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Systematic review of novel disinfection methods to reduce infection rates in high risk hospitalised populations

Technical 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 protocol

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 report.
Kelly Allen	Conducted searches of trial registers. Extracted data for time series analyses.
Jane Reid	Screened citations and full text articles, extracted data, 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).

Scope of the technical report

This technical report includes full description of the methods (reported in brief in the main systematic review report), together with appendices for more detailed methods and description of changes to protocol.

3. Methods

Methods reported were pre-specified in the protocol for this 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). Changes to the original protocol and the rationale for each change are reported in Appendix 4. These involved rewording to clarify eligibility criteria and the basis for GRADE judgements; the types of studies eligible for the review and all other methods were unchanged.

3.1 Criteria for considering studies for this review

3.1.1 Types of participants

High risk population groups, defined in the 2010 Guidelines as “patients with an increased probability of infection due to their underlying medical condition.” ((National Health and Medical Research Council 2010), p261)

Examples of high risk population groups are:

- patients in intensive care units (ICU)
- oncology, haematology, burns and renal patients
- patients who have received a solid organ transplantation (especially liver)
- neonates
- patients in any ward where there is a known outbreak of an eligible pathogen.

A high risk ward is defined as one that has a predominant population of high risk patients.

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.

Inclusion of studies involving sub-acute and non-acute care was limited to the following:

- Rehabilitation care (e.g. rehabilitation provided on an acute care ward or in a dedicated facility)
- Transitional aged care and sub-acute geriatric care (delivered in an acute care ward).

Studies in ambulatory care (e.g. primary care, hospital outpatient services), residential care facilities (e.g. residential aged care, nursing homes, assisted living), and home and community settings were excluded.

Geographical restrictions: Eligible studies were those set in countries or regions with health systems broadly comparable to those in Australia, especially in terms of the healthcare facilities and resourcing, specifically:

- Australia

- New Zealand
- Europe
- Canada
- United States of America

Eligible studies set in other countries or regions with broadly comparable heath systems were evaluated based on full text to determine whether the facility was comparable to an Australian setting.

Studies set in low or middle income countries were only excluded at abstract review if there was explicit mention that interventions were evaluated in a resource poor setting (or equivalent). Other studies were assessed in full text to determine if the setting might be comparable to hospitals in Australia, and all studies eligible for inclusion based on other criteria were referred to an arbiter (our clinical expert). In practice, most studies excluded on this criterion were clearly ineligible based on other criteria.

3.1.3 Types of interventions

Studies evaluating the effects of the following agents or modalities for disinfection were eligible for inclusion.

- Sodium hypochlorite (bleach): preparations of sodium hypochlorite, at any concentration, applied using any method and at any frequency.
- Automated ('no touch') systems or modalities of room decontamination involving ultra-violet light (UV light devices) or hydrogen peroxide vapour (HP vapour, HP mist and other systems).
- Electrolysed water. applied using any method and at any frequency.

These interventions may have been used alone or in combination with routine cleaning using detergent solutions alone or with disinfectant (providing the comparator involves an identical method of routine cleaning). Studies evaluating these interventions in combination with other interventions (e.g. use of ultra-microfibre cloths for cleaning, and then sodium hypochlorite disinfection; intensified infection control measures) were excluded unless the additional intervention was also used in the comparator. Studies in which automated systems for room decontamination (UV light, HPV) were used as an adjunct to standard cleaning/disinfection were eligible if compared to the same form of standard cleaning/disinfection.

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 (high-risk or frequently touched) surface was eligible including hard nonporous and porous surfaces, such as:

- Bed rails, bedside tables, over-bed tables, chairs, mattresses, bed curtains (but not window curtains or blinds), bedside commodes, doorknobs, light switches, ensuite facilities
- Intra-venous stands/poles, medical equipment (e.g. pumps, monitors), knobs, buttons.

Interventions tested only for minimal touch surfaces (e.g. floors, walls, window curtains or blinds), surfaces in non-patient care areas, invasive medical devices, and disposable items (e.g. dressings) were excluded.

3.1.4 Types of comparators

For studies testing the effects of UV light, HP vapour or electrolysed water, eligible comparators were those considered as the standard of care, specifically:

- Standard cleaning/disinfection practices ('routine' or 'usual' practice) without the addition of UV light, HP vapour or electrolysed water.

These standard cleaning/disinfection practices could include the following.

- *Detergents:* Cleaning with a detergent solution is generally the standard of care for routine infection control and prevention. Agents explicitly described as detergents (or detergent solutions) were eligible for inclusion. This included any type or preparation of detergent, applied using any method and at any frequency. Agents described as detergents in the study were be assumed to be detergents (for cleaning not disinfection; no antimicrobial claims on the label (Rutala 2008, Therapeutic Goods Administration 2012)).

- *Sodium hypochlorite (bleach)*: Sodium hypochlorite disinfection is generally the standard of care for patients known to have significant organisms (an MRO or *C. difficile*) or in outbreaks. Preparations of sodium hypochlorite, at any concentration, applied using any method and at any frequency were eligible comparators (for UV light, HP vapour, electrolysed water only) irrespective of whether sodium hypochlorite was used in the intervention arm.

- Other disinfectants, such as quaternary ammonium, but only if included in the intervention arm or explicitly described as being part of standard cleaning/disinfection practices.

- A combination of detergent-based cleaning, and either of the above disinfectants.

Where the intervention arm included any of the above, the preparation, frequency and methods of cleaning should, ideally, have been the same in both arms. Studies were not excluded on this basis, however such differences were noted or recorded as not reported.

We planned to exclude studies that directly compared two automated disinfection systems, but identified no eligible studies that compared two systems (e.g. pulsed xenon UV disinfection versus mercury UV disinfection, HP vapour versus HP mist, HPV versus UV).

For studies testing the effects of sodium hypochlorite, eligible comparators were HP disinfection, UV disinfection, electrolysed water (as above) or cleaning/disinfection practices that were the standard of care (usual practice).

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).

Studies reporting infection as an outcome were included irrespective of the metric reported, for example:

- Risk of infection: calculated as number of patients with an episode of infection as a proportion of the total number of patients

- Rate of infection: calculated as patient episodes of infection per total patient days, or patient episodes of infection per 10,000 patient days (Australian Commission on Safety and Quality in Health Care 2013).

Infection outcomes were eligible if determined through clinical evaluation of symptoms, physical signs of infection, or laboratory test results (Lewis 2016); however, clinical evaluation or signs 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. based on clinical isolates alone), were also 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). Studies reporting patient colonisation as an outcome were included irrespective of the metric reported (e.g. the proportion of patients positive for colonisation of the pathogen) or the method of detection.

Studies reporting environmental contamination or environmental colonisation as outcomes, without infection or patient colonisation outcomes, were excluded.

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

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).

- Randomised trials (RTs). Given the nature of the interventions, eligible trials were expected to be randomised at cluster level (i.e. at the hospital or ward level) rather than individual level. However, trials were not be excluded on the basis of level of randomisation.

- Non-randomised trials (NRTs). Studies in which participants (or clusters) were allocated to groups using a method that is not (truly) random. These studies include controlled trials (CTs).

- Interrupted-time-series (ITS) and repeated measures (RM) studies. To be eligible these studies must have had a clearly defined time point at which the intervention was introduced and at least three

outcome measures before and after intervention. Studies that presented time series data were eligible irrespective of how the study was described or analysed. When analysed appropriately, these studies are designed to detect whether the intervention has an effect greater than the underlying trend over time. These studies may or may not have a control group.

- Controlled before-after (CBA) studies. Studies with both an intervention group and a control group, in which outcomes are measured concurrently in both groups, before and after delivery of the intervention.

Controlled studies must have had at least two intervention and two control clusters to be eligible.

Studies using other designs (uncontrolled before-after studies where no time series data were reported and cross sectional studies) were excluded because it is difficult (if not impossible) to attribute observed changes in outcomes to the intervention (Effective Practice and Organisation of Care 2013). Full text of all studies with observations pre- and post- introduction of an eligible intervention were retrieved in order to confirm the availability of time series data.

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). In developing the search strategy for this review, we appraised and adapted the AHRQ search strategy. Terms or concepts not relevant to this review were removed and other terms added. The search terms include concepts relevant to a second commissioned review for the 2010 guidelines (antimicrobial surfaces), for which searching and screening was conducted concurrently because of significant overlap in eligibility criteria of the two reviews.

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. Embase was the principal database used for the AHRQ report and includes all MEDLINE records. We appraised the AHRQ search strategy, carefully cross-checking the inclusion criteria of both the AHRQ review and this review. We removed terms and concepts deemed not to be relevant to this review (e.g. cleaning personnel and training; measuring and monitoring cleanliness; and non-sodium hypochlorite disinfectants). We added concepts covered in our inclusion criteria but which were not reflected in the AHRQ criteria (e.g. electrolysed water, *Acinetobacter*, carbapenemase producing Enterobacteriaceae, furnishings and curtains) or which were explicitly excluded (e.g. paediatric studies). We applied the methodological filters for identifying randomised trials and excluding animal studies that Cochrane has developed for Embase. We converted the search syntax from embase.com to the Ovid platform.

3.2.2 Bibliographic and grey literature databases

We searched Embase (via Ovid) using the search strategy in Appendix 1. 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 Appendix 1.

Searches for the AHRQ review were conducted in February 2015. We searched Embase and the other databases for records added since January 2015. For the terms and concepts included in our review but not covered in the AHRQ review we identified unique records going back to 2006 that would not have been included in the original AHRQ search.

We had intended to search OpenGrey and the WHO ICTRP trials register but for pragmatic reasons decided to omit them from the search. This reflected the difficulty of constructing searches of these sources for the review topic and the low likelihood that included studies would have been retrieved through alternative sources.

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. The reference lists of eligible studies and any relevant systematic reviews identified were checked for additional studies. We also used Scopus to conduct forward citation searches for all included studies.

3.3 Data collection and analysis

3.3.1 Selection of studies

Citations identified from the literature searches, citation checking, and from the list of included and excluded studies in the AHRQ report were imported to EndNote and duplicates removed. Citations were then imported to Covidence (www.covidence.org), an online tool that streamlines the screening and data extraction stages of a systematic review. Two reviewers (SB, JR) independently screened citations (titles and abstracts) for inclusion in the review using a pre-tested screening guide based on the inclusion criteria. One reviewer screened citations in Covidence, while the second screened in EndNote. Endnote enabled categorisation of citations according to the question to which they pertained, which facilitated concurrent screening for the review of antimicrobial surfaces. Disagreements about eligibility were resolved through discussion, with involvement of a third reviewer if consensus could not be reached.

Full-text of all potentially eligible studies were retrieved and independently screened by two reviewers (SB, JR), with disagreements resolved using the same approach as for citation screening. Advice was sought from our review content expert (AC) to confirm eligibility based on PICO and our biostatistician (JM) to confirm eligibility based on study design. Eligibility of some studies published as conference abstracts could not be confirmed based on information reported in the abstract alone. We searched for published papers for these studies, but did not contact study authors because it was infeasible to include unpublished data in the review. These studies were therefore noted as studies awaiting further assessment. Citations that did not meet the inclusion criteria were excluded and the reasons for exclusion were recorded at full-text screening for all eligibility criteria.

Trial registration numbers (where available), author names, and study titles, locations, sample sizes and dates were used to identify multiple reports arising from the same study.

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.

Pre-testing of the data extraction and coding form was done by two reviewers (SB, JR), who extracted data from two studies purposefully selected from the included studies to cover the diversity of data types anticipated in the review (e.g. study designs, PICO characteristics). Advice was sought from the review content expert (AC) and biostatistician (JM) to ensure data extracted were as planned. Revisions to the data extraction form were made to maximise the quality and consistency of data collection.

We extracted information relating to the following characteristics of included studies:

- study design, whether the study was registered, and other details required to assess risk of bias
- year conducted
- setting and location (hospital, country, units on which the intervention was delivered)
- participant characteristics (including those needed to characterise risk group)
- intervention and comparator characteristics (e.g. materials, procedures, duration of process/contact time, frequency of use, personnel, surfaces cleaned, adherence to cleaning/disinfection protocols)
- outcomes measures (outcome category (infection, colonisation, adverse events), pathogen(s), measurement method/metric, outcome measurement period/follow-up times)
- results for primary and secondary outcomes (where eligible; including number of participants/clusters for each measurement), and adverse events
- ethics approval
- funding sources and funder involvement in study.

Six of the seven included studies reported time series data that we re-analysed. Methods for extracting these data are reported in the "Unit of analysis issues" section.

Items relating to the characteristics of interventions and comparators are based on the Template for Intervention Description and Replication (TIDieR) (Hoffmann 2014). Appendix 2 summarises how these domains were applied in the review.

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). Disagreements were resolved by discussion, with advice from a third reviewer (JM) if agreement could not be reached.

For ITS studies, we assessed risk of bias associated with the following seven domains:

1. intervention independent of other changes
2. shape of intervention effect pre-specified
3. intervention unlikely to affect data collection
4. blinding of participants, practitioners and outcome assessors to intervention allocation
5. incomplete outcome data
6. selective outcome reporting, and
7. other sources of bias (Effective Practice and Organisation of Care 2015).

For RTs and NRTs we assessed the risk of bias associated with the following domains:

8. sequence generation
9. allocation concealment
10. blinding of participants, personnel, and outcome assessors
11. incomplete outcome data
12. selective outcome reporting, and
13. other potential threats to validity (Higgins 2011).

For the single cluster-randomised crossover trial, we assess additional domains specific to clustered designs (imbalance of participant characteristics and outcome measures at baseline, and protection against contamination) and unique considerations relating to the crossover design.

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. Some domains are assessed separately for different outcome categories (blinding of outcome assessment, incomplete outcome data); where relevant, our judgments are reported by outcome for these domains. Our risk of bias judgments were summarised in tables reporting characteristics of included studies (Appendix 5).

For GRADE assessments we first drew conclusions about the overall risk of bias for each outcome (i.e. summarising risk of bias judgments across domains for each outcome within a study), and then summarised risk of bias assessments across studies for each outcome where results were summarised across studies. We followed the Cochrane EPOC guidance to inform judgements for each of these summary assessments (Effective Practice and Organisation of Care 2013). These summary assessments of risk of bias were used in determining the overall quality of the body of evidence using GRADE, and the basis for each is reported as footnotes to the summary of findings tables.

3.3.4 Measures of treatment effect

Interrupted time series studies. For interrupted time series designs, we report the following estimates (along with 95% confidence intervals) from regression analyses that adjust for autocorrelation: (i) change in level of the outcome at the first point after the introduction of the intervention (immediate effect of the intervention), (ii) the post-intervention slope minus the pre-intervention slope (long term effect of the intervention).

Randomised and non-randomised trials. For binary outcomes (e.g. whether a patient acquired an infection) and count outcomes (e.g. number of episodes of infection) we report risk ratios and rate ratios (along with 95% confidence intervals), respectively.

3.3.5 Unit of analysis issues - Statistical analysis of interrupted time series data

In this review, unit of analysis issues arose only from interrupted time series designs analysed as before after studies (Boyce 2008, Hacek 2010, McMullen 2007, Orenstein 2011). A further two studies conducted ITS analyses but reported selected results from these analyses (Haas 2014, Mitchell 2014) For five of these studies we re-analysed them as ITS analyses of monthly rates of infection (CDAD, MRO, and MRSA) using data extracted from figures (Boyce 2008, Haas 2014, Hacek 2010, McMullen 2007, Orenstein 2011). The package DigitizeIt (version 2.2) was used to obtain the data points from the figures. One study author (Mitchell 2014) provided monthly aggregate data (number of counts and patient-days) for a figure from which we were unable to extract data. For all analyses, we standardised the rates of infection to per 1,000 patient-days. These analyses are described in Appendix 3.

3.3.6 Dealing with missing data

Attrition rates were not available in any of the included studies; hence we are unable to present this data. We did not plan to undertake any imputation for missing data, however, we did assess the risk of bias in observed effect estimates resulting from attrition.

3.3.7 Assessment of heterogeneity

We did not assess heterogeneity visually by inspecting the overlap of confidence intervals on the forest plots, or through formal tests for heterogeneity because data were not combined across studies. Instead, the characteristics of studies (setting, population, interventions, comparators, outcomes, study design) were summarised and considered in interpreting results and summarising findings.

3.3.8 Assessment of reporting biases

In addition to undertaking an extensive search of the literature, we searched trial registries (see 'Search methods for identification of studies'). A registry entry was identified for one of the eight completed studies included in the review, so we were unable to confirm whether all outcomes for which data were collected and/or analysed were included in the final report for seven of eight studies. We planned to extract any discrepancies and reasons for discrepancies noted by authors, however none were reported.

We were unable to investigate the potential for small study-study effects because we did not perform meta-analysis.

3.3.9 Data synthesis

In line without our protocol, we did not combine effect estimates from studies using non-randomised study designs (i.e. the six studies reported as time series). Only one randomised trial was 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 other intervention characteristics, in tables structured by comparison, outcome, and study design.

3.3.10 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 the detailed GRADE guidance (Schunemann 2013), the following five domains were assessed (as briefly summarised below) and a judgement 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 (intervention, type of pathogen, patient population) or had other important difference that meant a pooled estimate or other synthesis of effects across studies would be uninterpretable. For this reason, we report GRADE assessments for individual studies and describe our approach to doing so below.

1. Risk of bias. Based on the summary assessment across studies for each outcome reported for a comparison (see 'Risk of bias' section). For individual studies, based on a summary assessment across domains. In ITS studies, the risk of bias was considered to be serious where there were concerns about concurrent changes and a risk of detection bias arising from the intervention affecting data collection. Where the study also had industry ties, the risk of bias was considered very serious.

2. Inconsistency. We assessed (1) whether there was heterogeneity in the observed intervention effects across studies that suggested important differences in the effect of the intervention (based on point estimates from individual studies and overlap in confidence intervals, but not statistical tests of heterogeneity because we did not combine effect estimates), and (2) whether this could potentially be explained (through qualitative assessment of differences across studies, for example arising from differences in PICO, participant characteristics or study design). Where a single non-randomised study contributed data for a comparison and outcome (as was the case for ultra-violet light disinfection), inconsistency was rated as serious and the limitations of interpreting single studies was incorporated when formulating conclusions. This was a deviation from our original plan to rate inconsistency as very serious for single studies.

3. Imprecision. We did not combine effect estimates, therefore imprecision was primarily assessed for individual studies. We examined whether interpretation of the upper and lower confidence limits leads to conflicting interpretations about whether the intervention has a clinically important effect (such studies were considered imprecise). A clinically important difference was judged to be a 30-50% reduction in rates of infection or colonisation. In ITS studies the assessment was based on the immediate effect. Where conclusions were drawn across studies our assessment was qualitative,

based on whether there was sufficient studies with precise effect estimates and consistent direction of effect to be confident about the intervention effects. Such decisions are inherently subjective, especially in the absence of multiple large studies showing large intervention effects.

4. Indirectness. We assessed whether there were important differences between the review questions (PICO) and the characteristics of included studies that may lead to important differences in the intervention effects (i.e. the applicability of the evidence). These assessment took account, for example, of whether outcome data were reported for high risk populations only or hospital wide. In the latter case, we would rate indirectness as serious.

5. Publication bias. Due to the small number of studies included in the review, it was not possible to use graphical or statistical methods (e.g. visual inspection of funnel plots or tests for funnel plot asymmetry) to assess publication bias. Instead, decisions to downgrade because of 'suspected publication bias' were based on whether the evidence was largely comprised of small studies that showed effects favouring intervention.

We planned to use GRADEpro GDT software (www.gradepro.org) to record decisions and derive an overall GRADE (high, moderate, low or very low) for the quality of evidence for each outcome, however because of the large number of times series studies, this proved impractical. We used GRADE rules in which randomised trials begin as 'high' quality evidence (score=4) and can be downgraded by -1 for each domain with serious concerns or -2 for very serious concerns. Non-randomised studies are considered at high risk of bias (and downgraded accordingly). We considered additional criteria for upgrading the quality of evidence in accordance with GRADE guidelines.

Evidence profiles (summary of findings and evidence statements) were prepared using a modified template from the GRADEpro GDT software (to incorporate evidence from studies analysed as a time series). For each comparison and outcome, the evidence profile includes estimates of treatment effects for both immediate effects and trends (ITS studies), and the overall GRADE (rating of quality). The evidence profiles also includes (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 (risk of bias, inconsistency, indirectness, imprecision, other considerations including publication bias), and (3) a plain language statement interpreting the evidence (an evidence statement describing clinical impact) for each comparison and outcome. Explanation of the judgements made when downgrading the rating of the quality of the evidence are reported in footnotes.

The plain language evidence statements were formulated using standard phrasing recommended by the Cochrane EPOC group and based on guidance for Cochrane Plain Language Summaries (Table 1).

Table 1 Standard phrasing used in plain language evidence statements (sources (Effective Practice and Organisation of Care 2013))

	Important difference	**Small difference (May not be important)**	**Little or no difference**
High certainty evidence	Improves/decreases/ prevents/ leads to [outcome]	Improves slightly/decreases slightly/leads to slightly fewer (more) [outcome]	Results in little or no difference in [outcome]
Moderate certainty evidence	Probably improves/ decreases/ prevents/ leads to [outcome]	Probably improves slightly/decreases slightly/leads to slightly fewer (more) [outcome]	Probably leads to little or no difference in [outcome]

Low certainty evidence	May improve/ decrease/prevent/lead to [outcome]	May slightly improve/slightly decrease/ lead to slightly fewer (more) [outcome]	May lead to little or no difference in [outcome]
Very low certainty evidence	It is uncertain whether [intervention] improves, decreases, prevents, leads to [outcome] because the certainty of the evidence is very low		
No data or no studies	[Outcome] was not measured or not reported, or no studies were found that evaluated the impact of [intervention] on [outcome]		

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Appendices

Appendix 1. Database search strategies

Embase

The search below is for Ovid Embase <1974 to 2016 August 23>and includes records that are unique to MEDLINE.

#	Concept	Query	Results
1	Infections (healthcare-associated)	healthcare associated infection/	2107
2		hospital infection/	37463
3		1 or 2	39251
4		(("health care acquired" adj1 (infection$ or pathogen$)) or ("healthcare acquired" adj1 (infection$ or pathogen$)) or ("hospital acquired" adj1 (infection$ or pathogen$)) or ("health care associated" adj1 (infection$ or pathogen$)) or ("healthcare associated" adj1 (infection$ or pathogen$)) or ("hospital associated" adj1 (infection$ or pathogen$))).ti,ab.	8375
5		(HAI or HAIs).ti.	449
6	Infections (specific terms bacterial	peptoclostridium difficile/	2065
7		clostridium difficile infection/	8503
8		methicillin resistant Staphylococcus aureus/	34931
9		methicillin resistant Staphylococcus aureus infection/	7533
10		enterococcus/	15071
11		vancomycin resistant Enterococcus/	3894
12		enterococcal infection/	1663
13		carbapenemase producing enterobacteriaceae/	384
14		actinobacteria/	8876
15		acinetobacter infection/	1797
16		extended spectrum beta lactamase/	6178
17		6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	78898
18		(((antibiotic or "multi-drug" or multidrug or methicillin or vancomycin) adj1 resistan$) or difficile or ("methicillin resistant" adj2 aureus) or ("vancomycin resistant" adj1 enterococc$)).ti,ab.	123311
19		("carbapenemase producing enterobacteriaceae" or acinetobacter or "extended spectrum beta lactase" or ESBL).ti,ab.	22764
20		(CDI or MRSA or VRE).ti.	6363
21	Limit to patients	exp patient/	1897096
22		(inpatient$ or patient$).ti,ab.	7344555
23		21 or 22	7470985
24		(17 or 18 or 19 or 20) and 23	65695
25	Combine infection sets	3 or 4 or 5 or 24	101084
26	Setting (facilities)	health care facility/	60225
27		hospital discharge/	81865
28		exp hospital/	889884
29		26 or 27 or 28	994208
30		("acute care" or "burn$1 unit" or "common area$1" or "critical care" or "healthcare facility" or "healthcare facilities" or "healthcare setting$1" or "health care setting$1" or hospital$1 or hospitalis$ or hospitaliz$ or ICU or institution$1 or "intensive care" or "patient care area$1" or "medical facility" or "medical facilities" or "patient room$1" or ward$1).ti,ab.	1754394
31	Setting (surfaces)	fomite/	329
32		hospital bed/	3530
33		exp hospital equipment/	81117
34		exp furniture/	24055
35		31 or 32 or 33 or 34	87494

36		(fomes or fomite$ or "environmental reservoir$1" or "surface contamination" or "surface microbes").ti,ab.	2313
37		(bathroom$ or "bed rail$1" or bedrail$ or cart$1 or chair$1 or "clinical surfaces" or commode$ or "environmental surfaces" or "high contact" or "high-touch" or "hospital bed$1" or "hospital surfaces" or "mobile equipment" or "portable medical equipment" or railing or toilet$ or "shared medical equipment" or wheelchair$).ti,ab.	47250
38		(furniture$ or furnishing$ or curtain$).ti,ab.	5189
39	Combine setting sets	29 or 30 or 35 or 36 or 37 or 38	2231743
40	Combine sets infection or setting	25 or 39	2276835
41	General cleaning	cleaning/	7586
42		disinfection/	21319
43		environmental sanitation/	6395
44		*infection control/	27219
45		41 or 42 or 43 or 44	59672
46		("cleaning method$1" or "cleaning practice$1" or "cleaning protocol$1" or "cleaning regimen$1" or "cleaning routines" or "cleaning technique$1" or "discharge cleaning" or "discharge room cleaning" or "enhanced cleaning" or "environmental cleaning" or "environmental decontamination" or "environmental disinfection" or "environmental sanitation" or "hospital cleaning" or "pre cleaning" or precleaning or "room cleaning" or "room decontamination" or "routine cleaning" or "surface cleaning" or "surface disinfection" or "surface decontamination" or "terminal cleaning" or "terminal disinfection" or "terminal room").ti,ab.	3675
47		(cleaning or decontamination or disinfect$ or "infection control").ti.	26037
48	Disinfectants	exp disinfectant agent/	203033
49		bleaching agent/	1380
50		48 or 49	204096
51		(biocidal or biocide$ or "chemical agent$1" or "chemical disinfection" or "cleaning agent$1" or disinfectant$ or "disinfecting agent$1" or "disinfection agent$1" or germicidal or germicide$ or sporicidal or sporicide$).ti,ab.	21008
52		("accelerated hydrogen peroxide" or bleach or bleaching or "calcium hypochlorite" or hypochlorite$ or "sodium hypochlorite").ti,ab.	15974
53		50 or 51 or 52	227456
54	Limit to disinfectant studies to cleaning	(clean$ or decontaminat$ or disinfect$ or housekeep$).ti,ab.	132167
55		53 and 54	19737
56	Automated devices	disinfection system/	115
57		ultraviolet irradiation/	11532
58		ultraviolet radiation/	83874
59		hydrogen peroxide/	74235
60		vapor/	7733
61		water vapor/	6987
62		56 or 57 or 58 or (59 and (60 or 61))	94957
63		((automated adj2 (cleaning or device$ or decontamination or disinfection)) or (("no-touch" or "non touch") adj1 disinfect$) or ("room sterili?ation" or "self disinfecting")).ti,ab.	1728
64		(("pulsed xenon" or ((ultraviolet or UV) adj1 (disinfection or light or irradiation or radiation))) and (clean$ or decontaminat$ or disinfect$ or room$1)).ti,ab.	2360
65		(("superoxidi?ed water" or "electroly?ed water" or ("hydrogen peroxide" or H2O2)) and (aerosol$ or fogging or mist or steam or system$1 or vapor$ or vapour$)).ti,ab.	17829
66	Enhanced coatings and surfaces	copper/	95566
67		material coating/	12219
68		66 and 67	180

69		(("self disinfecting" or (antimicrobial or copper or silver)) adj2 (coated or coating or impregnated or surface$)).ti,ab.	4133
70	Combine sets (cleaning concepts)	45 or 46 or 47 or 55 or 62 or 63 or 64 or 65 or 68 or 69	197512
71	Combine infection and cleaning concepts	40 and 70	22314
72	Trials filter	Randomized controlled trial/	416927
73		Controlled clinical study/	395470
74		random$.ti,ab.	1117107
75		randomization/	71561
76		intermethod comparison/	211445
77		placebo.ti,ab.	241668
78		(compare or compared or comparison).ti.	425289
79		((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.	1439897
80		(open adj label).ti,ab.	51936
81		((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.	187645
82		double blind procedure/	133477
83		parallel group$1.ti,ab.	18709
84		(crossover or cross over).ti,ab.	82484
85		((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.	240883
86		(assigned or allocated).ti,ab.	285205
87		(controlled adj7 (study or design or trial)).ti,ab.	249336
88		(volunteer or volunteers).ti,ab.	202985
89		human experiment/	357321
90		trial.ti.	211566
91		or/72-90	3699732
92	Animal studies filter	exp experimental organism/	551028
93		animal tissue/	1037101
94		animal cell/	1211677
95		exp animal disease/	285121
96		exp carnivore disease/	46998
97		exp bird/	221571
98		exp experimental animal welfare/	2921
99		exp animal husbandry/	41172
100		animal behavior/	79051
101		exp animal cell culture/	10628
102		exp mammalian disease/	170834
103		exp mammal/	21046787
104		exp marine species/	4925
105		nonhuman/	4820652
106		animal.hw.	4989598
107		or/92-106	23477323
108		107 not human/	6091716
109	Non-randomised study design filter	exp comparative study/	1137587
110		exp controlled study/	5270883
111		exp experimental study/	19170
112		exp observational study/	95264
113		exp field study/	2198
114		exp pilot study/	100224
115		exp prevention study/	2958
116		exp quasi experimental study/	3096
117		time series analysis/	17371
118		("interrupted time series" or "ITS analys?s" or cohort or "before and after").ti,ab.	813100
119		or/109-118	6734251
120	Combine study design sets	91 or 119	8397668
121	Combine infection control and	71 and 120	6426

	study design		
122	Exclude animal-only records	121 not 108	5658
123	Limit to records added to Embase since 01 Jan 2015	(2015$ or 2016$).ew.	3437428
124		122 and 123	**1204**
125	Identify paediatric records excluded from original AHRQ search (from 2006 onwards)	(adolescen$ or babies or child$ or fetal or infant or infants or neonat$ or newborn$ or NICU or paediatric$ or pediatric$ or school or schools or teen$ or youth$).ti.	1531605
126		limit 125 to yr="2006 -Current"	659844
127		122 and 126	303
128		127 not 124	**215**
129	Identify additional records for bacteria and fittings terms not included in original AHRQ search (from 2006 onwards)	13 or 15 or 16 or (19 and 23) or 34 or 38	42610
130		122 and 129	544
131		limit 130 to yr="2006 -Current"	412
132		131 not 124	**289**
133	Combine sets	124 or 128 or 132	**1679**

Ovid syntax

$ truncation character (unlimited truncation)
$*n* truncation limited to specified number (*n*) of characters (e.g. time$1 identifies time, timed, timer, times but not timetable)
? substitutes any letter (e.g. oxidi?ed identifies oxidised and oxidized)
adj*n* search terms within a specified number (*n*) of words from each other in any order
exp explodes controlled vocabulary term (i.e. includes all narrower terms in the hierarchy)
/ denotes controlled vocabulary terms (EMTREE)
* denotes a term that has been searched as a major subject heading
.ti. limit to title field
.ti,ab. limit to title and abstract fields
.ew. entry week to Embase

PubMed

The PubMed search is restricted to records that are not indexed for MEDLINE (i.e. in-process citations and citations from journals (or parts of journals) that are not currently MEDLINE-indexed) and to records added to PubMed since January 2006. The search comprises free-text terms only and replicates the free-text sets in the Embase search (converted from the Ovid syntax).

Date of search: 24/08/16

#	Query	Results[1]
1	((((("health care acquired"[TIAB] AND (infection*[TIAB] OR pathogen*[TIAB])) OR ("healthcare acquired"[TIAB] AND (infection*[TIAB] OR pathogen*[TIAB])) OR ("hospital acquired"[TIAB] AND (infection*[TIAB] OR pathogen*[TIAB])) OR ("health care associated"[TIAB] AND (infection*[TIAB] OR pathogen*[TIAB])) OR ("healthcare associated"[TIAB] AND (infection*[TIAB] OR pathogen*[TIAB])) OR ("hospital associated"[TIAB] AND (infection*[TIAB] OR pathogen*[TIAB]))))))	
2	((HAI[TI] OR HAIs[TI]))	
3	(((((antibiotic[TIAB] OR "multi-drug"[TIAB] OR multidrug[TIAB] OR methicillin[TIAB] OR vancomycin[TIAB]) AND resistan*[TIAB]) OR difficile[TIAB] OR ("methicillin resistant"[TIAB] AND aureus[TIAB]) OR ("vancomycin resistant"[TIAB] AND enterococc*[TIAB]))))	
4	((("carbapenemase producing enterobacteriaceae"[TIAB] OR acinetobacter[TIAB] OR "extended spectrum beta lactase"[TIAB] OR ESBL[TIAB])))	
5	((CDI[TI] OR MRSA[TI] OR VRE[TI]))	
6	((inpatient*[TIAB] OR patient*[TIAB]))	
7	((#3 OR #4 OR #5) AND #6)	
8	(#1 OR #2 OR #7)	

9	(("acute care"[TIAB] OR "burn* unit"[TIAB] OR "common area*"[TIAB] OR "critical care"[TIAB] OR "healthcare facility"[TIAB] OR "healthcare facilities"[TIAB] OR "healthcare setting*"[TIAB] OR "health care setting*"[TIAB] OR hospital*[TIAB] OR hospitalis*[TIAB] OR hospitaliz*[TIAB] OR ICU[TIAB] OR institution*[TIAB] OR "intensive care"[TIAB] OR "patient care area*" [TIAB] OR "medical facility"[TIAB] OR "medical facilities"[TIAB] OR "patient room*"[TIAB] OR ward*[TIAB]))	
10	((fomes[TIAB] OR fomite*[TIAB] OR "environmental reservoir*"[TIAB] OR "surface contamination"[TIAB] OR "surface microbes"[TIAB]))	
11	((bathroom*[TIAB] OR "bed rail*"[TIAB] OR bedrail*[TIAB] OR cart*[TIAB] OR chair*[TIAB] OR "clinical surfaces"[TIAB] OR commode*[TIAB] OR "environmental surfaces"[TIAB] OR "high contact"[TIAB] OR "high-touch"[TIAB] OR "hospital bed*"[TIAB] OR "hospital surfaces"[TIAB] OR "mobile equipment"[TIAB] OR "portable medical equipment"[TIAB] OR railing[TIAB] OR toilet*[TIAB] OR "shared medical equipment"[TIAB] OR wheelchair*[TIAB]))	
12	(furniture*[TIAB] OR furnishing*[TIAB] OR curtain*[TIAB])	
13	(#9 OR #10 OR #11 OR #12)	
14	(#8 OR #13)	
15	(("cleaning method*"[TIAB] OR "cleaning practice*"[TIAB] OR "cleaning protocol*"[TIAB] OR "cleaning regimen*"[TIAB] OR "cleaning routines"[TIAB] OR "cleaning technique*"[TIAB] OR "discharge cleaning"[TIAB] OR "discharge room cleaning"[TIAB] OR "enhanced cleaning"[TIAB] OR "environmental cleaning"[TIAB] OR "environmental decontamination"[TIAB] OR "environmental disinfection"[TIAB] OR "environmental sanitation"[TIAB] OR "hospital cleaning"[TIAB] OR "pre cleaning"[TIAB] OR precleaning[TIAB] OR "room cleaning"[TIAB] OR "room decontamination"[TIAB] OR "routine cleaning"[TIAB] OR "surface cleaning"[TIAB] OR "surface disinfection"[TIAB] OR "surface decontamination"[TIAB] OR "terminal cleaning"[TIAB] OR "terminal disinfection"[TIAB] OR "terminal room"[TIAB]))	
16	(cleaning[TI] OR decontamination[TI] OR disinfect*[TI] OR "infection control"[TI])	
17	((biocidal[TIAB] OR biocide*[TIAB] OR "chemical agent*"[TIAB] OR "chemical disinfection"[TIAB] OR "cleaning agent*"[TIAB] OR disinfectant*[TIAB] OR "disinfecting agent*"[TIAB] OR "disinfection agent*"[TIAB] OR germicidal[TIAB] OR germicide*[TIAB] OR sporicidal[TIAB] OR sporicide*[TIAB]))	
18	(("accelerated hydrogen peroxide"[TIAB] OR bleach[TIAB] OR bleaching[TIAB] OR "calcium hypochlorite"[TIAB] OR hypochlorite*[TIAB] OR "sodium hypochlorite"[TIAB]))	
19	(#17 OR #18)	
20	((clean*[TIAB] OR decontaminat*[TIAB] OR disinfect*[TIAB] OR housekeep*[TIAB]))	
21	(#19 AND #20)	
22	(((automated[TIAB] AND (cleaning[TIAB] OR device*[TIAB] OR decontamination[TIAB] OR disinfection[TIAB])) OR (("no-touch"[TIAB] OR "non touch"[TIAB]) AND disinfect*[TIAB]) OR ("room sterilization"[TIAB] OR "room sterilisation"[TIAB] OR "self disinfecting"[TIAB])))	
23	((("pulsed xenon"[TIAB] OR ((ultraviolet[TIAB] OR UV[TIAB]) AND (disinfection[TIAB] OR light[TIAB] OR irradiation[TIAB] OR radiation[TIAB]))) and (clean*[TIAB] OR decontaminat*[TIAB] OR disinfect*[TIAB] OR room*[TIAB])))	
24	((("superoxidized water"[TIAB] OR "superoxidised water"[TIAB] OR "electrolyzed water"[TIAB] OR "electrolysed water"[TIAB] OR ("hydrogen peroxide"[TIAB] OR H2O2[TIAB])) and (aerosol*[TIAB] OR fogging[TIAB] OR mist[TIAB] OR steam[TIAB] OR system*[TIAB] OR vapor*[TIAB] OR vapour*[TIAB])))	
25	((("self disinfecting"[TIAB] OR (antimicrobial[TIAB] OR copper[TIAB] OR silver[TIAB])) AND (coated[TIAB] OR coating[TIAB] OR impregnated[TIAB] OR surface*[TIAB])))	
26	(#15 OR #16 OR #21 OR #22 OR #23 OR #24 OR #25)	
27	(#14 AND #26)	
28	(2006/01:2016/08[EDAT] AND pubmednotmedline[SB])	
29	(#27 AND #28)	**274**

[1] **Saved searches in PubMed are rendered as a single search string, not individual search lines.**

PubMed syntax

* truncation character (unlimited truncation)
[TI] limit to title field
[TIAB] limit to title and abstract fields
[EDAT] date citation added to PubMed
[SB] PubMed subset

Cochrane Central Register of Controlled Trials

The search is restricted to free-text terms since MEDLINE-indexed records will been have been identified through the Embase search. The search also excludes records indexed with randomized controlled trial as a publication type to remove records from MEDLINE and Embase, as these too will have been identified through the Embase search.

Date of search: 24/08/16

#	Query	Results[2]
#1	(("health care acquired" near/1 (infection or pathogen)) or ("healthcare acquired" near/1 (infection or pathogen)) or ("hospital acquired" near/1 (infection or pathogen)) or ("health care associated" near/1 (infection or pathogen)) or ("healthcare associated" near/1 (infection or pathogen)) or ("hospital associated" near/1 (infection or pathogen))):ti,ab,kw (Word variations have been searched)	192
#2	(HAI or HAIs):ti,ab,kw (Word variations have been searched)	335
#3	(((antibiotic or "multi-drug" or multidrug or methicillin or vancomycin) near/1 resistan*) or difficile or ("methicillin resistant" near/2 aureus) or ("vancomycin resistant" near/1 enterococc*)):ti,ab,kw (Word variations have been searched)	3032
#4	("carbapenemase producing enterobacteriaceae" or acinetobacter or "extended spectrum beta lactase" or ESBL):ti,ab,kw (Word variations have been searched)	264
#5	(CDI or MRSA or VRE):ti,ab,kw (Word variations have been searched)	692
#6	(inpatient or patient):ti,ab,kw (Word variations have been searched)	527250
#7	(#3 or #4 or #5) and #6	2371
#8	#1 or #2 or #7	2838
#9	("acute care" or "burn unit" or "burns unit" or "common area" or "common areas" or "critical care" or "healthcare facility" or "healthcare facilities" or "healthcare setting" or "healthcare settings" or "health care setting" or hospital or hospitalis* or hospitaliz* or ICU or institution or "intensive care" or "patient care area" or "patient care areas" or "medical facility" or "medical facilities" or "patient room" or "patient rooms" or ward):ti,ab,kw (Word variations have been searched)	97208
#10	(fomes or fomite or "environmental reservoir" or "environmental reservoirs" or "surface contamination" or "surface microbes"):ti,ab,kw (Word variations have been searched)	14
#11	(bathroom or "bed rail" or "bed rails" or bedrail or cart or chair or "clinical surfaces" or commode or "environmental surfaces" or "high contact" or "high-touch" or "hospital bed" or "hospital beds" or "hospital surfaces" or "mobile equipment" or "portable medical equipment" or railing or toilet or "shared medical equipment" or wheelchair):ti,ab,kw (Word variations have been searched)	2385
#12	(furniture or furnishing or curtain):ti,ab,kw (Word variations have been searched)	283
#13	#9 or #10 or #11 or #12	99163
#14	#8 or #13	101021
#15	("cleaning method" or "cleaning methods" or "cleaning practice" or "cleaning practices" or "cleaning protocol" or "cleaning protocols" or "cleaning regimen" or "cleaning regimens" or "cleaning routines" or "cleaning technique" or "cleaning techniques" or "discharge cleaning" or "discharge room cleaning" or "enhanced cleaning" or "environmental cleaning" or "environmental decontamination" or "environmental disinfection" or "environmental sanitation" or "hospital cleaning" or "pre cleaning" or precleaning or "room cleaning" or "room decontamination" or "routine cleaning" or "surface cleaning" or "surface disinfection" or "surface decontamination" or "terminal cleaning" or "terminal disinfection" or "terminal room"):ti,ab,kw (Word variations have been searched)	155
#16	(cleaning or decontamination or disinfect* or "infection control"):ti,ab,kw (Word variations have been searched)	5289
#17	(biocidal or biocide or "chemical agent" or "chemical agents" or "chemical disinfection" or "cleaning agent" or "cleaning agents" or disinfectant or "disinfecting agent" or "disinfecting agents" or "disinfection agent" or "disinfection agents" or germicidal or germicide or sporicidal or sporicide):ti,ab,kw (Word variations have been searched)	591
#18	("accelerated hydrogen peroxide" or bleach or bleaching or "calcium hypochlorite" or hypochlorite or "sodium hypochlorite"):ti,ab,kw (Word variations have been searched)	1093
#19	(clean* or decontaminat* or disinfect* or housekeep*):ti,ab,kw (Word variations have been searched)	5341
#20	(#17 or #18) and #19	621

#21	((automated near/2 (cleaning or device or decontamination or disinfection)) or (("no-touch" or "non touch") near/1 disinfect*) or ("room sterilisation" or "room sterilization" or "self disinfecting")):ti,ab,kw (Word variations have been searched)	126
#22	(("pulsed xenon" or ((ultraviolet or UV) near/1 (disinfection or light or irradiation or radiation))) and (clean* or decontaminat* or disinfect* or room)):ti,ab,kw (Word variations have been searched)	28
#23	(("superoxidised water" or "superoxidized water" or "electrolyzed water" or "electrolysed water" or ("hydrogen peroxide" or H2O2)) and (aerosol or fogging or mist or steam or system or vapor or vapour)):ti,ab,kw (Word variations have been searched)	170
#24	(("self disinfecting" or (antimicrobial or copper or silver)) near/2 (coated or coating or impregnated or surface)):ti,ab,kw (Word variations have been searched)	233
#25	#15 or #16 or #19 or #21 or #22 or #23 or #24	6864
#26	#14 and #25	1518
#27	randomized controlled trial:pt (Word variations have been searched)	396856
#28	#26 not #27 Publication Year from 2006 to 2016	**504 (367)**

[2] These searches reflect results across all databases in the Cochrane Library. Of the 504 records in the final set, 367 were retrieved from the Trials database

CINAHL Plus (via EBSCO)

Search excludes records that are also indexed in MEDLINE. For 2015-2016, searches were not limited to study design terms. For 2006-2014, the additional terms excluded from the original AHRQ report were included and a study design limit applied (S59 to S71).

Date of search: 24/08/16

#	Query	Results
S71	S69 AND S70 Limiters - Exclude MEDLINE records	**79**
S70	(MH "Study Design+")	46,267
S69	S62 OR S68	1,268
S68	S67 NOT S58	342
S67	S54 AND S65	360
S66	S54 AND S65	480
S65	S63 OR S64	5,487
S64	S24 OR S29	4,363
S63	S11 AND S15	1,126
S62	S61 NOT S58	940
S61	S54 AND S60	1,014
S60	TI adolescen* or babies or child* or fetal or infant or infants or neonat* or newborn* or NICU or paediatric* or pediatric* or school or schools or teen* or youth*	285,600
S59	EM 2006* OR EM 2007* OR EM 2008* OR EM 2009* or EM 2010* OR EM 2011* OR EM 2012* OR EM 2013* OR EM 2014*	1,192,123
S58	S54 AND S57 Limiters - Exclude MEDLINE records	**989**
S57	S55 OR S56	206,350
S56	EM 2016*	82,863
S55	EM 2015*	123,487
S54	S31 AND S53	23,746
S53	S36 OR S37 OR S38 OR S39 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52	66,661
S52	(("self disinfecting" or (antimicrobial or copper or silver)) N2 (coated or coating or impregnated or surface))	373
S51	(MH "Copper")	1,403
S50	(("superoxidised water" or "superoxidized water" or "electrolyzed water" or "electrolysed water" or ("hydrogen peroxide" or H2O2)) and (aerosol or fogging or mist or steam or system or vapor or vapour))	352
S49	(("pulsed xenon" or ((ultraviolet or UV) N1 (disinfection or light or irradiation or radiation))) and (clean* or decontaminat* or disinfect* or room))	183
S48	((automated N2 (cleaning or device or decontamination or disinfection)) or (("no-touch" or "non touch") N1 disinfect*) or ("room sterilisation" or "room sterilization" or "self disinfecting"))	353
S47	(MH "Hydrogen Peroxide")	1,424

S46	S44 AND S45	3,004
S45	(clean* or decontaminat* or disinfect* or housekeep*)	21,208
S44	S41 OR S42 OR S43	4,824
S43	("accelerated hydrogen peroxide" or bleach or bleaching or "calcium hypochlorite" or hypochlorite or "sodium hypochlorite")	2,013
S42	(biocidal or biocide or "chemical agent" or "chemical agents" or "chemical disinfection" or "cleaning agent" or "cleaning agents" or disinfectant or "disinfecting agent" or "disinfecting agents" or "disinfection agent" or "disinfection agents" or germicidal or germicide or sporicidal or sporicide)	3,047
S41	S40	614
S40	(MH "Sodium Hypochlorite")	614
S39	(MH "Disinfectants")	2,099
S38	TI (cleaning or decontamination or disinfect* or "infection control")	8,102
S37	("cleaning method" or "cleaning methods" or "cleaning practice" or "cleaning practices" or "cleaning protocol" or "cleaning protocols" or "cleaning regimen" or "cleaning regimens" or "cleaning routines" or "cleaning technique" or "cleaning techniques" or "discharge cleaning" or "discharge room cleaning" or "enhanced cleaning" or "environmental cleaning" or "environmental decontamination" or "environmental disinfection" or "environmental sanitation" or "hospital cleaning" or "pre cleaning" or precleaning or "room cleaning" or "room decontamination" or "routine cleaning" or "surface cleaning" or "surface disinfection" or "surface decontamination" or "terminal cleaning" or "terminal disinfection" or "terminal room")	833
S36	S32 OR S33 OR S34 OR S35	62,043
S35	(MH "Infection Control+")	52,491
S34	(MH "Sanitation+")	10,019
S33	(MH "Sterilization and Disinfection+")	8,215
S32	(MH "Cleaning Compounds")	812
S31	S18 OR S30	609,064
S30	S21 OR S22 OR S26 OR S27 OR S28 OR S29	594,563
S29	(furniture or furnishing or curtain)	4,325
S28	(bathroom or "bed rail" or "bed rails" or bedrail or cart or chair or "clinical surfaces" or commode or "environmental surfaces" or "high contact" or "high-touch" or "hospital bed" or "hospital beds" or "hospital surfaces" or "mobile equipment" or "portable medical equipment" or railing or toilet or "shared medical equipment" or wheelchair)	15,111
S27	(fomes or fomite or "environmental reservoir" or "environmental reservoirs" or "surface contamination" or "surface microbes")	281
S26	S23 OR S24 OR S25	7,427
S25	(MH "Floors and Floorcoverings")	290
S24	(MH "Interior Design and Furnishings+")	3,722
S23	(MH "Beds and Mattresses+")	3,499
S22	("acute care" or "burn unit" or "burns unit" or "common area" or "common areas" or "critical care" or "healthcare facility" or "healthcare facilities" or "healthcare setting" or "healthcare settings" or "health care setting" or hospital or hospitalis* or hospitaliz* or ICU or institution or "intensive care" or "patient care area" or "patient care areas" or "medical facility" or "medical facilities" or "patient room" or "patient rooms" or ward)	416,501
S21	S19 OR S20	325,527
S20	(MH "Hospitals+")	84,785
S19	(MH "Health Facilities+")	325,527
S18	S1 OR S2 OR S3 OR S17	33,643
S17	S15 AND S16	9,562
S16	S9 OR S10 OR S11 OR S12	24,771
S15	S13 OR S14	1,221,750
S14	(inpatient* or patient*)	1,205,754
S13	(MH "Patients+")	195,306
S12	TI (CDI or MRSA or VRE)	2,325
S11	("carbapenemase producing enterobacteriaceae" or actinobacteria or acinetobacter or "extended spectrum beta lactase" or ESBL)	2,133
S10	(((antibiotic or "multi-drug" or multidrug or methicillin or vancomycin) N1 resistan*) or difficile or ("methicillin resistant" N2 aureus) or ("vancomycin resistant" N1 enterococc*))	19,016
S9	S4 OR S5 OR S6 OR S7 OR S8	10,818
S8	(MH "Actinobacteria+")	55
S7	(MH "Vancomycin Resistant Enterococci")	84
S6	(MH "Enterococcus+")	1,355
S5	(MH "Methicillin-Resistant Staphylococcus Aureus")	3,497

S4	(MH "Clostridium Infections+") OR (MH "Clostridium Difficile")	6,521
S3	HAI or HAIs	882
S2	(("health care acquired" N1 (infection or pathogen)) or ("healthcare acquired" N1 (infection or pathogen)) or ("hospital acquired" N1 (infection or pathogen)) or ("health care associated" N1 (infection or pathogen)) or ("healthcare associated" N1 (infection or pathogen)) or ("hospital associated" N1 (infection or pathogen)))	2,887
S1	(MH "Cross Infection+")	26,028

ClinicalTrials.gov

Date of search: 02/11/16

#	Query	Results
	("hospital acquired infection" OR "hospital-associated infection" OR "healthcare acquired infection" OR "healthcare associated infection" OR "HAI" OR "Multidrug Resistant" OR "MDRO" OR "Clostridium difficile")	1292
	The above search was combined with the terms below	
	"Antimicrobial"	433
	"Silver"	7
	"Copper"	5
	"Bleach"	1
	"Hydrogen peroxide"	3
	"UV" or "ultraviolet" or "ultra violet"	5
	"electrolysed" or "electrolyse" or "electrolyzed" or "electrolyze"	1
	Total unique records screened	**445**

Appendix 2. Intervention data collection mapped to TIDieR reporting items

TIDieR item	Infection control review item and subheadings	Notes (not all in DE form, additional guidance)
1. **Name**	Name or label used for the intervention	
2. **Why** – rationale, goal	What mechanism of action or rationale was provided for the intervention? [verbatim extract or precis]	Use for background, not in table reporting characteristics of included studies.
What 3. Materials	Materials • Equipment or physical materials • Dilution/preparation/composition	
4. Procedures	Procedures - Process	See additional elements under who provided, when & how much.
5. **Who provided** – including expertise, specialist training	Procedures – Personnel - note if a specialist or training required	
6. **How** – modes of delivery	Procedures - Process	
7. **Where** – types of location where intervention occurred	Facilities disinfected (or using antimicrobial materials) – units or wards or rooms Location (country, hospital location and description) Surfaces disinfected (or using antimicrobial materials)	[e.g. ward, patient room, isolation room; indicate if terminal clean]
8. **When & how much** – schedule, duration, intensity, dose	Procedures - Frequency of process Procedures - Duration of process/contact time	
9. **Tailoring** – if planned, what, why, when, how	Not collected other than if described under procedures.	Any changes to procedures etc for different pathogens, risk groups, other?
10. **Modifications** – if occurred, describe (what, why, when, how)	Did the investigators modify the intervention in any way during the intervention period? [verbatim extract or precis]	
How well 11. **Planned** – if adherence to protocol assessed, how, by whom, any attempt to increase adherence	Was there any assessment of *adherence to planned protocols* for disinfection or use of materials? [verbatim extract]	Including assessment of bacterial contamination of surfaces (measure of treatment fidelity)
12. **Actual** - if adherence to protocol assessed, describe extent to which intervention delivered a planned?	If 'yes' to previous, what were the findings (i.e. to what extent was there *adherence to/deviation from protocol*)? [verbatim extract]	Note availability of quantitative data on contamination of surfaces, but don't report data or analyses (typically covers all sites sampled, multiple time points).

Appendix 3. Statistical analysis of interrupted time series data

We undertook ITS analyses of monthly rates of infection (CDAD, MRO, and MRSA) using data extracted from figures (Boyce 2008, Haas 2014, Hacek 2010, McMullen 2007, Orenstein 2011). The package DigitizeIt (version 2.2) was used to obtain the data points from the figures. One study author (Mitchell 2014) provided monthly aggregate data (number of counts and patient-days) for a figure from which we were unable to extract data. For all analyses, we standardised the rates of infection to per 1,000 patient-days.

We fitted ordinary least squares segmented regression models adjusted for autocorrelation (see below). These models allow a regression line between rate and time to be fitted to each period (pre-intervention, post-intervention) (Wagner 2002).

Using the notation of Linden (Linden 2015), for ITS with two periods, we fitted the following regression model:

$$Y_t = \beta_0 + \beta_1 T_t + \beta_2 X_t + \beta_3 X_t T_t + \epsilon_t,$$

Model (1)

where Y_t is the observed rate of infection in month t, T_t is a continuous variable indicating the time in months since the start of the study, X_t is an indicator variable representing the intervention period, and $X_t T_t$ is an interaction term. In this model, β_0 represents the baseline infection rate at time 0; β_1 represents the slope, or change in infection rate with each month in the pre-intervention period; β_2 represents the *change in level* and β_3 the *change in slope*. The *change in level* represents the difference in the (i) predicted rate at the first point immediately following the introduction of the intervention based on the regression model in the first period, and (ii) the expected rate at the same point based on the regression model in the second period (Huitema 2011). The *change in slope* represents the difference between the first period and second period slopes.

Model (1) can be easily extended to include additional intervention periods, such as the following model for three periods:

$$Y_t = \beta_0 + \beta_1 T_t + \beta_2 X_t + \beta_3 X_t T_t + \beta_4 Z_t + \beta_5 Z_t T_t + \epsilon_t.$$

Model (2)

The coefficients β_0 to β_3 have the same interpretation as in *Model (1)*. Z_t is an indicator variable representing the start of the second intervention period, and $Z_t T_t$ is an interaction term. β_4 and β_5 represent the *change in level* and *change in slope* from the second period.

We fitted either Model (1) or Model (2), as appropriate, using ordinary least squares regression with Newey-West standard errors (Newey 1987). These standard errors allow adjustment for autocorrelation in the rates across time and potential heteroscedasticity. We chose to adjust all models for first-order correlation, rather than first test for autocorrelation and make a decision as to whether to adjust on the basis of the test result, since tests for autocorrelation have low power when the number of observations in the series is small (Huitema 2011). We did not adjust for any seasonal effects. We fitted a range of plots to examine autocorrelation (e.g. residuals versus time, partial autocorrelation plots), heteroscedasticity (residual versus fitted plots), normality of the residuals (kernel density plots), and influential observations (leverage plots). The models were implemented in the statistical package Stata (StataCorp 2015) using the itsa package (Linden 2015).

Table 1 provides information for each ITS study on the number of time points at each period, the statistical analysis that was performed in the paper, the source of the data we reanalysed and notes regarding any assumptions we made in the re-analysis.

For each study, we present estimates of the slopes in each period, and estimates of the *change in level(s)* and *change in slope(s)*, along with 95% confidence intervals and p-values. In addition, we present plots of the observed rates over time, overlaid with the predicted rates from the regression models.

References

Huitema, B. E. (2011). The analysis of covariance and alternatives : statistical methods for experiments, quasi-experiments, and single-case studies. Hoboken, N.J., Wiley.

Linden, A. (2015). "Conducting interrupted time-series analysis for single- and multiple-group comparisons." Stata Journal **15**(2): 480-500.

Newey, W. K. and K. D. West (1987). "A simple, positive semi-definite, heteroskedasticity and autocorrelation consistent covariance matrix." Econometrica **55**: 703-708.

StataCorp (2015). Stata Statistical Software: Release 14. College Station, TX: StataCorp LP. .

Wagner, A. K., S. B. Soumerai, F. Zhang and D. Ross-Degnan (2002). "Segmented regression analysis of interrupted time series studies in medication use research." J Clin Pharm Ther **27**(4): 299-309.

Table 1: Additional analysis information for the ITS studies

Study	No. pts 1	No. pts 2	No. pts 3	Statistical analysis reported in paper	Source of data and assumptions in re-analysis of the data
Boyce 2008	12	7	10	"To determine whether the incidence of CDAD was correlated with antimicrobial use patterns for the entire period from January 2004 through March 2006, simple linear regression methods were used." (pg 4, col 2)	Data source: Figure 1 of Boyce 2008. Data was collected from Jan 2004 to March 2006. The authors defined three periods: pre-epidemic period (Jan 2004 to Oct 2004); epidemic period (Nov 2004 to May 2005 - at which point control measures were implemented i.e. an intervention); intervention period (Jun 2005 to Mar 2006). However, the authors only analyse data from the 'pre-intervention' period Jun 2004 to Mar 2005 and the 'intervention period' Jun 2005 to Mar 2006. The reason given is "Because there may be seasonal variation in the incidence of CDAD,3 we compared the incidence of CDAD during the 10-month intervention period with the incidence during the same 10-month period in the preceding year." (pg 3, col 1). We have reanalysed the complete dataset using the three periods defined above, except that the second period is started at Dec 2004, instead of Nov 2004, because the authors state that "In late November 2004, control measures were implemented, including ..." (pg 2, col 2)
Haas 2014	12	12	NA	"Rates of CDI were compared by calculating incidence rate ratios with 95% confidence intervals. To compare time to hospital lacquired CDI cases in rooms previously housing a CDI patient, the median number of infection-free days in rooms during the preintervention and UVD period was compared using the Kaplan-Meier product-moment estimator and the log-rank test. Analyses were conducted in Stata (version 12.1; StataCorp, College Station, TX)." (pg 2, col 2)	Data source: Figure 1 of Nagaraja et al. American Journal of Infection Control 2015; 43: 940-5. Two months missing in the middle of the series because “The months of May and June in 2011 were excluded because UV disinfection was not used consistently until late June 2011.” (941, col 2) Therefore, these have been considered a lag period for the intervention, and so have been removed (see Wagner pg 303, col 2) Number of cases are available per month, but not the number of patient-days per month. The total number of patient-days are reported for the pre-intervention and post-intervention periods. Therefore, in the calculation of a rate per month, it has been assumed that the number of patient-days is equally distributed across the months.
Hacek 2010	10	24	NA	"Statistical significance was determined using the Poisson regression analysis." (pg 351, col 1)	Data source: Figure 1 of Hacek 2010.
Mitchell 2014	46	38	NA	"The comparison of MRSA bacteraemia and MRSA acquisition between the two periods was performed using Fisher’s exact test to determine any difference in the total incidence between these two arms. To explore this further, time series analysis was performed to examine the monthly incidence of MRSA bacteraemia and acquisition individually." (pg 3, col 2)	Data source: Contact with author to obtain data from Figure 2 of Mitchell 2014.
McMullen 2007	7	5	24	"Mantel-Haenszel x2 tests and relative risk (RR) calculations with 95% confidence intervals (CIs) were used to compare CDAD rates between the preintervention and postintervention periods." (pg 2, col 1)	Data source: Figure 1 of McMullen 2007.
Orenstein 2011	12	12	NA	"The incidences of hospital-acquired CDI on each unit and for both units combined were compared using Fisher's exact test to compare	Data source: Figure 1 of Orenstein 2011.

Study	No. pts 1	No. pts 2	No. pts 3	Statistical analysis reported in paper	Source of data and assumptions in re-analysis of the data
				the incidence of infection before and after the intervention." ([g 1, col 2)	

NA = not applicable; No. pts. X = Number of points in period 1, 2, or 3.

Appendix 4. Changes to protocol

Types of comparators

To account for disinfectants other than sodium hypochlorite that are used as the standard of care in some settings, we added the following: Other disinfectants, such as quaternary ammonium, but only if included in the intervention arm or explicitly described as being part of standard cleaning/disinfection practices.

We refined the following to clarify that we did not exclude studies when the cleaning method between the groups appeared similar, but this could not be confirmed from the study report: Where the intervention arm included any of the above, the preparation, frequency and methods of cleaning should, ideally, have been the same in both arms. Studies were not excluded on this basis, however such differences were noted or recorded as not reported.

We added previously missing comparator for sodium hypochlorite: For studies testing the effects of sodium hypochlorite, eligible comparators were HP disinfection, UV disinfection, electrolysed water (as above) or cleaning/disinfection practices that were the standard of care (usual practice).

Types of studies - ITS

For clarity and consistency with our a priori analysis plans, we added additional text to specify that studies that presented time series data were eligible irrespective of how they were described or analysed, and that we retrieved full text of all eligible studies that reported a BA design in order to confirm availability of such data. This change is not a change to the eligibility criteria.

Search methods

As described in the methods, we decided not to search OpenGrey and the WHO ICTRP trials register because of the difficulty of constructing searches of these sources for the review topic and the low likelihood that included studies would have been retrieved through alternative sources.

GRADE assessment

We were unable to meta-analyse studies (as no RTs were included in the review), which had implications for the way in which GRADE was applied. We therefore revised the description of the GRADE process to clarify how GRADE was applied to single studies (especially regarding assessment of imprecision and reporting of effects from time series studies), and how conclusions were drawn across time series studies.

Appendix 5. Characteristics of included studies

Study ID Anderson 2017

Study design(s)	Cluster randomised crossover trial
Setting / Population	Units: single occupancy 'seed rooms', defined as rooms from which the previous patient had "a microbiologically proven current or history of infection or colonisation" of a target pathogen. Environmental Services (EVS) personnel in hospitals were instructed to apply interventions to all 'contact precaution' rooms. Eligible patients were then determined from hospital records. Eligible patients were those exposed to a seed room for 24 hours or more (exposed patients). Location (country, hospital(s)): USA. Nine hospitals: two tertiary (853 and 950 bed), six community (148, 202, 218, 310, 335, and 660 bed), one Veterans Affairs (271 bed).
Intervention(s)	I1. Sodium hypochlorite for terminal room decontamination (MROs only, 3740 exposed patients) I2. Ultra violet light for terminal room decontamination as an adjunct to standard disinfection (MROs, 3920 exposed patients; *C. difficile* 2678 exposed patients) I3. Ultra violet light plus sodium hypochlorite for terminal room decontamination as an adjunct to standard disinfection (MROs only, 4663 exposed patients) All interventions were used as an adjunct to standard daily and terminal cleaning (see 'Comparators').
	7 months per intervention (one month wash-in, 6 month intervention). Each hospital received all four interventions (I1, I2, I3, and comparator) but in a different, randomly generated sequence over 28 months.
	Materials: All materials for intervention and comparators (microfiber cloths, buckets, dispensers, disinfectants) were provided to hospitals by the study. I1. Sodium hypochlorite – see 'Comparators'. I2 and I3. Commercial UV-disinfection system (Tru-D Smart UVCTM). Eight hospitals were provided with 1-4 devices (based on hospital size); one hospital purchased four devices.
	Process I1. Sodium hypochlorite terminal room disinfection. Daily clean with QA (as per comparator, MRO seed rooms), then terminal room clean with sodium hypochlorite (see 'Comparators' for procedure). Process I2 and I3. A single UV system was placed in the centre of each vacated room, positioned to minimise shadowing (areas not in direct line of UV light, draws/cupboards opened) and ensure light was emitted into the adjacent bathroom. To minimise room turnover time, a 1-stage disinfection protocol was used, rather than 2-stage (wherin system is operated twice, once in bathroom and once in patient room). Pre-testing was performed to assess effectiveness of 1-stage (based on colony counts on innoculated formica plates). Frequency of process: terminal room clean (after room vacated by patient(s) with "a microbiologically proven current or historic infection or colonisation" of a target pathogen) Duration of process/contact time: Not reported for sodium hypochlorite. UV light - Cycle run until "all eight sensors detected a sufficient reflected dose" of 12,000 µWs/cm2 (MROs) or 22,000 (*C. difficile*). Personnel: All cleaning/disinfection procedures were performed by environmental services personnel (EVS) within each hospital. At the start of each new intervention period, training in the protocol for the new cleaning/disinfection intervention was provided to EVS personnel.
	Surfaces disinfected: Not reported for sodium hypochlorite. UV light - any exposed surface within the room being decontaminated (see process).
Comparator(s)	Standard disinfection with quaternary ammonium (MRO seed rooms) Standard disinfection with sodium hypochlorite (*C. difficile* seed rooms)
	7 months (one month wash-in, 6 month intervention). Each hospital received all four 7-month interventions (including the comparator) in a different, randomly generated sequence over the 28-month study.
	Materials: MRO seed rooms: Quaternary ammonium-containing disinfectant (EnCompass Disinfectant and the EnCompass System, Ecolab) used for standard daily and terminal room disinfection. *C. difficile* rooms: commercial wipes (Clorox brand), pre-saturated with sodium hypochlorite (1:10 dilution bleach to water) used for standard daily and terminal room disinfection. Wipes were disposed of after use.

	Process: Daily cleaning protocols were unchanged from those used routinely in each hospital (materials/ disinfectants provided by the study). Standard protocols for terminal disinfection were provided to hospitals by the study. Training for EVS staff was provided as described under 'Interventions'.
Co-interventions (both periods)	Standard daily cleaning was used throughout all intervention periods (as described under comparator).
Adherence	Compliance with study protocols was monitored through: (1) random sampling of surfaces using pH pen to confirm use of QA or sodium hypochlorite; (2) recording all details of UV device deployment (room number, date, start/stop time, type of cylce, cycle completion status (reason for non-completion). Feedback was provided by study team during wash-in period (weekly), during first 1-2 months (weekly), then biweekly. Bacterial contamination of surfaces was measured (see 'Other outcomes').
Outcomes	Outcome category: Infection Outcome (metric): Incidence of hospital-acquired *C. difficile*-associated disease (cases per 1,000 exposure-days) Level of measurement: patients exposed to rooms in which previous patient had microbiologically confirmed CDAD (CDAD 'seed' rooms) Data collection periods: througout 28 month study (April 2012-July 2014 inclusive) Data collection methods: not specified. Assume electronic file audit to identify 'seed' rooms confirm patient eligibility. Outcome definition: patients (1) in a seed room, with a culture/test that was (2) positive for *C. difficile (i.e.* same target organism isolated from the preceding patient), obtained (3) during the index admission either during or after exposure to the seed room, or (4) within 28 days of discharge from the room. Outcome category: Infection or colonisation (composite) Outcome (metric): Incidence of hospital-acquired MROs (MRSA, VRE, MDR *Acinetobacter*; combined and individually) (cases per 1,000 exposure-days) Level of measurement: patients exposed to rooms in which previous patient had microbiologically confirmed MRSA, VRE or MDR *Acinetobacter* (MRO 'seed' rooms) Data collection periods: througout 28 month study (April 2012-July 2014 inclusive) Data collection methods: not specified. Assume electronic file audit to identify 'seed' rooms confirm patient eligibility. Outcome definition: patients (1) in a seed room, with a culture/test that was (2) positive for MRSA, VRE or MDR *Acinetobacter* (and the same target organism isolated from the preceding patient), and was obtained (3) during the index admission either during or after exposure to the seed room, or (4) within 90 days of discharge from the room.
Other outcomes	(1) Adverse events, safety and other considerations (2) Bacterial contamination of surfaces in intervention rooms (in two hospitals (20-28 randomly selected seed rooms per intervention group, 10 surfaces per room) (3) Health service delivery outcomes (room turnover time, emergency room wait time, time on diversion) (4) Infection arising from hospital-acquired MROs (MRSA, VRE or MDR *Acinetobacter*; combined and individually). Outcomes listed in trial registry; data not yet reported.
Pathogen(s)	MRSA, VRE, and multidrug-resistant Acinetobacter, C. difficile

Risk of bias assessment

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk of bias	A random number generator was used to determine the order in which hospitals would receive disinfection strategies, however due to a limited number of UV devices, once the number of devices had been allocated in a particular period, subsequent hospitals could not be assigned to one of the UV strategies for that period. For this set of hospitals, it was not clear how the order in which they received the strategies was determined (p2, col 2). However, given this is a crossover trial, it is unlikely that if there was any subversion, this would have an impact.

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk of bias	The person who allocated hospitals to the intervention sequence was not masked; however, we judged it unlikely that bias would arise through selective allocation of an intervention sequence to hospitals.
Baseline characteristics	Unclear risk of bias	Patient characteristics are reported by intervention group across all periods, without reporting separately by intervention sequence. Hence it is unclear whether there are differences across different periods, with the resulting risk of bias judged to be unclear.
Baseline outcome measurements	Unclear risk of bias	Outcome data are reported by intervention group across all periods, without reporting separately by intervention sequence. Hence it is unclear whether there are differences across different periods, with the resulting risk of bias judged to be unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk of bias	The risk of bias arising from incomplete data was judged low because all patients meeting eligibility criteria were included in analyses and data were derived from administrative sources. All patients meeting the inclusion criteria were included in the analysis. For *C-difficile*, a culture was likely to be taken when there were symptoms, so there was unlikely to be missing data (arising from missed cases). For MROs, it was not clear what percentage of 'exposed' patients had a culture taken. Patients who did not have a culture taken would be assumed to not be a case, so it was judged unclear whether there might be missing MRO cases. However, overall the risk of this biasing the results was deemed low given the number of hospitals and study duration.
Knowledge of the allocated interventions adequately prevented during the study	Low risk of bias (performance bias, outcome detection bias for MRO outcome) Unclear risk of bias (infection outcome, CDAD)	It was not possible to mask health professionals and outcome assessors to the intervention. Patient participants were likely to be unaware of the intervention (disinfection occurred in vacated rooms), and were unable to influence outcome measurement (not patient reported). Performance bias: We judged it unlikely that those applying the intervention or other staff could influence delivery of the intervention, since multiple controls were in place to monitor compliance. Infection/colonisation outcome (detection bias): The risk of bias was judged low for measurement of MRO acquisition, since testing appeared to be performed according to hospital protocols for surveillance. The risk of bias for measurement of CDAD was judged unclear, since test ordering might have altered in response to intervention and the trial authors note potential for acquisition bias (p9, col 1 limitations).
Protection against contamination	Low risk of bias	Implementation of each of the interventions required considerable resources (because of the type of intervention and extent of use within each hospital). Hence, the risk of exposure to interventions in use in other hospitals was considered low, and any contamination that might occur across sites was unlikely to be sufficient to bias observed effects.
Selective outcome reporting (reporting bias)	Low risk of bias	An additional eight infection outcomes were listed in the registry entry but not mentioned in the paper/supplementary files (MRSA, VRE, MDR *Acinetobacter*, and all three MROs combined, each measured among exposed patients; same four outcomes measured at hospital level). It is unclear whether the authors plan to report these separately. These are separate outcomes, so their omission doesn't bias the results for the outcomes reported in this review (hence risk of bias was judged as low, as conclusions for individual outcomes would not alter). However, infection was specified as a primary outcome for the review, hence these are important outcomes for which not data are currently available.
Other risks of bias	Low risk of bias	RoB arising from carryover of interventions between periods was judged as low: This is a cluster crossover trial, so each site serves as its own reference group/comparator. There is potential for hospitals to carry over interventions into subsequent periods; however, the investigators used safeguards against this. There was a one month wash-in between each intervention period, during which compliance with the new intervention was monitored and fed back to hospitals at

Bias	Authors' judgement	Support for judgement
		weekly meetings. There is also potential for participants to be carried over into the next intervention period, however the wash-in period meant it was unlikely that participants from one period would be included in the next period. RoB arising from conflict of interests was judged as low. Two authors had received consulting fees from the manufacturer of the bleach wipes used in the study. Other authors, including the contact author and the PI on the registry entry, did not declare any industry ties. The manufacturers of the interventions used in all arms of the trial were identified as having made "significant material contributions to the study ... but played no role in the funding, design, analysis, or manuscript preparation." (p9)

Study ID Boyce 2008

Study design(s)	Time series (re-analysed)
Setting / Population	Units: 5 wards, all rooms (No. rooms/cleans not reported). On 3 of 5 wards, all rooms were decontaminated at the same time. On 2 wards, rooms were decontaminated over a 2 week period. Location (country, hospital(s)): USA, university-affiliated hospital (500-bed)
Intervention(s)	Hydrogen peroxide vapour room decontamination
	June 2005 - March 2006 (10 months)
	Materials: Commercial HPV decontamination system (Bioquell) Dilution/disinfectant preparations: see process
	Process: Rooms were vacated, then cleaned of any visible dirt with a detergent-based cleaning agent. Heating, ventilation, and air conditioning ducts were sealed using tape. HPV system generators were used to convert 30% liquid hydrogen peroxide into HPV, which was injected into sealed rooms until approximately 1 µm of hydrogen peroxide was deposited on exposed surfaces before being converted to oxygen and water vapor by catalytic converters. Rooms from which patients with CDAD were discharged were also cleaned daily with sodium hypochlorite solution (1,000 ppm). Frequency of process: terminal clean (after room vacated by patient(s) with CDAD) Duration of process/contact time: 3–4 hours for a patient room; ~ 12 hours for a ward Personnel: unclear who conducted the HPV decontamination (e.g. Bioquell, trained staff). Bioquell personnel conducted an engineering review (including heating, ventilation, air conditioning systems) prior to commencemen of HPV decontamination.
	Surfaces disinfected: Not reported (any exposed surface within the room being decontaminated).
Comparator(s)	Standard cleaning/disinfection alone
	Nov 2004 - May 2005 (7 months)
	Standard cleaning/disinfection, details of which were not reported.
Co-interventions (both periods)	Standard cleaning/disinfection was used throughout intervention and pre-intervention period. Additional infection control measures (reminding physicians to avoid prescribing high-risk antimicrobial agents, performing *C. difficile* toxin assays more frequently, placing patients with CDAD in isolation, using contact precautions during patient care, using soap and water for hand hygiene after caring for patients with CDAD, and disinfecting rooms of patients with CDAD with a 1:10 dilution of household bleach (sodium hypochlorite)). It is unclear whether the additional controls are just reminders or whether some are new practices.
Adherence	Bacterial contamination of surfaces was measured, initially to optimise and then to monitor cycle time.
Outcomes	Outcome category: Infection

	Outcome (metric): incidence of hospital-acquired *C. difficile*-associated disease (cases per 1,000 patient-days) Level of measurement: hospital-wide Data collection periods: pre-intervention June 2003 - March 2005 (only Nov 04 - Mar 05 was re-analysed), intervention period Jun 2005 - Mar 2006 (monthly throughout both 10 month periods) Data collection methods: retrospective electronic file audit to identify new nosocomial CDAD cases amongst *C. difficile* toxin-positive patients (pre-intervention period and 6 months of intervention period). Prospective identification of cases in the first and last 2 months of the intervention period during which there was surveillance for the epidemic *C. difficile* strain NAP1. Outcome definition (new hospital-acquired cases): patients with diarrhea and a positive *C. difficile* toxin tests > 72 hours after admission or < 72 hrs after re-admission for patients discharged within the preceeding 3 months.
Other outcomes	(1) Adverse events, safety and other considerations (noted in discussion, unclear if any systematic data collection) (2) Bacterial contamination of surfaces in intervention rooms (immediately before and after HPV disinfection)
Pathogen(s)	*C. difficile*

Risk of bias assessment

Bias	Authors' judgement	Support for judgement
Intervention independent of other changes (ITS)	high risk of bias	The authors considered changes concurrent with the intervention, suggesting most were unlike to explain observed outcomes, including: antibiotic prescribing (significant correlations between CDAD and antimicrobial use (less use in intervention period of all antimicrobials, fourth-generation cephalosporins); reported that this was "unlikely to explain reduced CDAD incidence during the intervention period"), compliance with hand hygiene and contact precaution policies (no difference when compliance in late 2004 compared to Dec 2005; data not reported), epidemic strain (present at beginning and near end of intervention period so "not a potential explanation"), co-interventions (used in both periods). The authors could not exclude seasonal variation (unclear effects) and regression to the mean as a possible explanation for observed effects.
Shape of the intervention effect pre-specified (ITS)	low risk of bias	Reanalysis of data was conducted using ITS methods, with a clearly defined intervention point.
Intervention unlikely to affect data collection (ITS)	high risk of bias	There was more frequent testing for CDAD during the intervention period (through laboratory based surveillance), which could lead to an increase in cases identified. This could bias results in favour of the control, although it may also result in earlier use of control measures, potentially reducing the number of cases.No other changes to the source or method of data collection were reported in either intervention or control period, and the intervention is unlikely to directly affected data collection (which requires laboratory testing, then identification of patients from routinely collected data).
Knowledge of the allocated interventions adequately prevented during the study (ITS)	low risk of bias	Likely or possible that personnel, including those keeping patient chart records and requesting laboratory testing for *C. difficile* toxin, would have been aware of the intervention. This may have increased requests for screening, potentially increasing the number of cases detected (accounted for in the previous domain). Cases were based on file audit of the infection control database (some retrospective, some prospective); it is unclear whether those doing file audits knew the period in which cases fell (intervention or control). However, it seem unlikely that this would have an important influence on outcome measurement.
Incomplete outcome data	low risk of bias	No mention of incomplete data. Hospital wide data, from routinely collected sources, so it is unlikely that data are missing or that data were more likely to be missing in the intervention than control period.

Bias	Authors' judgement	Support for judgement
adequately addressed (ITS)		
Selective outcome reporting (ITS)	low risk of bias	Selective reporting cannot be completely ruled out (study is not prospectively registered; no published protocol), but results for all outcomes mentioned in the methods have been reported and outcomes likely to be measured are reported.
Other risks of bias (ITS)	high risk of bias	The intervention tested was provided by the service provider at discount. Two authors received salary from the intervention service provider (Bioquell) and appear to be employees of the company. There is no information about author contributions, so it is unclear what role the Bioquell employees took in the design, conduct and reporting of this study. There is no mention of steps taken to safegaurd against potential biases, such as pre-registration or publication of a study protocol. Hence the study is considered to be at risk of bias.

Study ID Haas 2014

Study design(s)	Time series (original analysis)
Setting / Population	Units: contact precautions rooms (*C. difficile* and MRO patients), burns unit, operating rooms, dialysis unit. Other units on request. (No. rooms/cleans not reported). Location (country, hospital(s)): USA, 643-bed tertiary care hospital (including 180 ICU beds; and referral center for highly immunocompromised patients).
Intervention(s)	Pulsed xenon ultra-violet room disinfection
	July 2011 - April 2013 (UVD was introduced in May, but "was not used consistently until late June" Nagaraja 2015, p941)
	Materials: Pulsed xenon UVD (Xenex Corporation, Austin, TX)
	Process: Unoccupied rooms (including bathrooms) were cleaned, then the UVD machine was operated with the door closed. Furnishings and fitting were placed in the path of UV light (e.g. drawers, bed rails, blood pressure cuffs were move, closets were opened). Glass windows and doors were covered. Notification to deploy UVD was integrated in the bed management system. Frequency of process: varied by type of room. On discharge - contact precautions rooms, burns unit. End of day - operating rooms. Weekly - dialysis unit. On request - long stay patients, units with high MRO or *C. difficile* presence. Routine use of UVD in bathrooms of occupied patient rooms was introduced in May 2012. Duration of process/contact time: determined by room size and the manufacturer's protocol; longest setting was used (6 minutes each in bathroom, 12 minutes at head and foot of bed in single patient room OR 6 at head and foot of each bed in shared rooms). Personnel: Environmental services staff (outsourced service), with supervisor responsible for deployment to required rooms. Staff received training that commenced in May 2011 and ran through to when the UVD system was in routine use (July 2011)
	Surfaces disinfected: Any exposed surface.
Comparator(s)	Standard cleaning/disinfection alone
	Jan 2009 - June 2011 (30 months)
	Standard cleaning/disinfection with bleach (sodium hypochlorite 0.55%) daily and at discharge (including for contact precaution rooms).
Co-interventions (both periods)	Standard cleaning/disinfection was used throughout intervention and pre-intervention period.

Adherence	Weekly monitoring of use of UVD (based on logbook and machine location; validated against contact precautions discharge records), and coding of reasons why opportunites to use UVD were missed. Time for cleaning and UVD, and the location of the UVD were also recorded. The authors reported that 76% of contact precaution rooms received UVD (range 66-93% per month).
Outcomes	Outcome category: Infection Outcome (metric): incidence rates of hospital-acquired MROs and *C. difficile*-associated disease (cases per 1,000 patient-days) Level of measurement: hospital-wide Data collection periods: pre-intervention January 2009- June 2011 (30 months), intervention period July 2011-April 2013 (22 months) (quarterly throughout both periods) Data collection methods: retrospective audit of infection control databases Outcome definition (new hospital-acquired cases): patients with onset of symptoms and either (i) a positive culture for an MRO or (ii) positive *C. difficile* toxin test > 72 hours after admission and < 48 hrs after discharge. MROs tested for were VRE, MRSA, MRGN bacteria.
	Incidence rates for individual pathogens were reported (VRE, MRSA, MRGN bacteria, *C. difficile*), but not included here because only pre- and post intervention rates were reported and analysed. The authors note that "overall decreases in MRO plus CD were led by a decrease in VRE" (p590).
Other outcomes	(1) Adverse effects, safety: outcome not reported (2) Length of stay before CDAD (during and after discontinuation of contact precautions; reported in Nagaraja 2015) (3) Nonhospital-acquired CDAD (reported in Nagaraja 2015) (4) Additional time for discharge arising from use of UVD (estimated at 51 minutes per discharge) (5) Feasibility of use: based on % cancellations for UVD "because of immediate need for the room for patient care"
Pathogen(s)	VRE, MRSA, MRGN bacteria, *C. difficile*

Risk of bias assessment

Bias	Authors' judgement	Support for judgement
Intervention independent of other changes (ITS)	high risk of bias	The authors considered changes concurrent with the intervention (including "many other simultaneous infection control interventions"), suggesting most were unlikey to explain observed outcomes because "none appeared temporally associated with any reduction" (p590). Concurrent changes included: CD reduction initiatives such as use of bleach-based disinfectants (July 2008 – Dec 2009, pre-UVD; no change in CD rates). UVD used in MICU and burns units (Jan 2009 - June 2010, pre-UVD). New environmental services contractor (Jan 2011, 4 months pre-UVD; similar monitoring of cleaning by both contractors, no decrease in CDI rates observed in this period). New discharge cleaning checklist (Sep 2012, during UVD). More sensitive test for *C. difficile* toxin (July 2010, pre-UVD), RT of chlorhexide bathing on one unit (dates not reported), weekly intensive clean of high risk units for limited period (pre-UVD and UVD periods), expansion of paediatric oncology to include highly immunosuppressed patients (2011, immediately prior to UVD). In a later paper (Nagaraja 2015), community acquired CDI rates increased by 18% during the UVD period. Antibiotic utilisation was not evaluated. Due to the number and complexity of concurrent changes, it is unlikely that alternative explanations for the observed effects can be ruled out.
Shape of the intervention effect pre-specified (ITS)	low risk of bias	Analysis of data was conducted using ITS methods, with a clearly defined intervention point.
Intervention unlikely to affect	high risk of bias	More sensitive testing for *C. difficile* toxin was introduced approximately half way through the pre-intervention period, but 12 month prior to intervention (July 2010). An increase in overall CDAD rates concurrent with the intervention period may have increased

Bias	Authors' judgement	Support for judgement
data collection (ITS)		screening/test ordering, leading to changes in detection. No other changes to the source or method of data collection were reported in either intervention or control period, and the intervention is unlikely to directly affected data collection (which requires laboratory testing, then identification of patients from routinely collected data).
Knowledge of the allocated interventions adequately prevented during the study (ITS)	low risk of bias	Likely or possible that personnel, including those keeping patient chart records and requesting tests for MROs or *C. difficile* toxin, would have been aware of the intervention. This may have increased requests for screening, potentially increasing the number of cases detected (accounted for in previous domain). Cases were based on retrospective file audit of the infection control database; it is unclear whether those doing file audits knew the period in which cases fell (intervention or control). However, it seem unlikely that this would have an important influence on outcome measurement.
Incomplete outcome data adequately addressed (ITS)	low risk of bias	No mention of incomplete data. Hospital wide data, from routinely collected sources, so it is unlikely that data are missing or that data were more likely to be missing in the intervention than control period.
Selective outcome reporting (ITS)	low risk of bias	Selective reporting cannot be completely ruled out (study is not prospectively registered; no published protocol), but results for all outcomes mentioned in the methods have been reported and outcomes likely to be measured are reported.
Other risks of bias (ITS)	low risk of bias	The authors declare that they have no conflicts of interest, and that the project was approved by the New York Medical College Committee for the Protection of Human Subject (Nagaraja 2015). There is no explicit statement about funding or support.

Study ID Hacek 2010

Study design(s)	Time series (re-analysed)
Setting / Population	Units: Any room vacated by a patient with CDAD (No. rooms/cleans not reported). Location (country, hospital(s)): USA, all three hospitals in the NorthShore University HealthSystem (~850 beds, 40,000 annual admissions)
Intervention(s)	Sodium hypochlorite (bleach clean; on discharge)
	August 2005 - August 2007 (25 months)
	Materials: Sodium hypochlorite (bleach) Dilution/preparation: 1:10 dilution of bleach:tap water (~ 5000 ppm sodium hypochlorite)
	Process: Surfaces were by applying the dilute bleach solution with heavy cloth towels to thoroughly wet the surfaces. A room cleaning checklist is reported on p351. Frequency of process: terminal clean (after patients with known CDAD had vacated the room, either through room transfer or discharge). Daily clean was as per standard practice (see control group) Duration of process/contact time: Not reported. Personnel: Environmental services (ESP) personnel (no other details reported). Infection control preventionists monitored admissions of patients with CDI, and notified ES personnel at discharge with reminders to use bleach for terminal clean.
	Surfaces disinfected: Hard non-porous, for example: door handles, bed (e.g. frame, side rails, bed controls), over-bed table, bedside table, bathroom Other: surfaces that were not high-touch were also cleaned with the bleach solution (e.g. floors, walls to shoulder height)
Comparator(s)	Standard cleaning/disinfection (quaternary ammonium)

	Oct 2004 - July 2005 (10 months)
	Quaternary ammonium compound (QAC, no details reported about preparation or process). Frequency of process: terminal clean (after patients with known CDAD had vacated the room, either through room transfer or discharge). Daily clean of these rooms was as per standard practice, using QAC.
Adherence	The authors report that "periodic, unannounced cleaning observations also were carried out by the ICPs" (p2). No data on compliance were reported.
Outcomes	Outcome category: Infection Outcome (metric): rate of hospital-acquired *C. difficile*-associated disease (cases per 1000 patient-days) Level of measurement: hospital-wide Data collection periods: pre-intervention 1 October 2004 to 31 July 2005 (10 months), intervention period 1 August 2005 to 31 August 31 2007 (25 months) (monthly throughout both periods) Data collection methods: retrospective electronic file audit to identify cases matching outcome definition. Outcome definition (new hospital-acquired cases): postive *C. difficile* toxin test > 48 hours after admission
Other outcomes	(1) Adverse events, safety. outcome not reported. The authors noted that by restricting the use of bleach to terminal cleaning of rooms that had been vacated by patients with known CDAD, "concerns over adverse effects" may be reduced. (2) Bacterial contamination of surfaces: outcome not reported
Pathogen(s)	*C. difficile*

Risk of bias assessment

Bias	Authors' judgement	Support for judgement
Intervention independent of other changes (ITS)	high risk of bias	There was limited consideration of changes concurrent with the intervention; the authors note that during the study there was no changes to "infection control or nursing care practices … directed toward C difficile ", "antimicrobial agent formulary" and "no measurable improvement in hand hygiene compliance" (p351, data not reported or included in analysis). Other explanations for the observed effects were not considered and cannot be ruled out.
Shape of the intervention effect pre-specified (ITS)	low risk of bias	Reanalysis of data was conducted using ITS methods, with a clearly defined intervention point.
Intervention unlikely to affect data collection (ITS)	high risk of bias	The intervention was introduced in response to an increase in the rate of pathogen acquisition (outbreak), hence knowledge of the outbreak may have prompted an increase in screening. No other changes to the source or method of data collection were reported in either intervention or control period, and the intervention is unlikely to directly affected data collection (which requires laboratory testing, then identification of patients from routinely collected data).
Knowledge of the allocated interventions adequately prevented during the study (ITS)	unclear risk of bias	Unclear whether personnel, including those keeping patient chart records and requesting tests for *C. difficile* toxin, would have been aware of the intervention. Awareness of the intervention period may have increased requests for screening, potentially increasing the number of cases detected (accounted for in previous domain). There is no information about who performed file audits required to confirm eligibility of patients with positive *C. difficile* toxin test. It is unclear, for example, whether Infection Control Personnel who reminded staff to perform the intervention based on identification of CDAD cases in the EMR, were also involved in the EMR audits required for data collection. Hence, the study is assessed at unclear risk of bias because of concerns that those implementing the intervention may also have assessed outcomes.

Bias	Authors' judgement	Support for judgement
Incomplete outcome data adequately addressed (ITS)	low risk of bias	No mention of incomplete data. Hospital wide data, from routinely collected sources, so it is unlikely that data are missing or that data were more likely to be missing in the intervention than control period.
Selective outcome reporting (ITS)	low risk of bias	Selective reporting cannot be completely ruled out (study is not prospectively registered; no published protocol), but results for all outcomes mentioned in the methods have been reported and outcomes likely to be measured are reported.
Other risks of bias (ITS)	low risk of bias	The authors declare that they have no conflicts of interest. There is no explicit statement about funding or support, or information about ethics approval.

Study ID McMullen 2007

Study design(s)	Time series (re-analysed)
Setting / Population	Units: 19-bed medical intensive care unit (MICU). All patient rooms (No. rooms/cleans not reported), nursing station, staff restroom, staff conference room, and waiting room on the MICU. During the period described in the paper as "post-intervention" (Jan 2003 - Dec 2004), the intervention was only used in rooms of patients with CDAD. Location (country, hospital(s)): USA, university-affiliated tertiary care facility (1,400-bed)
Intervention(s)	I1. Sodium hypochlorite (daily bleach clean; all rooms) I2. Sodium hypochlorite (daily bleach clean; rooms of patients with CDAD)
	I1. (daily bleach clean all rooms) August to December 2002 (5 months) I2. (daily bleach clean in rooms of patients with CDAD) January 2003 to December 2004 (described in paper as post-intervention period)
	Materials: Sodium hypochlorite (bleach). Commercial hypochlorite wipe cloths (Hype-Wipe disinfecting towel, Current Technologies) were used for sensitive equipment Dilution/preparation: 1:10 dilution of bleach: water (~ 5000 ppm sodium hypochlorite).
	Process: Not reported. Frequency of process: Daily room cleaning. Twice daily wiping of sensitive equipment (computers, monitoring equipment). Duration of process/contact time: Not reported. Personnel: Not reported for room clean. Patient care technician wiped senstive equipment. Co-interventions: One-off intense cleaning of carpets (quaternary ammonium disinfectant, then general carpet cleaner).
	Surfaces disinfected: Not reported (except for noting cleaning of electronic equipment)
Comparator(s)	Standard cleaning/disinfection (quaternary ammonimum)
	Jan - July 2002 (7 months; pre-intervention period)
	Standard cleaning/disinfection with quaternary ammonimum (pre-intervention period, Jan-July 2002) Note the period described in the paper as "post-intervention" in the MICU (Jan 2003 - Dec 2004) involved daily bleach clean in rooms of patients with CDAD, hence only the pre-interventin period is considered an eligible comparator intervention. It is unclear what the "post-intervention" period in the SICU (Oct 2002 - Dec 2004) involved.
Adherence	Not reported
Outcomes	Outcome category: Infection

	Outcome (metric): incidence rate of hospital-acquired *C. difficile*-associated disease (cases per 1,000 patient-days) Level of measurement: Medical intensive care unit (MICU). Insufficient data collection points during intervention period for re-analysis of Surgical Intenstive Care Unit (SICU) data. Data collection periods: pre-intervention Jan 2002-Jul 2002 (includes endemic period (Jan-May) and outbreak period (Jun-Jul)), intensive intervention period August 2002 to December 2002(monthyly throughout all periods), less intensive intervention period Jan 2003 - December 2004. Data collection methods: not reported Outcome definition (new hospital-acquired cases): patients with diarrhea (unformed stools) and postive *C. difficile* toxin test > 48 hours after admission
Other outcomes	(1) Adverse effects: outcome not reported (2) Bacterial contamination of surfaces: outcome not reported
Pathogen(s)	*C. difficile*

Risk of bias assessment

Bias	Authors' judgement	Support for judgement
Intervention independent of other changes (ITS)	high risk of bias	The authors considered changes concurrent with the intervention, including: a hospital-wide intervention to increase hand hygiene (completed early 2003, unclear if concurrent with one or both intervention periods; "no statistically significant difference" in CDAD rate before or after this intervention), potential for increased compliance with infection control measures in response to the outbreak/feedback on CDAD rates (data not collected on compliance), patient characteristics (age, sex, LoS, mortality "did not differ significantly" between periods; data not reported), antibiotic use (fluoroquinolone and clindamycin use "did not differ significantly" between periods; data not reported). Other factors were not considered, and it unlikely that alternative explanation for observed effects can be ruled out.
Shape of the intervention effect pre-specified (ITS)	low risk of bias	Reanalysis of data was conducted using ITS methods, with a clearly defined intervention point.
Intervention unlikely to affect data collection (ITS)	high risk of bias	The intervention was introduced in response to an increase in the rate of pathogen acquisition (outbreak), hence knowledge of the outbreak may have prompted an increase in screening. No other changes to the source or method of data collection were reported in either intervention or control period, and the intervention is unlikely to directly affected data collection (which requires laboratory testing, then identification of patients from routinely collected data).
Knowledge of the allocated interventions adequately prevented during the study (ITS)	unclear risk of bias	Methods of data collection are not reported, (e.g. whether based on file audit, and if so who conducted the audit and whether they were masked to the intervention), so it is unclear whether there is a risk of bias arising from outcome assessors having knowledge of the allocated intervention. It is likely those responsible for test ordering were aware of the intervention (daily bleach clean). This may have increased requests for screening, potentially increasing the number of cases detected (accounted for in the previous domain).
Incomplete outcome data adequately addressed (ITS)	low risk of bias	No mention of incomplete data. Although not explicitly stated, it is likely that outcome data come from routine data sources and missing data are unlikely.
Selective outcome reporting (ITS)	low risk of bias	Selective reporting cannot be completely ruled out (study is not prospectively registered; no published protocol), but results for all outcomes mentioned in the methods have been reported and outcomes likely to be measured are reported.

Bias	Authors' judgement	Support for judgement
Other risks of bias (ITS)	unclear risk of bias	The paper does not include a declaration of interest, statement about funding or support, or information about ethics approval. Potential biases arising from conflicts can therefore not be assessed.

Study ID Mitchell 2014

Study design(s)	Time series (re-analysed)
Setting / Population	Units: Rooms accommodating MRSA patients (3629 discharge cleans; 1712 in HP arm). Location (country, hospital(s)): Australia; 300-bed public hospital providing acute care facilities
Intervention(s)	Dry hydrogen peroxide vapour room decontamination (single rooms); hydrogen peroxide solution (shared rooms)
	November 2009 - December 2012 (38 months)
	Materials: Dry hydrogen peroxide (HP) vapour room decontamination system (Nocospray, EquipMed, North Ryde, New South Wales, Australia) (single rooms, N=1363; ~80%). Hydrogen peroxide solution (shared rooms, N=349) Dilution/preparation: HP vapour - 6%. HP liquid - Oxivir TB 0.5% (Diversey, Smithfield, New South Wales, Australia)
	Process: Rooms were first cleaned (methods as per comparator arm), then HP vapour decontamination was "conducted according to the manufacturer's instructions" (p2). In shared rooms, a HP solution was applied to surfaces using a cloth, as per the manufacturer's instructions. Frequency of process: following discharge of patients with MRSA Duration of process/contact time: not reported Personnel: Cleaning staff were in-house hospital employees and not contractual staff. To ensure competency, the number of staff responsible for discharge cleaning was limited, these staff received competency-based training, and were supervised by the researchers.
	Surfaces disinfected: Any exposed surface. Surfaces sampled for MRSA contamination: ceiling vent, sink, console, bed, patient/visitor chair, patient table, bedside locker, mattress and pillow.
Comparator(s)	Standard cleaning/disinfection alone
	Jan 2006 - Oct 2009 (46 months)
	Standard cleaning/disinfection ('detergent arm'): Following discharge of MRSA patients, rooms were cleaned twice with a pH neutral detergent (mixed in warm water).
Co-interventions (both periods)	Standard cleaning/disinfection was used throughout intervention and pre-intervention period.
Adherence	Bacterial contamination of surfaces was monitored, and data fed back to cleaning and clinical staff (both study arms). An external quality control process was also undertaken by the HPV system manufacturer, using test strips specific to the system. The test strips were used intermittently in HPV decontaminated rooms throughout study.
Outcomes	Outcome category: Colonisation and/or infection Outcome (metric): incidence rate of hospital-acquired MRSA acquisition (cases per 10,000 patient care days) Level of measurement: hospital-wide

	Timing of data collection: pre-intervention January 2006 - October 2009, intervention period November 2009 - December 2012 (monthly throughout both periods; quarterly data reported) Data collection methods: routine surveillance for MRSA on admission (at risk sub-groups); from January 2010, weekly MRSA screening for all inpatients Outcome definition (hospital-acquired MRSA acquisition): not specified. Definition for bacteraemia was an MRSA-positive culture, taken 48 h or longer after admission.
	Incidence rates of hospital-acquired MRSA bacteraemia (cases per 10,000 patient care days) were also reported, but not included here because pre- and post intervention rates were reported without time series data or all statistics from the time series analysis.
Other outcomes	(1) Adverse effects, safety: outcome not reported (2) Bacterial contamination of surfaces following 3629 discharge cleans (1917 detergent arm; 1712 HP arm). See intervention description for surfaces sampled.
Pathogen(s)	MRSA

Risk of bias assessment

Bias	Authors' judgement	Support for judgement
Intervention independent of other changes (ITS)	high risk of bias	The authors considered changes concurrent with the intervention, concluding that "the impact of additional changes other than cleaning over the study period cannot be excluded". The authors systematically accounted for these in their analysis and interpretation of the results. Factors considered included: hand hygiene compliance (monitored in intervention period; "no statistical increase" when April 2010 compared to end of 2012 - coincided with intervention to improve hand hygiene compliance), antibiotic prescribing (recorded throughout; "significant" reduction in fluoroquinolone and increase in cephalosporin use), enhanced screening activity with feedback to staff and change in laboratory methods (leading to faster/increased detection and, possibly, improved control of MRSA). Overall, the authors conclude that the observed effects were likely "the result of several initiatives, including disinfectant cleaning, focus on terminal cleaning (including staff feedback), additional MRSA screening, quicker laboratory methods and isolation." (p6)
Shape of the intervention effect pre-specified (ITS)	low risk of bias	Reanalysis of data was conducted using ITS methods, with a clearly defined intervention point.
Intervention unlikely to affect data collection (ITS)	high risk of bias	The hospital had an established MRSA screening program (on admission, then weekly testing added from Jan 2010, 3 months into the intervention period), with monitoring of compliance in 2010/2011 (intervention period). This may have led to an increase in MRSA detection during the intervention period. Given routine screening was in place, the intervention itself is unlikely to directly affected data collection in other ways (which requires laboratory testing, then identification of patients from routinely collected data).
Knowledge of the allocated interventions adequately prevented during the study (ITS)	low risk of bias	It is not possible to mask clinical staff to the HPV disinfection, so it is likely or possible that staff involved in requesting MRSA tests would have knowledge of the allocated intervention. However, the hospital had an established MRSA screening program (on admission, then weekly testing added from Jan 2010) and compliance was monitored in 2010/2011, so it is unlikely that changes in test ordering would have occurred in response to knowledge of the intervention (and any changes are accounted for in the previous domain). Outcomes were assessed from routinely collected data in the hospital electronic medical records, and the data were based on laboratory testing for pathogens. Knowledge of the intervention therefore seems unlikely to have an important influence on outcome measurement, which largely relies of objective data.

Bias	Authors' judgement	Support for judgement
Incomplete outcome data adequately addressed (ITS)	low risk of bias	No mention of incomplete data. Hospital wide data, from routinely collected sources, so it is unlikely that data are missing or that data were more likely to be missing in the intervention than control period.
Selective outcome reporting (ITS)	low risk of bias	Selective reporting cannot be completely ruled out (study is not prospectively registered; no published protocol), but results for all outcomes mentioned in the methods have been reported and outcomes likely to be measured are reported.
Other risks of bias (ITS)	low risk of bias	This study did not have specific funding, had no industry involvement, and the authors declared they had no competing interests. No other potential biases were identified.

Study ID Orenstein 2011

Study design(s)	Time series (re-analysed)
Setting / Population	Units: all patient rooms on units with a high incidence of hospital-acquired CDI (2 contiguous units; No. rooms/cleans not reported), including rooms not occupied by patients with CDI. Type of units not reported. Location (country, hospital(s)): USA, 1,249-bed hospital
Intervention(s)	Sodium hypochlorite wipes (daily bleach clean)
	August 2009 - July 2010 (12 months)
	Materials: Bleach wipes (Clorox) Dilution/preparation/composition: 0.55% active chlorine Co-interventions: contact isolation of patients with CDI was practiced throughout the pre-intervention and intervention periods.
	Process: Cleaning procedures for rooms and high-touch surfaces were reported as being the same throughout the pre-intervention and intervention periods. These procedures were not described. Frequency of process: daily Duration of process/contact time: Bleach was allowed to dry to achieve the recommended 10 minute contact time to inactivate *C. difficile* spores. Personnel: housekeeping staff
	Surfaces disinfected: Not reported.
Comparator(s)	I. Sodium hypochlorite wipes (daily bleach clean) C. Standard cleaning/disinfection (quaternary ammonimum)
	Aug 2008 - July 2009 (12 months)
	Standard cleaning/disinfection daily and at hospital discharge with a quarternary ammonium compound (HB-Quat). Process not described but reported as being the same in both the pre-intervention and intervention periods.
Adherence	(1) Routine checks of room cleanliness (supervisor inspection; ATP bioluminscence) (2) Sampling of high-touch surfaces in randomly selected rooms following terminal clean (5 rooms pre-intervention; 5 rooms on 3 occassions during the intervention period). (3) Random practice audits by environmental services management (2 during pre-intervention period; 4 during the intervention period)
Outcomes	Outcome category: Infection Outcome (metric): incidence rate of hospital-acquired *C. difficile*-associated disease (cases per 10,000 patient-days)

	Level of measurement: units on which the intervention was tested Data collection periods: pre-intervention August 2008 - July 2009, intervention period August 2009 - July 2010 (monthly throughout both 12 month periods) Data collection methods: not reported Outcome definition (new cases): patients with diarrhea (> 3 loose stools within 24 hours) or toxic megacolon and either a positive *C. difficile* toxin test or pseudomembranous colitis (identified by endoscopy or histopathology), with onset >72 hours after admission or < 60 days from discharge from one of the units.
Other outcomes	(1) Adverse effects, safety: outcome not reported (2) Time between hospital-acquired CDI cases (3) Overall CDI incidence (per 10,000 patient-days) (4) Cost of bleach wipes (cost of control disinfectant material not reported). The authors also estimate costs that may have been averted based on the observed reduction in CDI cases and the estimated incremental cost of a hospital acquired CDI case.
Pathogen(s)	*C. difficile*

Risk of bias assessment

Bias	Authors' judgement	Support for judgement
Intervention independent of other changes (ITS)	high risk of bias	The authors considered changes concurrent with the intervention and other factors that could explain the observed effects including: patient characteristics and staffing ("unchanged throughout the study period"), overall CDI rate in the 2 units (rates not interpreted in relation to observed rates of HAI), compliance with contact isolation precautions (not reported by period; full adherence for median of 86% room entries, range 63-100%), room cleanliness (pre-intervention: 98% pass rate; intervention period: 97%), and hand hygiene ("high rates of compliance", data not reported). Although some factors may be ruled out, alternative explanations for the observed effects seem plausible.
Shape of the intervention effect pre-specified (ITS)	low risk of bias	Reanalysis of data was conducted using ITS methods, with a clearly defined intervention point.
Intervention unlikely to affect data collection (ITS)	high risk of bias	The intervention was introduced in response to an increase in the rate of pathogen acquisition (outbreak), hence knowledge of the outbreak may have prompted an increase in screening. No other changes to the source or method of data collection were reported in either intervention or control period, and the intervention is unlikely to have directly affected data collection (which requires laboratory testing, then identification of patients from routinely collected data).
Knowledge of the allocated interventions adequately prevented during the study (ITS)	unclear risk of bias	Methods of data collection are not reported, (e.g. whether based on file audit, and if so who conducted the audit and whether they were masked to the intervention), so it is unclear whether there is a risk of bias arising from outcome assessors having knowledge of the allocated intervention. It is likely those responsible for test ordering were aware of the intervention (daily bleach clean). This may have increased requests for screening, potentially increasing the number of cases detected (accounted for in previous domain).
Incomplete outcome data adequately addressed (ITS)	low risk of bias	No mention of incomplete data. Although not explicitly stated, it is likely that outcome data come from routine data sources and missing data are unlikely.
Selective outcome reporting (ITS)	low risk of bias	Selective reporting cannot be completely ruled out (study is not prospectively registered; no published protocol), but results for all outcomes mentioned in the methods have been reported and outcomes likely to be measured are reported.

Bias	Authors' judgement	Support for judgement
Other risks of bias (ITS)	high risk of bias	One of the investigators consults for the manufacturer of the intervention. The manufacturers supplied 214/444 buckets of the product tested in the intervention period free of charge, and provided a 30% discount on purchase of additional product. There is no mention of steps taken to safegaurd against potential biases, such as pre-registration or publication of a study protocol. Hence the study is considered to be at risk of bias.

Study ID Passaretti 2013

Study design(s)	Controlled before-after
Setting / Population	Intervention units (3 high risk): surgical ICU (19 bed, single occupancy), neurosurgical ICU (22 bed, single occupancy), high-risk surgical unit (30 bed; 73% single occupancy). Total of 437 room occupations. Control units (3 high risk): medical unit (16 bed), cardiothoracic surgery unit (18 bed), surgical oncology ICU (20 bed). Total of 5913 room occupations (927 in rooms with a prior room occupant infected or colonised with an MRO; 4986 without). Location (country, hospital(s)): USA, 994-bed tertiary referral center
Intervention(s)	Hydrogen peroxide vapour room decontamination
	January 2008 through June 2009 (18 months)
	Materials: HPV decontamination (Bioquell) Dilution/preparation/composition: Not reported
	Process: After routine cleaning and disinfection, vacated rooms were sealed and decontaminated using HPV. Daily and discharge cleaning of floors and surfaces was the same as in rooms in the control group. Frequency of process: terminal (on discharge of patients from units allocated to the intervention group). Duration of process/contact time: ~ 1.5 to 3 hours Personnel: The authors reported that HPV decontamination was performed by "dedicated personnel", referencing in Boyce 2008 for description. Boyce reported that: Bioquell personnel conducted an engineering review (including heating, ventilation, air conditioning systems) prior to commencemen of HPV decontamination. It was unclear who conducted the HPV decontamination (e.g. Bioquell, trained staff).
	Surfaces disinfected: Not reported (any exposed surface within the room being decontaminated). Equipment from other rooms and shared rooms was "commonly" placed in rooms undergoing decontamination.
Comparator(s)	Standard cleaning/disinfection alone
	Concurrent with intervention: Jan 2008 - June 2009 (18 months)
	Daily and discharge cleaning of floors and surfaces with a quaternary ammonium compound, applied using commercial disposable wipes. Rooms of patients with *C. difficile* were cleaned with liquid cleaner/disinfectant including hydrogen peroxide.
Co-interventions (both periods)	Standard cleaning/disinfection was used in both arms.
Adherence	Each cycle was validated using a biological indicator, placed in the corner of the room and cultured according to the manufacturer's instructions. The proportion of eligible rooms that were decontaminated with HPV was reported (1334/1872, 71.3%), together with reasons why decontamination had not occurred (primarily due to restrictions on the hours of operation of the HPV service to Mon-Fri, 8am to 8pm). Bacterial contamination of surfaces was measured in both intervention and control rooms (see other outcomes).
Outcomes	Outcome category: Colonisation and/or infection

	Outcome (metric): Incident rate of any hospital-acquired MRO (cases per 1000 patient-days). Rates reported for individual pathogens (VRE, MRSA, MRGN, *C. difficile*), and all pathogens combined. Level of measurement: Units assigned to the intervention or control Timing of data collection: pre-intervention January 2007- December 2007 (12 months), intervention period January 2008 - June 2009 (18 months) (continuous data collection throughout both periods; single rate reported for each period) Data collection methods: Analysis of electronic patient records; all patients at risk of an MRO (no history of an MRO on the EMR; room stay >48 hour) were included in the analysis. Outcome definition (acquisitions): identification of an MRO or *C. difficile* ⩾48 hours after admission in a patient with no known history of that organism. Routine surveillance for MRSA and VRE was performed on admission and weekly. *C. difficile* testing was performed if clinically indicated (details referenced but not reported). There was no screening for uvd.
Other outcomes	(1) Adverse effects, safety: the authors reported that there were 'no health and safety incidents during the study' and that 'the technology was well accepted by unit staff' (p32) but did not report methods of data collection or data supporting these findings. (2) Bacterial contamination of surfaces: sampling for MRSA, VRE, and MRGN from standard high-touch surfaces including bedrails and monitoring equipment in both intervention and control rooms (first 6 months of the intervention, and the 3 months prior). (3) Other considerations: one room required repainting after it 'showed some incompatability with the [HPV] process' (p32)
Pathogen(s)	VRE, MRSA, MRGN bacteria, *C. difficile*

Risk of bias assessment

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	high risk of bias	Units were allocated to intervention or control without randomisation, therefore the allocation sequence was not randomly generated.
Allocation concealment (selection bias)	high risk of bias	The study is not randomised. The methods by which units were allocated to intervention/control groups are not described (e.g. it is unclear how decisions were made about which units would receive HPV or how control units were selected). Given this, there is a risk that units were allocated to the intervention based on difference in patient characteristics (including their potential to benefit).
Baseline characteristics	low risk of bias	The authors report that there is no important imbalance in participant demographic characteristics at baseline (data reported Table 1), and adjusted for the following factors in their analysis: hospital unit, age, mortality risk score, human immunodeficiency virus status, end-stage renal disease status, compliance with MRO surveillance procedures, and calendar time (p30).
Baseline outcome measurements	low risk of bias	There appears to be no important imbalance in outcome measures at baseline. The MRO incidence rates on the two HPV units were 14 and 11.2 per 1000-patient days at baseline (pre-intervention); and for the two control units incidence rates were 16.1 and 13.9 per 1000-patient days.
Incomplete outcome data (attrition bias) All outcomes	low risk of bias	Not reported, however routinely collected data were used for this study, hence it is unlikely that outcome data were missing.
Knowledge of the allocated interventions adequately	low risk of bias	It is not possible to mask clinical staff to HPV disinfection, however the colonisation outcome is objectively measured so unlikely to be biased by knowledge of the allocated intervention. Outcomes were assessed from routinely collected data in the hospital electronic medical records, and the data were based on laboratory testing for pathogens. It is unlikely that knowledge of the intervention would have influenced this data. Although staff involved in

Bias	Authors' judgement	Support for judgement
prevented during the study		requesting tests may have had knowledge of the allocated intervention, routine surveillance of two of the pathogens was required (admission and weekly testing for VRE, MRSA) and *C. difficile* testing was required if clinically indicated.
Protection against contamination	low risk of bias	Deployment of HPV requires considerable resources and coordination, so it is unlikely that the intervention would have been used in the control units to an extent likely to influence the outcomes of the study.
Selective outcome reporting (reporting bias)	low risk of bias	While it is possible that not all analyses are reported, the outcomes reported seem complete and it is unlikely any were ommitted.
Other risks of bias	high risk of bias	One author is employed by the manufacturer of the HPV system tested in this study (Bioquell), and contributed to the study design, collection of data, and the writing of the report. The analysis was done by "Johns Hopkins employees and Bioquell personnel were not involved." (p34) Industry funding through the provision of the disinfection service tested in this study. There is no mention of steps taken to safegaurd against potential biases, such as pre-registration or publication of a study protocol. Hence the study is considered to be at risk of bias.

Appendix 6. Characteristics of ongoing studies

Study ID Maragakis 2015

Trial registry number	NCT02605499
Are data available?	No - estimated completion date of study is March 2018 (Dec 2017 for collection of primary outcome data)
Study design(s)	Cluster -randomised trial (cross over design)
Setting / Population	Not reported "preselected hospital units" (11,000 patients, 16 years and above) One university affiliated hospital Country: USA
Intervention(s)	UV light disinfection as an adjunct to routine daily and discharge cleaning.
	Surfaces: High touch, all exposed
Comparator(s)	Standard cleaning/disinfection without UV disinfection
Outcomes	Infection, colonisation or both (primary outcome): (1) incidence rate of hospital-acquired VRE (infection or colonisation), (2) incidence rate of hospital-acquired MROs or *C. difficile* (colonisation, hospital onset bacteremias, CDAD, central line associated bloodstream infections). Secondary outcomes: acquisition of individual MROs or *C. difficile*
Pathogen(s)	MRSA, VRE, *C. difficile*, MDR gram negative bacteria

Appendix 7. Characteristics of excluded studies (near miss exclusions)

Reason for exclusion	Reference	Excluded on 2 or more criteria?
INTERVENTION		
Excluded intervention: HP solution	Boyce, J. M., K. A. Guercia, N. L. Havill and L. K. Sullivan (2016). "Impact of an improved hydrogen peroxide (IPH) Disinfectant versus a quaternary ammonium-based (Quat) disinfectant on surface contamination and healthcare outcomes." American Journal of Infection Control 44(6): S28.	no
Excluded intervention: UV air steriliser	Gomez-Sanchez, E., M. Heredia-Rodriguez, E. Alvarez-Fuente, M. Lorenzo-Lopez, E. Gomez-Pesquera, M. Aragon-Camino, P. Liu-Zhu, A. Sanchez-Lopez, A. Hernandez-Lozano, M. T. Pelaez-Jareno and E. Tamayo (2016). "Impact of ultraviolet air sterilizer in intensive care unit room, and clinical outcomes of patients." Critical Care 20: no pagination.	yes
Excluded intervention: "Deep clean" program, can't isolate effects of eligible interventions because sites chose their own intervention.	Newitt, S., P. R. Myles, J. A. Birkin, V. Maskell, R. C. B. Slack, J. S. Nguyen-Van-Tam and L. Szatkowski (2015) "Impact of infection control interventions on rates of Staphylococcus aureus bacteraemia in National Health Service acute hospitals, East Midlands, UK, using interrupted time-series analysis." 90, 28-37 DOI: 10.1016/j.jhin.2014.12.016.	no
COMPARISON		
Excluded comparison: co-intervention(s) (e.g. infection control bundle) not included in the comparator (i.e. can't isolate effects of eligible intervention)	Barbut, F., J. Pham, S. Yezli, M. Mimoun and J. A. Otter (2011). "Reducing the spread of *Acinetobacter baumannii* and methicillin-resistant *Staphylococcus aureus* on a burns unit through the intervention of an infection control bundle including hydrogen peroxide vapour decontamination." Clinical Microbiology and Infection 17: S371-S372.	yes
Excluded comparison: co-intervention(s) (e.g. infection control bundle) not included in the comparator (i.e. can't isolate effects of eligible intervention)	Barbut, F., S. Yezli, M. Mimoun, J. Pham, M. Chaouat and J. A. Otter (2013). "Reducing the spread of *Acinetobacter baumannii* and methicillin-resistant *Staphylococcus aureus* on a burns unit through the intervention of an infection control bundle." Burns 39(3): 395-403.	yes
Excluded comparator: Active intervention [different HPV system]	Blazejewski, C., F. Wallet, A. Rouze, R. Le Guern, S. Ponthieux, J. Salleron and S. Nseir (2015). "Efficiency of hydrogen peroxide in improving disinfection of ICU rooms." Critical Care 19(1): no pagination.	yes
Excluded comparison: co-intervention(s) (e.g. infection control bundle) not included in the comparator (i.e. can't isolate effects of eligible intervention)	Fisher, D. (2015). "Controlling VRE using technology." Journal of Microbiology, Immunology and Infection 48(2 SUPPL. 1): S27.	yes
Excluded comparison: co-intervention(s) (e.g. infection control bundle) not included in the comparator (i.e. can't isolate effects of eligible intervention)	Fisher, D., L. Pang, S. Salmon, R. T. P. Lin, C. Teo, P. Tambyah, R. Jureen, A. R. Cook and J. A. Otter (2016). "A Successful Vancomycin-Resistant Enterococci Reduction Bundle at a Singapore Hospital." Infection Control & Hospital Epidemiology 37(1): 107-109.	no
Excluded comparator: Active intervention (chlorine dioxide)	Goldenberg, S. D., A. Patel, D. Tucker and G. L. French (2012). "Lack of enhanced effect of a chlorine dioxide-based cleaning regimen on environmental contamination with Clostridium difficile spores." J Hosp Infect 82(1): 64-67.	no
Excluded comparison: co-intervention(s) (e.g. infection control bundle) not included in the comparator (i.e. can't isolate effects of eligible intervention)	Grabsch, E. A., A. A. Mahony, D. R. Cameron, R. D. Martin, M. Heland, P. Davey, M. Petty, S. Xie and M. L. Grayson (2012). "Significant reduction in vancomycin-resistant enterococcus colonization and bacteraemia after introduction of a bleach-based cleaning-disinfection programme." J Hosp Infect 82(4): 234-242.	yes
Excluded comparator: Active intervention (HPV)	Havill, N. L., B. A. Moore and J. M. Boyce (2012). "Comparison of the microbiological efficacy of hydrogen peroxide vapor and ultraviolet light	yes

Reason for exclusion	Reference	Excluded on 2 or more criteria?
	processes for room decontamination." Infect Control Hosp Epidemiol 33(5): 507-512.	
Excluded comparison: co-intervention(s) (e.g. infection control bundle) not included in the comparator (i.e. can't isolate effects of eligible intervention)	Hill, L., F. Dignan, N. Blagburn, M. Saif and E. Tholouli (2016). "Managing carbapenemase-producing Enterobacteriaceae in a transplant setting." Bone Marrow Transplantation 51: S560.	yes
Excluded comparison: co-intervention(s) (e.g. infection control bundle) not included in the comparator (i.e. can't isolate effects of eligible intervention)	Whitaker J, Brown BS, Vidal S, Calcaterra M: Designing a protocol that eliminates Clostridium difficile: a collaborative venture. Am J Infect Control 2007, 35(5):310-314.	no
POPULATION or SETTING		
Excluded population: No patients/inoculation of surfaces	Bartels, M. D., K. Kristoffersen, T. Slotsbjerg, S. M. Rohde, B. Lundgren and H. Westh (2008). "Environmental meticillin-resistant Staphylococcus aureus (MRSA) disinfection using dry-mist-generated hydrogen peroxide." J Hosp Infect 70(1): 35-41.	yes
Excluded population: not reported	Chan, H. T., P. White, H. Sheorey, J. Cocks and M. J. Waters (2011). "Evaluation of the biological efficacy of hydrogen peroxide vapour decontamination in wards of an Australian hospital." J Hosp Infect 79(2): 125-128.	yes
Excluded setting: long term care facility Excluded population: Not high risk	Miller, R., S. Simmons, C. Dale, J. Stachowiak and M. Stibich (2015). "Utilization and impact of a pulsed-xenon ultraviolet room disinfection system and multidisciplinary care team on Clostridium difficile in a long-term acute care facility." American Journal of Infection Control 43(12): 1350-1353.	no
Excluded setting: skilled nursing/long term care facility	Wiltshire, M. M., C. Dale and S. Simmons (2015). "Impact of Full Spectrum Ultraviolet Light Disinfection on Recurrent Clostridium Difficile Cases Within a Skilled Nursing Facility...42nd Annual Conference Abstracts, APIC 2015, Nashville, TN June 2015." American Journal of Infection Control 43: S25-S25.	yes
OUTCOME		
Excluded outcome: Bacterial count on surface (neither infection nor colonisation)	Andersen, B. M., H. Banrud, E. Boe, O. Bjordal and F. Drangsholt (2006). "Comparison of UV C light and chemicals for disinfection of surfaces in hospital isolation units." Infection Control and Hospital Epidemiology 27(7): 729-734.	yes
Excluded outcome: Bacterial count on surface (neither infection nor colonisation)	Anderson, D. J., M. F. Gergen, E. Smathers, D. J. Sexton, L. F. Chen, D. J. Weber and W. A. Rutala (2013). "Decontamination of targeted pathogens from patient rooms using an automated ultraviolet-C-emitting device." Infect Control Hosp Epidemiol 34(5): 466-471.	yes
Excluded outcome: Bacterial count on surface (neither infection nor colonisation)	Barbut, F., D. Menuet, M. Verachten and E. Girou (2009). "Comparison of the efficacy of a hydrogen peroxide dry-mist disinfection system and sodium hypochlorite solution for eradication of clostridium difficile spores." Infection Control and Hospital Epidemiology 30(6): 507-514.	no
Excluded outcome: Bacterial count on surface (neither infection nor colonisation)	Beal, A., N. Mahida, K. Staniforth, N. Vaughan, M. Clarke and T. Boswell (2016). "First UK trial of Xenex PX-UV, an automated ultraviolet room decontamination device in a clinical haematology and bone marrow transplantation unit." Journal of Hospital Infection 93(2): 164-168.	yes
Excluded outcome: Bacterial count on surface (neither infection nor colonisation)	Best, E. L., P. Parnell, G. Thirkell, P. Verity, M. Copland, P. Else, M. Denton, R. P. Hobson and M. H. Wilcox (2014). "Effectiveness of deep cleaning followed by hydrogen peroxide decontamination during high Clostridium difficile infection incidence." J Hosp Infect 87(1): 25-33.	yes
Excluded outcome: Any surgical site infection, not specific to MDROs	Catalanotti, A., D. Abbe, S. Simmons and M. Stibich (2016). "Influence of pulsed-xenon ultraviolet light-based environmental disinfection on surgical site infections." American Journal of Infection Control 44(6): e99-e101.	no

Reason for exclusion	Reference	Excluded on 2 or more criteria?
Excluded outcome: Bacterial count on surface (neither infection nor colonisation)	Croteau, M. E. and T. Grover (2015). "Evaluating the Efficacy of UV Technology in Acute Care...42nd Annual Conference Abstracts, APIC 2015, Nashville, TN June 2015." American Journal of Infection Control 43: S39-S40.	yes
Excluded outcome: Bacterial count on surface (neither infection nor colonisation)	Doan, L., H. Forrest, A. Fakis, J. Craig, L. Claxton and M. Khare (2012). "Clinical and cost effectiveness of eight disinfection methods for terminal disinfection of hospital isolation rooms contaminated with Clostridium difficile 027." J Hosp Infect 82(2): 114-121.	no
Excluded outcome: Bacterial count on surface (neither infection nor colonisation)	Ferrari, M., A. Bocconi and A. Anesi (2015). "Evaluation of the effectiveness of environmental disinfection by no touch hydrogen peroxide technology against MDR bacteria contamination and comparison with active chlorine disinfectant." Antimicrobial Resistance and Infection Control 4: no pagination.	yes
Excluded outcome: Bacterial count on surface (neither infection nor colonisation)	Ghantoji, S. S., M. Stibich, J. Stachowiak, S. Cantu, J. A. Adachi, I. I. Raad and R. F. Chemaly (2015). "Non-inferiority of pulsed xenon UV light versus bleach for reducing environmental Clostridium difficile contamination on high-touch surfaces in Clostridium difficile infection isolation rooms." Journal of medical microbiology 64: 191-194.	no
Excluded outcome: Bacterial count on surface (neither infection nor colonisation)	Jolly, J., H. Jackson and A. H. Buchaklian (2016). "2-111 - Efficacy of a Multiple Emitter UV-C Whole Room Disinfection System on Bacterial Contamination at a Children's Hospital...43rd Annual Conference Abstracts, APIC 2016, Charlotte, NC June 2016." American Journal of Infection Control 44: S34-S34.	yes
Excluded outcome: Bacterial count on surface (neither infection nor colonisation)	Mahida, N., N. Vaughan and T. Boswell (2013). "First UK evaluation of an automated ultraviolet-C room decontamination device (Tru-D)." J Hosp Infect 84(4): 332-335.	yes
Excluded outcome: Bacterial count on surface (neither infection nor colonisation)	Manian, F. A., S. Griesenauer, D. Senkel, J. M. Setzer, S. A. Doll, A. M. Perry and M. Wiechens (2011). "Isolation of *Acinetobacter baumannii* complex and methicillin-resistant *Staphylococcus aureus* from hospital rooms following terminal cleaning and disinfection: Can we do better?" Infection Control and Hospital Epidemiology 32(7): 667-672.	yes
Excluded outcome: Bacterial count on surface (neither infection nor colonisation)	Rutala, W. A., M. F. Gergen and D. J. Weber (2010). "Room decontamination with UV radiation." Infect Control Hosp Epidemiol 31(10): 1025-1029.	yes
Excluded outcome: Bacterial count on surface (neither infection nor colonisation)	Shapey, S., K. Machin, K. Levi and T. C. Boswell (2008). "Activity of a dry mist hydrogen peroxide system against environmental Clostridium difficile contamination in elderly care wards." J Hosp Infect 70(2): 136-141.	yes
Excluded outcome: Bacterial count on surface (neither infection nor colonisation)	Stewart, M., A. Bogusz, J. Hunter, I. Devanny, B. Yip, D. Reid, C. Robertson and S. J. Dancer (2014). "Evaluating use of neutral electrolyzed water for cleaning near-patient surfaces." Infect Control Hosp Epidemiol 35(12): 1505-1510.	yes
STUDY DESIGN		
Excluded study design: before-after design (no data reported in paper that are suitable for ITS analysis)	Dalton, C. M., J. Ferrelli, J. Price, C. Henry, F. Ricci, S. M. Fejka, R. S. Hariri, M. H. Yassin and Y. Doi (2013). "Effectiveness of eliminating Acinetobacter baumannii through environmental cleaning." American Journal of Infection Control 41(6 SUPPL. 1): S42-S43.	no
Excluded study design: before-after design (no data reported in paper that are suitable for ITS analysis)	Green, C. M., D. W. Johnson, J. C. Pamplin, K. N. Chafin, C. K. Murray and H. C. Yun (2016). "Pulsed-xenon ultraviolet light disinfection in a burn unit: Impact on environmental bioburden, multidrug-resistant organism acquisition and healthcare associated infections." Journal of Burn Care and Research 37: S108.	no
Excluded study design: before-after design (no data reported in paper that are suitable for ITS analysis)	Horn, K. and J. A. Otter (2015). "Hydrogen peroxide vapor room disinfection and hand hygiene improvements reduce Clostridium difficile infection, methicillin-resistant Staphylococcus aureus, vancomycin-resistant enterococci, and extended-spectrum β-lactamase." American Journal of Infection Control 43(12): 1354-1356.	no
Excluded study design: before-after design (no data reported	Levin, J., L. S. Riley, C. Parrish, D. English and S. Ahn (2013). "The effect of portable pulsed xenon ultraviolet light after terminal cleaning on hospital-	no

Reason for exclusion	Reference	Excluded on 2 or more criteria?
in paper that are suitable for ITS analysis)	associated Clostridium difficile infection in a community hospital." Am J Infect Control 41(8): 746-748.	
Excluded study design: before-after design (no data reported in paper that are suitable for ITS analysis)	Manian, F. A., S. Griesnauer and A. Bryant (2013). "Implementation of hospital-wide enhanced terminal cleaning of targeted patient rooms and its impact on endemic Clostridium difficile infection rates." Am J Infect Control 41(6): 537-541.	no
Excluded study design: before-after design (no data reported in paper that are suitable for ITS analysis)	Napolitano, N. A., T. Mahapatra and W. Tang (2015). "The effectiveness of UV-C radiation for facility-wide environmental disinfection to reduce health care-acquired infections." American Journal of Infection Control 43(12): 1342-1346.	no
Excluded study design: before-after design (no data reported in paper that are suitable for ITS analysis)	Ray, A., F. Perez, A. M. Beltramini, M. Jakubowycz, P. Dimick, M. R. Jacobs, K. Roman, R. A. Bonomo and R. A. Salata (2010). "Use of vaporized hydrogen peroxide decontamination during an outbreak of multidrug-resistant Acinetobacter baumannii infection at a long-term acute care hospital." Infection Control and Hospital Epidemiology 31(12): 1236-1241.	no
Excluded study design: before-after design (no data reported in paper that are suitable for ITS analysis)	Vianna, P. G., C. Dale, S. Simmons, M. Stibich and C. Licitra (2015). "The Impact of Ultraviolet Disinfection on Hospital Acquired Infection Rates in a Tertiary Care Community Hospital...42nd Annual Conference Abstracts, APIC 2015, Nashville, TN June 2015." American Journal of Infection Control 43: S19-S20.	no
Excluded study design: before-after design (no data reported in paper that are suitable for ITS analysis)	Vianna, P. G., C. R. JrDale, S. Simmons, M. Stibich and C. M. Licitra (2016). "Impact of pulsed xenon ultraviolet light on hospital-acquired infection rates in a community hospital." American Journal of Infection Control 44(3): 299-303.	no

Appendix 8. List of all studies excluded following full text review

1. (2015). "Benefits of Ultraviolet Light as a Room Disinfectant." AACN Bold Voices 7(11): 8-8.
2. (2015). "Prevention Update...Healthcare-Associated Infections." Healthcare Purchasing News 39(5): 20-20.
3. (2015). "Rapid onset of asthma in healthcare workers." Hospital Employee Health 34(9): 100-100.
4. (2016). "Cleaning Agent Leads to Asthma-Like Symptoms." Hospital Infection Control & Prevention 43(8): 95-95.
5. (2016). "New paper supports hydrogen peroxide vapour (HPV) efficacy." Operating Theatre Journal (304): 3-3.
6. Alfa, M. J., E. Lo, A. Wald, C. Dueck, P. DeGagne and G. K. Harding (2010). "Improved eradication of Clostridium difficile spores from toilets of hospitalized patients using an accelerated hydrogen peroxide as the cleaning agent." BMC Infect Dis 10: 268.
7. Alfa, M. J., E. Lo, N. Olson, M. MacRae and L. Buelow-Smith (2015). "Use of a daily disinfectant cleaner instead of a daily cleaner reduced hospital-acquired infection rates." Am J Infect Control 43(2): 141-146.
8. Allen, V., L. Barnes, M. Scott and B. Yoder (2015). "Environmental Disinfection, Monitoring and Training: The Impact of Combined Environmental Hygiene Interventions on Environmental Hygiene and Infection Control Outcomes...42nd Annual Conference Abstracts, APIC 2015, Nashville, TN June 2015." American Journal of Infection Control 43: S42-S43.
9. Andersen, B. M., H. Banrud, E. Boe, O. Bjordal and F. Drangsholt (2006). "Comparison of UV C light and chemicals for disinfection of surfaces in hospital isolation units." Infection Control and Hospital Epidemiology 27(7): 729-734.
10. Anderson, D. J., M. F. Gergen, E. Smathers, D. J. Sexton, L. F. Chen, D. J. Weber and W. A. Rutala (2013). "Decontamination of targeted pathogens from patient rooms using an automated ultraviolet-C-emitting device." Infect Control Hosp Epidemiol 34(5): 466-471.
11. Anonymous (2015). "Abstracts from the 3rd International Conference on Prevention and Infection Control, ICPIC 2015." Antimicrobial Resistance and Infection Control 4: no pagination.
12. Bache, S. E., M. MacLean, J. G. Anderson, G. Gettinby, J. E. Coia, S. J. MacGregor and I. Taggart (2011). "Laboratory inactivation of healthcare-associated isolates by a visible HINS-light source and its clinical application in the burns unit." Burns 37: S6.
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Appendix 9. Abbreviations

AHRQ	Agency for Healthcare Research and Quality
C. difficile	*C. difficile* associated disease
CBA	Controlled before-after studies
CDAD	*C. difficile* associated diarrhoea (or disease)
CLSI	Clinical and Laboratory Standards Institute
CPE	Carbapenemase-producing Enterobacteriaceae
CPE	Cephalosporin-resistant
EPOC	Cochrane Effective Practice and Organisation of Care
ESBL	Extended spectrum beta lactamase
EUCAST	European Committee on Antimicrobial Susceptibility Testing
GRADE	Grading of recommendations assessment, development and evaluation
HA	Hospital-acquired
HAIs	Healthcare-associated infections
HP	Hydrogen peroxide
HPV	Hydrogen peroxide (vapour)
ICGAC	Infection Control Guidelines Advisory Committee
ICU	Intensive care unit
ITS	Interrupted-time-series studies
KPC	Klebsiella pneumoniae carbapenemases (carbapenemase producing gene)
MBLs	metallo-β-lactamases (carbapenemase producing gene)
MDR	Multidrug resistant
MIC	Minimum inhibitory concentration
MICU	Medical intensive care unit
MRGN	Multi-resistant Gram-negative
MROs	Multidrug resistant organisms
MRSA	*Methicillin-resistant Staphylococcus aureus*
NHMRC	National Health and Medical Research Council
NICU	Neonatal intensive care unit
NRT	Non-randomised trials
PCR	Polymerase chain reaction
PICO	Participants/Population, Intervention, Comparator, Outcomes
PICU	Paediatric intensive care unit
RM	Repeated measures
RoB	Risk of bias
RT	Randomised trials
SICU	Surgical intensive care unit
TGA	Therapeutic Goods Administration
the Commission	Australian Commission on Safety and Quality in Health Care
TIDieR	Template for Intervention Description and Replication
UV	Ultra-violet
UVD	Ultra-violet disinfection
VRE	vancomycin resistant enterococcus
WHO ICTRP	World Health Organisation International Clinical Trials Registry Platform