean	Colony Forming Units/100 cm² Standard Error of Mean	% Reduction	p Value
Prado et al, 2010	Copper	90 rooms with 990 copper surfaces	1.851 (per room)	NR	84%	<0,0001*
	Control	90 rooms with 990 control surfaces	11.620 (per room)	NR		
Schmidt et al, 2012	Copper	501 surfaces	2.521	342	83%	<0,0001*
	Control	511 surfaces	14.813	1.812		
Casey et al, 2010	Copper	10 surfaces	No overall mean reported	NR	Between 90% and 100%	Statistical significance in nine of the ten paired analyses (and in all ten unpaired analyses)$
	Control	10 surfaces	No overall mean reported	NR		
Karpanen et al, 2012	Copper	14 surfaces	No overall mean reported	NR	8/14 surfaces had significant lower microbial counts	<0,05@
	Control	14 surfaces	No overall mean reported	NR		
Marais et al, 2010	Copper	1 room with 11 copper surfaces	59.000	NR	71%	<0,001 ^
	Control	1 room with 11 regular surfaces	200.000	NR		
Mikolay et al, 2010	Copper	144 surfaces	NR	NR	37%	>99.9%&
	Control	144 surfaces	NR	NR		
Schmidt et al, 2013	Pre-cleaning Copper (11.5 hours since last cleaning)	383 surfaces (Bed Rails)	698	368	88%	0.006$
	Pre-cleaning Control (11.5 hours since last cleaning)	455 surfaces (Bed Rails)	6.102	2.572		
	Hour 6.5 after cleaning Copper	383 surfaces (Bed Rails)	434	236	92%	<0,0001$
	Hour 6.5 after cleaning Control	455 surfaces (Bed Rails)	5.198	2.368		
Schmidt et al, 2012	Copper	668 surfaces	172	NR	88%	<0,0001*/$
	Control	652 surfaces	1.381	NR		
Seesma Rai et al, 2012	Copper	97 surfaces	NR	NR	89%	<0,0001*
	Control	53 surfaces	NR	NR		

* Kruskal-Wallis test for two groups
$ Wilcoxon signed Rank test P-value and Mann-Whitney U test
@ Mann-Whitney U test
^ Nor reported & T-test
NR: Not Reported

TABLE 2: Summary of findings (SoF)

Antimicrobial copper compared to control for reducing HAIs
Patient or population: Adults and children hospitalized in ICUs rooms/high-touch surfaces
Setting: Hospitalized patients **Intervention:** Antimicrobial copper surfaces **Comparison:** Regular surfaces

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with Control	Risk with Antimicrobial Copper				
Healthcare-associated infections incidence rate assessed with: per 1000 patients-day follow up: range 11 months	159 per 1.000	118 per 1.000 (89 to 155)	Rate ratio 0.74 (0.56 to 0.97)	1569 (3 RCTs)	⊗⊗⊗◯ MODERATE[1, 2]	
Surfaces achieving minimum benchmark (<250 CFU/100 cm²)	325 per 1.000	887 per 1.000 (595 to 1.000)	RR 2.73 (1.83 to 4.07)	2468 (5 observational studies)	⊗⊗⊗◯ MODERATE[3]	
HAIs-related mortality rate: follow up: range 11 months to 12 months	126 per 1.000	123 per 1.000 (92 to 161)	Rate Ratio 1.17 (0.3 to 4.36)	440 (1 RCT)	⊗◯◯◯ VERY LOW[1, 4]	

Antimicrobial Copper compared to Control for reducing HAIs
Patient or population: Adults and children hospitalized in ICUs rooms/high-touch surfaces
Setting: Hospitalized patients **Intervention:** Antimicrobial copper surfaces **Comparison:** Regular surfaces

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with Control	Risk with Antimicrobial Copper				
Adverse effects	Adverse effects were not observed among the health care workers or patients exposed to copper-surfaced items.			515 (1 RCT)	⊗⊗◯◯ LOW[1, 4]	
Total microbial burden reduction	-	-	-	(9 studies)	-	Not pooled (See Table 1)

*The risk in the intervention group **(and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).**

[1] Risk of bias
[2] CI near 1
[3] Heterogeneity
[4] Wide CI

- CI: **Confidence interval**; RR: **Risk ratio**
- GRADE Working Group grades of evidence
- High quality: **We are very confident that the true effect lies close to that of the estimate of the effect**
- Moderate quality: **We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different**
- Low quality: **Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect**
- Very low quality: **We have very little confidence in the effect estimate: The true effect is likely to be substantially different**

antimicrobial copper was calculated, based on expert opinions, to be £30,600 higher than baseline rooms (£105,000 vs. £74,400). The average cost of infection was based in a previous study (40) at £1,000 per patient-day. In conclusion, the model predicts that the cost of implementing copper in a 20 bed ICU will be recovered in two months. In a five-year breakdown, there is a potential cost saving of £1.9m associated with the introduction of copper alloys and 352 fewer infections. The cost per infection averted is calculated to be £94,10. These results must be analyzed with caution. All costs and other information used in the model are based in the United Kingdom setting, a HIC, making difficult to extrapolate the results to other settings. The cost of the intervention, and other possible costs should be described in more detail. In spite of this, these results are promising, with interesting potential use for policymakers.

One limitation of this review is that we only included studies published in Spanish or English. As the original search did not include language filters, one study in Greek and one in German were found that could have met the inclusion criteria, but were excluded (41, 42). Another potential bias of this review is that copper-related private companies funded almost all of the studies included in the analysis. It was not possible to assess the publication bias with a funnel plot. The studies that assessed the outcomes selected in this review were fairly small-sized, with two of them not being sufficiently powered according to their statistical power calculation assumptions. Because of this, is unclear if the reduction in the incidence of HAIs would be maintained in larger trials. Nevertheless, considering that there is no biologic plausibility that lower microbial burden should lead to an increase of HAIs rates, it is conceivable that better-structured RCTs and times-series experimental designs could demonstrate an even greater reduction in the HAIs rates. Additionally, all of the studies presented important protocol deviations. In some cases, patients from the control group were exposed to copper and patients from the intervention group were exposed to regular surfaces. This may have contributed to underestimating the real effectiveness of copper in reducing the HAIs rates.

The findings of this systematic review showed that additional research to assess the efficacy of antimicrobial copper in preventing HAIs in necessary. There are only three studies that reported this outcome. More high-level quality RCTs and time-series experimental studies are needed to be more certain in the positive results presented here. These future studies need to have a longer follow-up period, be sufficiently powered, and present fewer probabilities of introducing bias and confounding.

Similar studies are needed in LMICs, where actual evidence is limited. It is essential to assess the potential benefits of antimicrobial copper surfaces in countries where the rate of HAIs is significantly higher than in the rest of the world. In the same way, studies focusing in sub-groups with more risk of acquiring HAIs could be useful for policymakers in order to prioritize resources. A proper economic evaluation of the introduction of this technology is needed to determine the monetary impact of this intervention.

The increasing rate of antimicrobial resistance and high rates of HAIs, especially in LMICs, are some of the major public health concerns in the world. Different types of interventions have been proposed to tackle this problem. Copper, a safe, effective and relatively cheap technology may be considered in addition to current policies in order to deliver a safe medical care to all patients. The reduction of the incidence rate of HAIs presented in this systematic review by nearly a quarter shows that copper has the potential to revolutionize the fight against this public health issue.

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APPENDIX A: Characteristic of included studies

Study	Country	Design	Population and setting	Intervention and Control	Outcome measure	Author's conclusion
Casey et al, 2010 (29)	United Kingdom	NR-C	Busy acute medical ward, which included gastroenterology patients. United Kingdom	I: Three copper-containing items; toilet seat, a set of brass tap handles and a brass door push plate C: Regular surfaces	Median CFU/cm^2	"The results of this trial clearly demonstrate that copper-containing items offer the potential to significantly reduce the numbers of micro-organisms in the clinical environment. However, the use of antimicrobial surfaces should not act as a replacement for cleaning in clinical areas, but as an adjunct in the fight against HCAI."
Casey et al 2011 (25)	United Kingdom	RCT	Two critical care units at the University Hospitals Birmingham National Health Service Foundation Trust	I: 50 copper-containing pens (CuZn15; 85% copper, 15% zinc) C: 50 stainless steel pens	Median number of CFU isolated	"Our findings clearly demonstrate that the use of copper-containing pens significantly reduces the level of microbial contamination on writing instruments. Thus, copper pens may provide a tool to prevent reinoculation of decontaminated hands. The use of copper also may be applied to other surfaces in the healthcare setting."
Karpanen et al, 2012 (27)	United Kingdom	CO	Acute care medical ward with 19 beds at a large university hospital	I: Antimicrobial copper surfaces in high-touch surfaces C: Regular surfaces	CFU reduction	"Copper furnishings may therefore be a beneficial adjunct to standard hospital cleaning and hygiene procedures in reducing environmental contamination and the risk of cross-transfer of microorganisms within the healthcare environment."
Lazary et al, 2014 (36)	Israel	B/A	108 patients hospitalized in the Head Injury Ward at The Reuth Medical Centre, Tel Aviv	I: Copper-containing linens (replacing all the regular non- biocidal linens and personnel uniforms with copper oxide impregnated biocidal products) C: Regular linens	Rate of HAIs, Rate of fever days, Total days of antibiotics, Cost reduction	"The results of this study clearly demonstrate that the use of copper oxide impregnated linens in a long-term care ward reduce HAI and antibiotic and other infection-related treatments, and can be an important addition to the arsenal of measures taken in hospitals to reduce an important source of nosocomial pathogens and the risk of HAI."

Study	Country	Design	Population and setting	Intervention and Control	Outcome measure	Author's conclusion
Mikolay et al, 2010 (30)	Germany	NR-C	144 surfaces in an oncological/pneumological and a geriatric ward at Asklepios Hospital Wandsbek, Hamburg	I: Antimicrobial copper alloys surfaces C: Aluminium and plastic surfaces	CFU reduction	"The presented data clearly indicate that use of copper alloys for touch surfaces decreases the number of living bacterial cells adhering to these surfaces. Further, these surfaces probably decreased the repopulation rate of these germs."
Prado et al, 2010 (26)	Chile	RCT	ICU rooms at Hospital del Cobre de Calama, Chile	I: Copperized surfaces (bed rails, bed lever, tray tables, chair arms, touch screen monitor pen, and IV poles) C: Regular surfaces	The mean microbial burden (mMB), determined as colony forming units (CFU)/100cm^2	"The antimicrobial effects of copper on critical contact surfaces within ICU rooms was evident and significant in this hospital located in this arid region of Chile throughout the 30 week trial. The antimicrobial properties of copper were of a broad spectrum in that a reduction in the total microbial burden was seen for each class of microbe characterized in ICU rooms containing copper."
Seema Rai 2012 (31)	United States	NR-C	Outpatient infectious disease clinic, United States	I: 134 copperized surfaces I high touch surfaces of phlebotomy chairs C: 60 noncopperized surfaces	Total CFU/100 cm^2 reduction.	"Covering high-touch surfaces with antimicrobial copper may provide an adjunctive infection control measure to minimize the spread of bacteria. The microbicidal activity of copper was effective in significantly reducing the total median burden by 90% on arm tops and by 88% on copperized trays. Deployment of copper surfaces within high-risk patient environments is warranted to enhance patient safety."
Rivero et al, 2014 (24)	Chile	RCT	440 patients hospitalized in ICU rooms at Hospital Van Buren, Valparaiso	I: Antimicrobial copper surfaces C: Regular surfaces	HAIs incidence rate, mean day average before HAIs, Total antibiotic cost, HAIs mortality rate.	"The use of copper as a surface in the ICU showed no statistically significant differences in rates of nosocomial infections during the study period, however, these results could be related to the sample size."

Study	Country	Design	Population and setting	Intervention and Control	Outcome measure	Author's conclusion
Salgado et al, 2013 (23)	United States	RCT	614 patients in the ICUs of 3 hospitals, US	I: Antimicrobial copper surfaces C: Regular surfaces	Rates of incident HAI and/or colonization with methicillin-resistant Staphylococcus aureus (MRSA) or vancomycin-resistant Enterococcus (VRE)	"Patients cared for in ICU rooms with copper alloy surfaces had a significantly lower rate of incident HAI and/or colonization with MRSA or VRE than did patients treated in standard rooms. Additional studies are needed to determine the clinical effect of copper alloy surfaces in additional patient polulations and settings."
Schmidt et al, 2012 (32)	United States	NR-C	16 rooms in ICUs in three hospitals, US	I: Copper-alloy surfaces C: Regular surfaces	The mean microbial burden (mMB), determined as colony forming units (CFU)/$100cm^2$	"The introduction of copper surfaces to objects formerly covered with plastic, wood, stainless steel, and other materials found in the patient care environment significantly reduced the overall MB on a continuous basis, thereby providing a potentially safer environment for hospital patients, health care workers (HCWs), and visitors."
Schmidt et al, 2013 (33)	United States	NR-C	75 beds in ICUs rooms	I: Copper surfaces in bed rails C: Regular surfaces	The mean microbial burden (mMB), determined as colony forming units (CFU)/$100cm^2$	"Copper-alloyed surfaces offer a continuous way to limit and/or control the environmental burden. Hospital and environmental services need not perform additional steps, follow complex treatment algorithms, obtain "buy-in" from other providers, or require additional training or oversight."
Schmidt et al, 2016 (34)	Chile	NR-C	8 rooms from the ICU (PICU) and 8 rooms from the intermediate care unit (PIMCU), Roberto del Rio, Santiago	I: Copper surfaces in high-touch surfaces C: Regular surfaces	CFU/100 cm^2	"Copper surfaces warrant serious consideration when contemplating the introduction of no-touch disinfection technologies for reducing burden to limit acquisition of HAIs."

Study	Country	Design	Population and setting	Intervention and Control	Outcome measure	Author's conclusion
von Dessauer et al, 2016 (28)	Chile	NR-C	8 rooms from the ICU (PICU) and 8 rooms from the intermediate care unit (PIMCU), Roberto del Rio, Santiago	I: Copper surfaces in high-touch surfaces C: Regular surfaces	Diagnosis of an HAI event associated with patient stay within the PICU or PIMCU Safety	"Exposure of pediatric patients to copper-surfaced objects in the closed environment of the intensive care unit resulted in decreased HAI rates when compared with noncopper exposure; however, the RRR was not statistically significant. The clinical effect size warrants further consideration of this intervention as a component of a systems-based approach to control HAIs."
Marais et al, 2010 (35)	South Africa	NR-C	Two consulting rooms in a rural region of the Western Cape, South Africa.	I: Copper sheets on touch surfaces C: Regular surfaces	Mean CFU/100cm^2 reduction	"The study showed that the antimicrobial activity of copper touch surfaces reduced environmental bioburden to a far greater extent than standard materials and would be beneficial in the healthcare environment."

NR-C: Nonrandomized, controlled study CO: Crossover

RCT: Randomize Controlled Trial B/A: Before and after study CFU: Colony forming units