Cochrane Australia

Systematic review of antimicrobial surfaces to reduce infection rates in hospitalised populations

Report prepared by
Cochrane Australia

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Contents

In June 2016 Cochrane Australia was contracted by the National Health and Medical Research Council (NHMRC) to design and undertake this systematic review. This review is one of several independent contracted evidence evaluations being undertaken to update or inform new sections of the *2010 Australian Guidelines for the Prevention and Control of Infection in Healthcare*. The design and conduct of the review was done in collaboration with the Infection Control Guidelines Advisory Committee (ICGAC) and NHMRC.

Authors and contributors to the review

Sue Brennan	Senior Evidence Officer responsible for leading the review. Contributed to the design and conduct of the review (e.g. screening, data extraction, risk of bias assessment). Wrote the protocol and systematic review report with contributions from other authors as described.
Steve McDonald	Developed the search strategy and conducted the search. Wrote the search methods and results. Critical review of the protocol and systematic review report.
Joanne McKenzie	Developed the analysis plan and conducted the analysis. Wrote the analysis methods, method for reporting treatment effects and results from the times series analyses. Critical review of the protocol and systematic review report.
Allen Cheng	Provided expert clinical advice, especially in relation to selection of studies for the review, interpretation of analyses and reporting results. Wrote the implications for clinical practice. Critical review of the protocol and systematic review report.
Sally Green	Critical review of the protocol and systematic review report.
Kelly Allen	Conducted searches of trial registers. Extracted data for time series analyses.
Jane Reid	Screened citations and full-text articles, extracted data and assessed risk of bias assessment of included studies (critical appraisal).

Declarations of interest

All authors declare they have no financial, personal or professional interests that could be construed to have influenced the conduct or results of this systematic review.

Professor Allen Cheng is a member of the Infection Control Guidelines Advisory Committee (ICGAC).

1. Background

The National Health and Medical Research Council (NHMRC), in collaboration with the Australian Commission on Safety and Quality in Health Care (the Commission), is updating the 2010 *Australian Guidelines for the Prevention and Control of Infection in Healthcare* (2010 Guidelines) to ensure the Guidelines reflect the best available evidence and are current and relevant for the Australian context. This systematic review is one of several contracted evidence evaluations being undertaken to update or inform new sections of the 2010 Guidelines. Cochrane Australia was contracted to undertake this independent systematic review of environmental fittings with antimicrobial properties (antimicrobial surfaces) to provide the NHMRC and the Commission with assurance that this revision of the Guidelines is grounded in the most up-to-date and relevant scientific evidence.

1.1 Description of the condition and setting

The 2010 Guidelines identified healthcare-associated infections (HAIs) as the most common complication affecting patients in hospital. Acquired in healthcare facilities or as a result of healthcare interventions, these infections can cause significant morbidity for patients and are costly to the health system. Infections caused by key hospital pathogens, including multiresistant organisms (MROs) and *Clostridium difficile* are of particular concern (National Health and Medical Research Council 2010). Methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin resistant enterococcus (VRE) are clinically significant as they are associated with increased healthcare costs and poorer patient outcomes (McLaws 2009, Slimings 2014). While less prevalent, carbapenemase-producing Enterobacteriaceae (CPE) are resistant to antibiotics used to treat the most serious infection (so called "last resort" antibiotics), so preventing their spread is critical to ensuring ongoing availability of effective antibiotics (Falagas 2009, Weber 2013, Public Health England 2014, Department of Health and Human Services Victoria 2015).

1.2 Description of the intervention and how it might work

Healthcare-associated infections are potentially preventable, and hence the aim of the 2010 Guidelines was "to promote and facilitate the overall goal of infection prevention and control ... through the implementation of practices that minimise the risk of transmission of infectious agents" ((National Health and Medical Research Council 2010), p7). Based on "the best available evidence and knowledge of the practicalities of clinical procedures" at the time, the guideline made recommendations about implementing a broad range of interventions. These interventions included standard precautions to be applied at all times, and transmission-based precautions to be implemented "in the presence of suspected or known infectious agents that represent an increased risk of transmission" and in "the management of multi-resistant organisms (MROs) or outbreak situations" ((National Health and Medical Research Council 2010), p11).

Environmental controls, including cleaning and disinfection, are used to prevent transmission of infectious agents to patients occurring either through direct contact with surfaces or indirect contact via an intermediary ((National Health and Medical Research Council 2010), p21). The 2010 Guidelines recommend routine cleaning of surfaces with detergent solution as a standard precaution (i.e. a first-line approach that should be used with all patients). Disinfection is recommended in addition to cleaning as a transmission-based precaution. Its use is recommended "where the suspected or confirmed presence of infectious agents represents an increased risk of transmission" and for the management of MROs (e.g. MRSA, MRGN, VRE). Unlike cleaning with detergent, disinfection involves the use of chemical or physical methods to kill microorganisms (including pathogens)

(Rutala 2008, Therapeutic Goods Administration 2012). In Australia, claims of disinfectant properties are subject to regulation by the Therapeutic Goods Administration (TGA) and approved disinfectants are registered after demonstrating compliance with essential principles for quality, safety and performance (Therapeutic Goods Administration 2012).

This review focuses on the use of disinfectant modalities that have emerged or undergone further development for use in healthcare facilities subsequent to the review of evidence for the 2010 Guidelines. Specifically, the review considers the effects of self-disinfecting materials used to coat or impregnate surfaces in patient care areas. These materials include heavy metal alloys (copper and silver), light activated antimicrobial coatings, and surfaces with altered topography designed to inhibit bacterial growth. The review examines the effects (including harms) of using each of these interventions, compared to standard materials, on clinical outcomes.

The use of surfaces, fittings or furnishing containing materials with antimicrobial (self-disinfecting) properties has been suggested to reduce the concentration of bacteria on surfaces, in turn reducing environmental exposure to pathogens. The expected benefit is a reduction in colonisation and infection. Self-disinfecting materials considered for use in healthcare facilities include the use of heavy metal alloy coatings on furniture and fittings (e.g. copper or silver coatings for bedrails, tray tables, call buttons, IV stands), coatings with antimicrobial properties activated by light, and materials that inhibit bacterial colonisation of surfaces (i.e. surfaces with altered topography) (Leas 2015). Previous reviews have found little or no evidence about the safety of these materials (Leas 2015).

2. Objectives

To examine the effect of environmental surfaces, fittings or fixtures with antimicrobial properties on infection rates in hospital patients compared with standard surfaces on clinical outcomes.

3. Methods

Methods for this review were pre-specified in the protocol for the review (Brennan 2016) and are based on the *Cochrane Handbook for Systematic Reviews of Interventions* and the Cochrane Effective Practice and Organisation of Care group (Effective Practice and Organisation of Care (EPOC) 2015). Additional methodological considerations pertinent to public health questions are addressed where appropriate (Armstrong 2011). The review is reported in accordance with the PRISMA statement (Liberati 2009, Moher 2009). The methods are described in full, together with documentation of any changes to the protocol, in the accompanying Technical report. A brief outline of the approach follows.

3.1 Criteria for considering studies for this review

3.1.1 Types of participants

Any admitted patient in an eligible setting.

3.1.2 Types of settings

Type of healthcare facility: Studies set in hospital wards (primarily acute care), including inpatient facilities and patient rooms, were considered for inclusion in the review. Studies set in countries with health systems broadly comparable to those in Australia were eligible.

3.1.3 Types of interventions

Studies evaluating the effects of environmental surfaces coated or impregnated with antimicrobial (self-disinfecting) materials including:

- Heavy metal alloys (copper, silver) coating or impregnation
- Light activated antimicrobial coatings
- Altered topography designed to inhibit microbial colonisation of surfaces
- Other antimicrobial releasing agents.

Types of surfaces

Eligible studies must have involved interventions for use in patient surroundings, defined in the 2010 Guidelines as "inanimate surfaces that are touched by or in physical contact with the patient and surfaces frequently touched by healthcare workers while caring for the patient" (p262). Any high-touch surface was eligible including hard nonporous and porous surfaces.

3.1.4 Types of comparators

Studies reporting a standard environment (i.e. not an antimicrobial surface) as the comparator were eligible for inclusion.

Studies that directly compared the effects of two or more of the interventions eligible for this review were also excluded.

3.1.5 Types of outcome measures

Primary outcome
Healthcare associated infection (confirmed or unconfirmed) arising from the following pathogens:

- *Clostridium difficile* (*C. difficile*)
- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Vancomycin resistant enterococcus (VRE)
- *Acinetobacter* spp.
- An Enterobacteriaceae (including *Escherichia coli*, *Klebsiella sp. Enterobacter sp.* and others) where a carbapenemase producing gene is detected (including MBLs and KPC) resulting in a high minimum inhibitory concentration (MIC) to carbapenems in vitro (based on standard lab criteria including EUCAST or CLSI) (Department of Health and Human Services Victoria 2015, Guh 2015)
- Extended spectrum beta lactamase (ESBL) producing organisms (includes extended-spectrum cephalosporin-resistant CPE listed above and *Acinetobacter* spp. (Falagas 2009).

A post hoc decision was made to broaden this criterion to include eligible studies that reported any hospital-acquired infection, irrespective of pathogen. This decision was taken due to the sparsity of evidence that met this a priori inclusion criterion. Only one study, Salgado 2013 met the original criterion, with only the secondary outcome, not the primary, meeting this inclusion criterion. This decision to broaden the criterion led to the inclusion of one additional study, of which we had prior knowledge before changing the criterion. However the decision was taken prior to any data extraction or analysis.

Clinical evaluation or signs of infection must have been accompanied by testing to confirm acquisition of an MRO or *C. difficile*. Studies that reported outcomes in which infection and colonisation were not distinguished (e.g. acquisition of MRSA), combined outcomes across multiple pathogens (e.g. acquisition of any MRO), or reported unconfirmed infection (e.g. clinical isolates alone), were eligible.

Secondary outcome

Colonisation with multi-resistant organisms (MROs) where colonisation is defined as the "sustained presence of replicating infectious agents on or in the body without the production of an immune response or disease" ((National Health and Medical Research Council 2010), p17).

Adverse effects

Data on adverse effects (harms, safety) was collected and included in our review when the data were reported in included studies that measured at least one of the primary or secondary outcomes (i.e. infection, colonisation), or in eligible studies that explicitly aimed to examine adverse effects. We considered only patient or health professional health outcomes, not broader impacts on health services delivery.

3.1.6 Types of studies

- Randomised trials (RTs).
- Non-randomised trials (NRTs).
- Interrupted-time-series (ITS) and repeated measures (RM) studies, including studies with data suitable for reanalysis as a time series.
- Controlled before-after (CBA) studies.

The types and definition of study designs eligible for inclusion are based on guidance from the Cochrane Effective Practice and Organisation of Care (EPOC) group (Effective Practice and Organisation of Care 2013), and are provided in the Technical Report.

Date and language restrictions. Only studies published from 2006 onwards were eligible for inclusion. Studies published in languages other than English were ineligible except for randomised trials.

3.2 Search methods for identification of studies

The overall search approach was based on the search methods used for the recent Technical Brief prepared for the Agency for Healthcare Research and Quality (AHRQ) (Leas 2015). The search terms include concepts relevant to a second commissioned review for the 2010 guidelines (novel disinfectants), for which searching and screening was conducted concurrently.

Potentially eligible studies published between 2006 and 2014 were identified from the lists of included and excluded studies from the AHRQ report. The lists were supplemented by additional searches for the same period for terms or concepts not covered by the AHRQ report, and by an update of the AHRQ search for the period January 2015 to August 2016. The review considered both peer reviewed literature, as well as unpublished literature. No language or geographic limitations were applied when searching.

3.2.1 Search terms

The search strategy was developed for Embase via Ovid (used for the AHRQ report and includes all MEDLINE records). Methods for developing terms, use of filters and syntax for the search are in the Technical Report.

3.2.2 Bibliographic and grey literature databases

We searched Embase (via Ovid) for records added since January 2015 (back to 2006 for terms not covered by AHRQ). The search strategy was translated for PubMed (limited to in-process citations and citations not indexed in MEDLINE), the Cochrane Library and CINAHL Plus. We also searched ClinicalTrials.gov. The full search strategies for each source are provided in the Technical report, Appendix 1.

3.2.3 Other sources

We screened all studies included in the AHRQ report plus all studies that had been excluded from the AHRQ report after full-text screen. Checks of reference lists and forward citation searches were also use.

3.3 Data collection and analysis

3.3.1 Selection of studies

Two reviewers (SB, JR) independently screened citations (titles and abstracts) and full text studies for inclusion in the review against the eligibility criteria, with discussion and specialist advice from our review content expert (AC) and our biostatistician (JM) where disagreement arose. Citations that did not meet the inclusion criteria were excluded and the reasons for exclusion were recorded at full-text screening. Multiple papers from the same study were matched using trial registry numbers, bibliographic and study design details.

3.3.2 Data extraction and management

For each included study, two reviewers independently extracted data using a pre-tested data extraction and coding form. Disagreements were resolved by discussion and with advice from the review content expert (AC) and biostatistician (JM). The Technical report lists the information extracted from each study (section 3.3.2).

3.3.3 Assessment of risk of bias of included studies

Two reviewers (SB, JR) independently assessed the risk of bias for each included study, using the Cochrane risk of bias tool (Higgins 2011) and additional criteria developed by the Cochrane EPOC Group (Effective Practice and Organisation of Care 2015) for cluster randomised trials and ITS studies. Disagreements were resolved by discussion, with advice from a third reviewer (JM) if agreement could not be reached. The domains assessed are listed in the Technical report (section 3.3.3).

For each study, we report our judgment of risk of bias (low, high, unclear) by domain and provide a rationale for the judgment with supporting information (summarised in the results and reported in full in Technical report, Appendix 4, characteristics of included studies). Summary assessments of risk of bias for each comparison and outcome were used in determining the overall quality of the body of evidence using GRADE.

3.3.4 Measures of treatment effect

Non-randomised trials. We calculated incident rate ratios for the infection outcomes, along with 95% confidence intervals and p-values.

3.3.5 Unit of analysis issues, missing data, assessment of heterogeneity and reporting bias

There were no unit of analysis issues. Methods for dealing with missing data, and assessment of heterogeneity and reporting bias are described in the Technical report (sections 3.3.6, 3.3.7, 3.3.8).

3.3.6 Data synthesis

In line without our protocol, we did not combine effect estimates from studies using non-randomised study designs. No randomised trials were included in the review, hence no-meta-analyses were conducted. We present available effect estimates (95% confidence intervals, p-values), along with risk of bias assessments and study characteristics, in tables structured by comparison, outcome, and study design.

3.3.7 Summary of findings tables and assessment of quality of the body of evidence

For each comparison and outcome, we assessed the quality of the evidence using the GRADE approach. In accordance with GRADE guidance (Schunemann 2013), we assessed the following five domains: (1) risk of bias,

(2) inconsistency, (3) imprecision, (4) indirectness, and (5) publication bias. A judgement was made about whether there were serious, very serious or no concerns in relation to each domain. While some overall conclusions are drawn across studies, most studies addressed different questions (comparisons, type of pathogen, patient population) or had other important differences that meant synthesis of effects across studies would be uninterpretable. For this reason, we report GRADE assessments for individual studies and describe our approach in the Technical report (section 3.3.10).

Evidence profiles (including a summary of findings and an evidence statement) were prepared for each comparison and outcome. The evidence profile includes estimates of treatment effects, and the overall GRADE (rating of quality). The evidence profiles also include (1) the study design(s), number of data collection points (time series studies) or number of participants contributing data (i.e. the type and size of the evidence base), (2) our assessment of each of the five GRADE domains (with footnotes explaining judgements), and (3) a plain language statement interpreting the evidence (i.e. an evidence statement describing clinical impact).

4. Results

4.1 Results of the search

The searches of Embase, PubMed, Cochrane Trials Register and CINAHL Plus were conducted on 23 August 2016 and retrieved 3388 records. Screening the references considered for the AHRQ report and ClinicalTrials.gov added a further 622 records. After removing duplicates, we screened 3854 records. Figure 1 shows the flow of references through the review. (See Technical report, Appendix 1 for the search results for each source.) The figure includes all studies screened for this review, and the review of novel disinfectants. The full-text of 172 reports were screened; from which 165 were excluded from the antimicrobial surfaces review.

The full publication of six studies (one of antimicrobial surfaces; five of novel disinfectants) that were potentially eligible but which were reported only as conference abstracts were searched for separately in Scopus and PubMed. We also used SCOPUS to conduct forward citation searches for all studies included in the review. One additional publication was identified which was the full publication from one of the conference abstracts; this study was excluded following full-text review. The six remaining studies were all of novel disinfectants, so were excluded from the current review.

After screening and full-text review, we included four studies (reported in three papers and four trial registry entries) in the antimicrobial surfaces review. Two of the studies reported in registry entries are yet to be published so are listed as ongoing studies (Lautenbach 2015; Shankaran 2015).

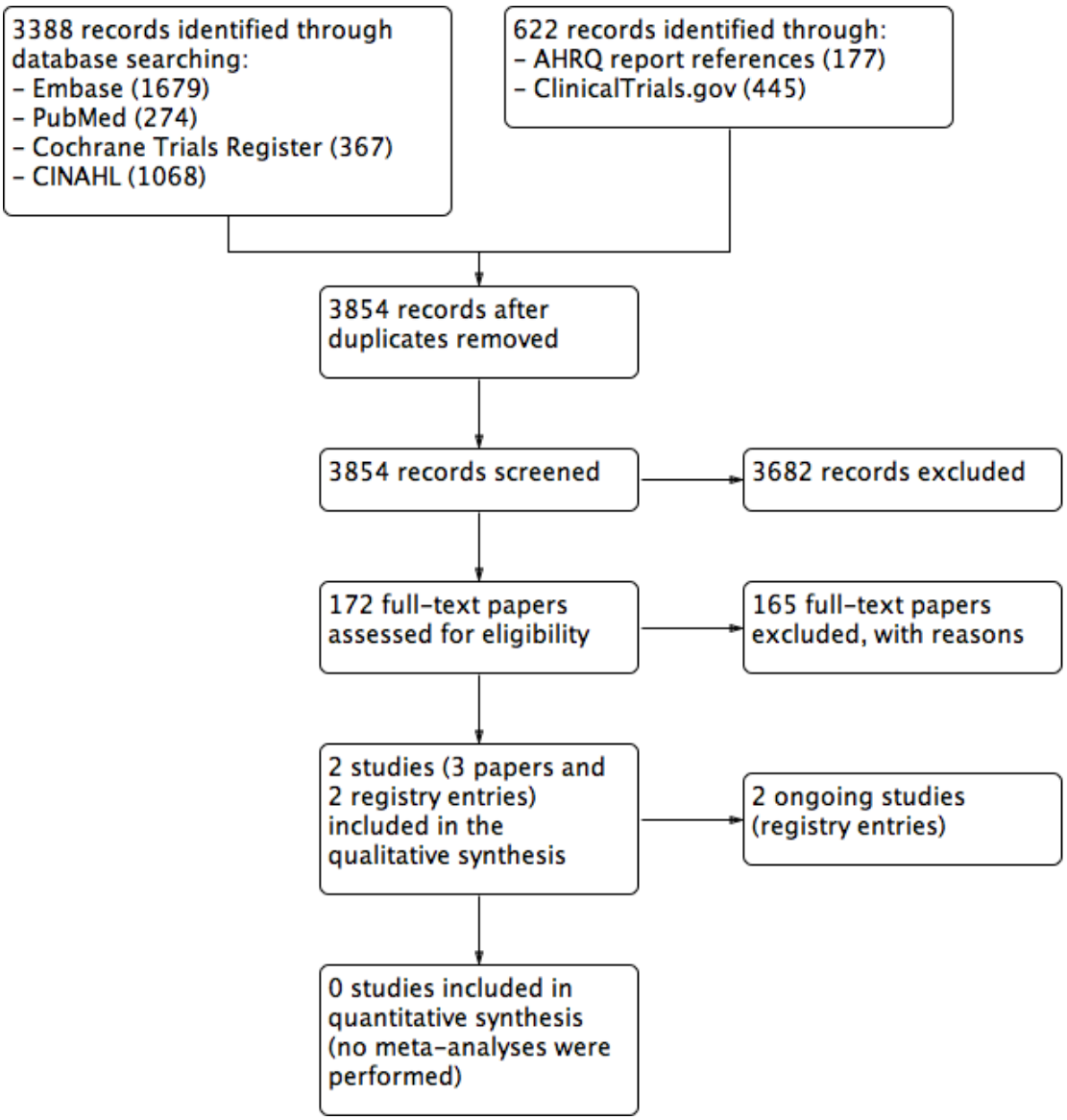

Figure 1: Study flow diagram

4.2 Description of studies

Included studies

Characteristics of the two included studies are summarised in Table 1 and reported in detail in Technical report, Appendix 4 (Characteristics of included studies). Both included studies examined the effects of copper surfaces compared to standard surfaces on hospital-acquired infection (any type, any pathogen). No eligible studies were identified that examined the effects of any other type of antimicrobial surfaces.

Copper surfaces compared to standard surfaces

Settings and populations. Both studies were set in intensive care units. Salgado 2013 was set in adult intensive care units (ICUs) at three participating hospitals. At all sites, intervention rooms were adjacent to control rooms (8 intervention rooms in 3 ICUs, 294 patients contributed study data; 8 control in 3 ICUs, 320 patients contributed study data). One of the hospitals was a cancer care hospital, one a university affiliated tertiary care hospital, and one a Veteran's Affairs medical centre. One of the studies was conducted in the United States (Salgado 2013) and the other in Chile (von Dessauer 2016).

Von Dessauer 2016 was set in a paediatric intensive care unit (PICU) and a paediatric intermediate care unit (PIMCU). There were four intervention rooms (261 patients contributed study data) and four control rooms (254 patients contributed study data) in each. Intervention rooms were adjacent to control rooms. The study was set in a tertiary care hospital.

Intervention protocols and duration. Both studies fitted intervention rooms with copper alloy surfaced objects; all high-touch non-porous surfaces. In Salgado 2013, the surfaces were those shown in a previous study to have consistently high bacterial burden. The type of objects surfaced with copper varied across the three study sites; all had copper bed rails, overbed tables, intravenous poles and arms of visitors' chairs. Other objects were call buttons and parts of computer equipment (e.g. mouse, palm rest of a laptop). The objects were in place nine months prior to study commencement (i.e. prior to data collection), and during the 12-month intervention period. The same standard cleaning/disinfection protocol was followed in both intervention and control rooms (see Technical report, Appendix 4, Characteristics of included studies). Daily inventories were kept to monitor contamination across study arms arising from movement of copper objects between rooms.

In von Dessauer 2016, the objects surfaced with copper were bed rails, bed rail levers, intravenous poles, sink handles and the nurses' workstation. The same standard cleaning/disinfection protocol was followed in both intervention and control rooms (no details were reported). As in Salgado 2013, inventories were kept to monitor potential contamination across study arms arising from movement of copper objects between rooms.

Study design and other outcomes. Both studies were non-randomised trials, in which incidence rates of infection or colonisation in the copper intervention group were compared to rates measured concurrently in the control group. Both studies measured hospital-acquired infection, reporting all infections irrespective of type or pathogen. Infections were clinically diagnosed and, in Salgado 2013, type of pathogen was identified through surveillance (routine for MRSA, all sites; VRE at two sites) or testing of clinical isolates. In von Dessauer 2016, type of pathogen is reported for all HAIs, but there is no information on how these data were collected. Salgado 2013 reported two outcomes contributing to this review: (1) a combined measure of all hospital-acquired infections (any type, any pathogen) and MRO colonisation (MRSA or VRE) (the study's primary outcome), and (2) colonisation (MRSA or VRE). von Dessauer 2016 reported hospital-acquired infections (any type, any pathogen). In addition to the outcome reported in this review, both studies reported bacterial contamination of surfaces (reported in a separate paper for von Dessauer 2016).

Table 1 Characteristics of included studies

Study ID	**Salgado 2013**	**von Dessauer 2016**
Country	USA	Chile
Study design	Non-randomised trial	Non-randomised trial
Intervention and comparison	I. Rooms fitted with copper alloy-surfaced objects (e.g. bedrails, intravenous poles) C. Standard-surfaced objects	I. Rooms fitted with copper alloy-surfaced objects (e.g. bedrails, intravenous poles) C. Standard-surfaced objects
Duration	I/C (concurrent): Jul 2010 - Jun 2011 (12 months)	I/C (concurrent): Nov 2012 - Nov 2013 (12 months)
Setting	Adult intensive care units; 8 intervention rooms (294 patients), 8 control rooms (320 patients) Three hospitals: tertiary care academic hospital (660-bed), academic cancer hospital (460-bed), Veterans' Affairs hospital (98-bed)	Paediatric intensive or intermediate care units; 8 intervention rooms (261 patients), 8 control rooms (254 patients) Tertiary care hospital (249-bed)
Main outcome (metric)	Infection/colonisation (composite): incidence rate of hospital-acquired infection (any type, any pathogen), colonisation, or both (number of cases)	Infection: incidence rate of hospital-acquired infection (any type) (cases per 1,000 patient days)
Pathogen(s)	Any (infection); MRSA or VRE (colonisation)	Any (including non-MDROs)

Ongoing studies

Characteristics of the two ongoing studies are described in the Technical report, Appendix 5. Both are randomised trials evaluating the effects of copper impregnated linen used for patient beds and gowns (Lautenbach 2015; Shankaran 2015). Both studies are single-site studies, set in intensive care units in hospitals in the United States (421 patients, unclear number of wards in Lautenbach 2015; 1302 patients, two wards in Shankaran 2015). The primary outcome for Lautenbach 2015 is the incidence rate of hospital-acquired infection or colonisation (MROs, pathogens not reported). The estimated date of completion for the trial is May 2017. The primary outcome in Shankaran 2015 is antibiotic use (ineligible for this review), but clinical infection (any type, pathogens not reported) is a secondary outcome. The estimated date of completion for the trial was August 2015, but we have not identified any reports of results from this study.

Excluded studies

Reasons for excluding the 15 studies that were considered 'near misses' are described in Technical report, Appendix 6. These studies are those that evaluated an eligible intervention, and met most other criteria (i.e. could not clearly be excluded without screening all/most criteria). Of these, of potential relevance are studies that met all other criteria but measured bacterial contamination of surfaces without reporting a clinical outcome (9 studies). These studies are identified in the Technical report, Appendix 6. A full list of studies excluded after full text review is provided in the Technical report, Appendix 7. This list includes the 15 near miss studies, and 143 studies that were clearly ineligible for the surfaces review (including 121 papers relevant to the novel disinfectants review).

Studies awaiting assessment

We were able to confirm eligibility for all studies screened for this review, hence there are no studies awaiting assessment.

4.3 Risk of bias in included studies

Our assessment of the risk of bias for the time series studies is summarised in Table 2. The complete assessment for each study, including the rationale for the judgement of each domain is reported in the Technical report, Appendix 4 (Characteristics of included studies).

Non-randomised trials

Salgado 2013 reported that patients were "randomly assigned" to groups, but no method was described for sequence generation. The trial registry entry (NCT01565798) reported that bed control services sequentially placed patients in either intervention or control rooms. This suggests allocation was not truly random, and it may have been possible for bed allocation staff to guess which group patients were being assigned to. Hence, the study is judged to be at risk of selection bias which may lead to systematic differences between the characteristics of patients in the intervention and control groups. Outcome assessment was done from electronic records, by assessors masked to the intervention group. Although initial diagnoses were by treatment teams aware of the intervention, the copper surfaces were in place nine months prior to data collection, so it is unlikely that any changes in clinical practice arising from awareness of the intervention would be sustained. For these reasons, the outcome assessment was judged to be at low risk of bias. There are no missing data unaccounted for and no evidence of selective outcome reporting, hence these domain were judged at low risk of bias. The study authors did have multiple industry ties, and the trial was retrospectively registered, so there is a risk of other bias arising from these ties.

Von Dessauer 2015 was not randomised; as in Salgado 2013, patients were sequentially assigned to either intervention or control rooms. There is no other information about group allocation, therefore the study is judged to be at high risk of selection bias for the reasons reported above. Patients in one control room were excluded because of long length of stay/chronic care. This was not pre-specified in the study inclusion criteria

(registry entry), hence the study is judged at risk of bias due to missing data. There was independent outcome assessment (24% sample) using routinely collected data, which appeared to include data requiring a positive test for a pathogen (not described, but data are reported). For this reason, the outcome assessment was judged to be at low risk of bias. There is no evidence of selective outcome reporting, hence this domain was judged at low risk of bias. The authors declared no conflicts of interest, however one author was also an investigator on Salgado 2013 where they reported multiple industry ties. The trial was also prospectively registered by an industry body; hence the study is at risk of bias arising from industry ties.

Table 2. Summary of RoB assessments for non-randomised trials

Bias/Study ID	Salgado 2013	Von Dessauer 2016
Random sequence generation	Unclear	High
Allocation concealment	High	High
Incomplete outcome data addressed	Low	High
Knowledge of the allocated interventions adequately prevented (masking of participants, personnel and outcome assessors)	Low	Low
Selective outcome reporting	Low	Low
Free of other risks of bias?	High	High

4.4 Effects of interventions

Copper surfaces compared to standard surfaces

Results from the two non-randomised are presented in Table 3. Table 4 reports the summary of findings for this comparison, including the GRADE assessment and evidence statement.

In Salgado 2013, a 44% reduction was observed in the incidence rate of hospital-acquired infection or colonisation (combined) in rooms with copper-surfaced objects compared to no copper (IRR 0.56 (95%CI: 0.32, 0.98), p=0.03; 614 participants, low quality evidence). Although the point estimate suggests a clinically important reduction, the confidence intervals are wide and include the possibility of a negligible reduction (as little as 2%). For the colonisation outcome, the point estimate indicates a 63% reduction in rooms with copper surfaces objects compared to no copper (IRR 0.37 (95%CI: 0.08, 1.12), p=0.07; 614 adults, very low quality evidence), however the confidence interval includes the possibility of a small increase in colonisation (21%).

In von Dessauer 2016, a small reduction of 18% was observed in the incidence rate of hospital-acquired infection (any type, any pathogen) in rooms with copper-surfaced objects compared to no copper (IRR 0.82 (95%CI: 0.49, 1.37), p=0.41; 515 children aged 0-17 years, very low quality evidence). However, the confidence interval is wide and includes the possibility of a 37% increase in colonisation with copper surfaces.

Table 3. Effect of copper-surfaced objects on rates of hospital-acquired infection and colonisation

	Rate (cases per 1000 patient days)				
Study, outcome	Intervention (copper)	Control (no copper)	IRR	95%CI	p-value
Salgado 2013	n= 294 adults 1487 patient days	n=320 adults 1635 patient days			
Infection/colonisation Incidence of HAI or colonisation	14.1	25.1	0.56	(0.32, 0.98)	0.03
Colonisation Incidence of colonisation (MRSA or VRE)	2.7	7.3	0.37	(0.08, 1.21)	0.07
von Dessauer 2016	n=261 children 3012 patient days	n=254 children 2531patient days			
Infection Incidence of HAI (any type, any pathogen)	10.6	13.0	0.82	(0.49, 1.37)	0.41

HAI = hospital acquired infection; IRR= incidence rate ratio; 95%CI = 95% Confidence Interval.

Table 4 Summary of findings and evidence statement

Quality assessment		Summary of findings			
		No of patients			
		Int.	Control	Summary of effect (based on single study)	Quality
Copper-surfaced objects in patient rooms vs standard-surfaced objects					
Salgado 2013 Infection/colonisation - incidence rate of hospital-acquired infection or colonisation (combined) (cases per 1,000 patient-days) (Outcome importance: Important, but not critical in decision making)					
Non-randomised trial	Risk of bias: Serious[1] Inconsistency: Cannot assess[2] Indirectness: Not serious Imprecision: Serious[3] Other considerations: None	294 adults	320 adults	Rooms with copper-surfaced objects may reduce the rate of hospital acquired infection or colonisation (combined), but the size of the effect is uncertain. A clinically important (44%) reduction in the rate of hospital-acquired infection or colonisation was found in rooms with copper-surfaced objects compared to rooms with standard objects (IRR 0.56 (95%CI: 0.32, 0.98), p=0.03). However, the confidence interval does not exclude the possibility that the true intervention effect could be little or no reduction (2%).	⊕⊕⊖⊖ Low due to serious risk of bias, imprecision. Single study (consistency cannot be assessed).
Colonisation - incidence rate of hospital-acquired colonisation (MRSA or VRE) (cases per 1,000 patient-days) Outcome importance: Important, but not critical in decision making					
Non-randomised trial	Risk of bias: Serious[1] Inconsistency: Cannot assess[4] Indirectness: Not serious Imprecision: Very serious[5] Other considerations: None	294 adults	320 adults	The effect of copper-surfaced objects on the rate of hospital acquired MRSA or VRE colonisation is uncertain due to very low quality evidence. A clinically important (63%) reduction in the rate of hospital-acquired MRSA or VRE colonisation was found in rooms with copper-surfaced objects compared to rooms with standard objects (IRR 0.37 (95%CI: 0.08, 1.21), p=0.07). However, the confidence interval does not exclude the possibility that the true intervention effect could be a 21% increase in colonization with copper surface	⊕⊖⊖⊖ Very low due to serious risk of bias, very serious imprecision. Single study (consistency cannot be assessed).
von Dessauer 2016 Infection - incidence rate of hospital-acquired infection (any type, any pathogen) (cases per 1,000 patient-days) Outcome importance: Critical for decision making					
Non-randomised trial	Risk of bias: Serious[6] Inconsistency: Cannot assess[4] Indirectness: Serious[7] Imprecision: Serious[8] Other considerations: None	261 children	254 children	The effect of copper-surfaced objects on the rate of hospital acquired infection is uncertain due to very low quality evidence. A small (18%) reduction in the rate of hospital-acquired infection was found in rooms with copper-surfaced objects compared to rooms with standard objects (IRR 0.82 (95%CI: 0.49, 1.37), p=0.41). However, the confidence interval does not exclude the possibility that the true intervention effect could be a 37% increase in colonisation with copper surfaces.	⊕⊖⊖⊖ Very low due to serious risk of bias, indirectness, and imprecision. Single study (consistency cannot be assessed).

[1] RoB (-1) due to the potential for selection bias (unclear randomisation, group allocation not concealed), industry ties.

[2] Inconsistency: although downgraded for most single non-randomised studies, not downgraded for this outcome. There is greater certainty around this effect estimate compared to others in the table; however, the outcome should be considered to be of low-very low quality.

[3] Imprecision (-1) due to wide confidence intervals that include both large and very small reductions in the rate of MRO colonisation.

[4] Inconsistency (-1) for all single non-randomised studies. Two or more studies are required to assess the consistency of effects.

[5] Imprecision (-2) due to very wide confidence intervals that include both large reductions and small increases in MRO colonisation.

[6] RoB (-1) due to the potential for selection bias (unclear randomisation, group allocation not concealed), and incomplete data arising from removal of one control room from the analysis based on long length of stay/chronic care (not a pre-specified eligibility criterion for study).

[7] Indirectness (-1) due to the outcome being hospital acquired infection, arising from any pathogen, so the outcome is not specific to MROs.

[8] Imprecision (-2) due to very wide confidence intervals that include both large reductions and small increases in rate of infection.

Quality assessment		Summary of findings			
		No of patients		Summary of effect (based on single study)	Quality
		Int.	Control		
No studies Adverse effects Outcome importance: Critical for decision making					
Von Dessauer monitored skin or other allergic reactions during the study (patients, hospital staff). None were identified.					

5.0 Discussion

Summary of main results

This review included two completed and two ongoing studies of antimicrobial surfaces. Results for the latter are yet to be reported by the study investigators, but both examine the effects of copper impregnated textiles (Lautenbach 2015; Shankaran 2015). Of the two completed studies, both evaluated the effects of copper-surfaced objects in intensive care units, one among adult patients in three hospitals in the United States (Salgado 2013) and the other among paediatric patients in a hospital in Chile (von Dessauer 2015). von Dessauer 2015 also included a paediatric intermediate care unit (PIMCU).

Based on the findings of these two non-randomised trials, the effects of copper surfaces on hospital-acquired infection are uncertain. Salgado 2013 found that rooms with copper-surfaced objects may reduce the rate of hospital-acquired infection or MRO colonisation (combined outcome) when compared to rooms with no copper objects. However, the effect estimates were too imprecise to determine whether copper is likely to have a clinically important or trivial effect (43% reduction in rates (95%CI: from a 2% to 68% reduction); 614 adults, low quality evidence). The effect of copper on the incidence rate of hospital-acquired MRSA or VRE colonisation was uncertain, with the possibility of a clinically important reduction or an increase in rate (63% reduction (95%CI: from a 92% reduction to a 21% increase); 614 adults, very low quality evidence). Findings from von Dessauer 2015 were also equivocal.

Overall completeness and applicability of the evidence

Evidence about the effects of copper surfaces on hospital-acquired infection is sparse. With only two non-randomised trials, both with uncertain results, it is not possible to draw conclusions from this evidence. The two ongoing studies both examine the effects of copper impregnated fabrics, addressing an additional but different question about the effects of copper surfaces than the studies in this review. There were no eligible studies identified of any other antimicrobial surfaces. The literature identified during the review consisted mainly of studies that examined bacterial contamination of surfaces, without assessing clinical outcomes (we excluded two non-randomised trials of copper surfaces and three of other antimicrobial materials for this reason). This is an important gap, with evidence about the clinical outcomes of antimicrobial surfaces required to evaluate the potential benefits of these interventions for infection control.

Quality of the evidence

Overall the evidence contributing to this review was of very low quality, due to the small number of studies and imprecise estimates of effect observed in both included studies. Both were non-randomised studies, and were at risk of biases that further reduced certainty about the effects observed.

Potential biases in the review process

The review was conducted according to a pre-specified protocol with the aim of minimising biases in the review process. We conducted a comprehensive search to update a recent review published as a Technical Brief for the Agency for Healthcare Research and Quality (AHRQ) (Leas 2015). We performed independent screening, data extraction, and risk of bias assessment to minimise bias and errors. However this was a rapid review, which inherently requires some methodological compromises that may introduce bias.

First, we relied on the AHRQ report for the majority of studies published between 2006 and February 2015. While the searches from that report were appraised and appeared comprehensive, it is possible that some studies may have been missed. However additional screening of reference lists for related reviews, and our independent search of all records in ClinicalTrials.gov identified no additional studies that were missing from the AHRQ report. We combined all citations from that report with our updated search, and independently screened these without cross-referencing their decisions during the screening process. After final inclusions

decisions were made, we verified our list against the AHRQ report and found no discrepancies. We did not search grey literature, or approach study authors or manufacturers about whether they were aware of unpublished studies.

Second, we did not contact authors for further information or data. This meant we may have missed subsequent publications of some studies published only as conference abstracts. It also meant we relied on published data for our assessment of study design, risk of bias and for calculating effect estimates that were not reported in the paper.

6.0 Authors' conclusions

Implications for practice

We found that there is currently limited evidence to support the use of environmental fittings with antimicrobial properties (antimicrobial surfaces) to prevent infections with multi-resistant organisms. Although the estimate of effect suggests a clinically relevant benefit of copper-surfaced fittings, the evidence is of very low quality which means the true effect is likely to be substantially different (Schunemann 2013). The results of ongoing studies of copper impregnated fabrics are awaited. The effectiveness of antimicrobial surface is yet to be established, so the cost effectiveness of these interventions is unknown.

Implications for research

We found few well-designed studies suited to establishing the effects of antimicrobial surfaces on clinical outcomes. The inclusion of infection and colonisation outcomes in future studies is key to determining whether these interventions have a clinically important impact; this is an important gap in the current literature which has largely focused on whether antimicrobial surfaces reduce bacterial contamination.

The optimal design to assess the causal effects of an intervention is one which involves random allocation of individuals or clusters of individuals to treatment groups. Individually randomised trials are unlikely to be possible in this setting because of the risk of contamination between treatment groups. For example, patients allocated to control rooms may be moved to intervention rooms during the course of their admission. Cluster randomisation by ward may reduce contamination between treatment groups, but will not resolve the issue completely because of movement of patients between wards. Therefore, the optimal design would be a cluster randomised trial where clusters are hospitals.

Interrupted time series designs are more prone to bias than randomised trials, and therefore it is more difficult to ascribe observed treatment effects to the treatment. However, they are an important design that may be useful when a randomised trial is not possible. ITS designs can be strengthened by including a long series, both pre- and post-intervention (allowing for investigation of seasonal effects and minimising issues of regression to the mean and over-fitting); including a sufficient number of observations at each time-point; collection of potential confounding factors over time (such as changes to the composition of the population that may explain the outcome); documentation of co-interventions (e.g. when they occurred, what they involved); consistent methods for data collection in the pre- and post-intervention periods; and, masking of outcome assessment. Further, collection of 'control' outcomes not expected to respond to the intervention (e.g. urinary tract infections, Methicillin-sensitive *Staphylococcus aureus*) over time, or the inclusion of control sites, may provide more confidence in ascribing observed treatment effects to the treatment if no changes are observed in the control outcomes or sites.

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