Cochrane Australia

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

Report prepared by
Cochrane Australia

7 April 2017

Trusted evidence.
Informed decisions.
Better health.

Contents

Authors and contributors to the protocol 4

Declarations of interest 4

1. Background 5

1.1 Description of the condition and setting 5

1.2 Description of the intervention and how it might work 5

Ultra-violet light 6

Hydrogen peroxide vapour/mist 6

Electrolysed water 6

Sodium hypochlorite 6

2. Objectives 7

3. Methods 7

3.1 Criteria for considering studies for this review 7

3.1.1 Types of participants 7

3.1.2 Types of settings 7

3.1.3 Types of interventions 7

3.1.4 Types of comparators 8

3.1.5 Types of outcome measures 8

3.1.6 Types of studies 9

3.2 Search methods for identification of studies 9

3.2.1 Search terms 9

3.2.2 Bibliographic and grey literature databases 9

3.2.3 Other sources 10

3.3 Data collection and analysis 10

3.3.1 Selection of studies 10

3.3.2 Data extraction and management 10

3.3.3 Assessment of risk of bias of included studies 10

3.3.4 Measures of treatment effect 10

3.3.5 Unit of analysis issues, missing data, assessment of heterogeneity and reporting bias 11

3.3.6 Data synthesis 11

3.3.7 Summary of findings tables and assessment of quality of the body of evidence 11

4. Results 11

4.1 Results of the search 11

4.2 Description of studies 12
4.2.1 Included studies 12
4.2.2 Ongoing studies 18
4.2.3 Excluded studies 18
4.2.4 Studies awaiting assessment 18
4.3 Risk of bias in included studies 18
4.3.1 Randomised and non-randomised trials 18
4.3.2 Time series studies 19
4.4 Effects of interventions 21
4.4.1 Sodium hypochlorite versus standard cleaning/disinfection 21
4.4.2 Hydrogen peroxide vapour versus standard cleaning/disinfection 27
4.2.3 Ultra-violet light disinfection versus standard cleaning/disinfection 33
5.0 Discussion 38
5.1 Summary of main results 38
5.2 Overall completeness and applicability of the evidence 38
5.3 Quality of the evidence 39
5.4 Potential biases in the review process 40
6.0 Authors' conclusions 40
6.1 Implications for practice 40
6.2 Implications for research 41
References **42**
References to studies included in this review 42
References to ongoing studies 43
References to studies awaiting further assessment 43
Other references 43

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).

1. Background

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

1.1 Description of the condition and setting

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

1.2 Description of the intervention and how it might work

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

Environmental controls, including cleaning and disinfection, are used to prevent transmission of infectious agents to patients occurring either through direct contact with surfaces or indirect contact via an intermediary ((National Health and Medical Research Council 2010), p21). The 2010 Guidelines recommend routine cleaning of surfaces with detergent solution as a standard precaution (i.e. a first-

line approach that should be used with all patients). Disinfection is recommended in addition to cleaning as a transmission-based precaution. Its use is recommended "where the suspected or confirmed presence of infectious agents represents an increased risk of transmission" and for the management of MROs (e.g. MRSA, MRGN, VRE). Unlike cleaning with detergent, disinfection involves the use of chemical or physical methods to kill microorganisms (including pathogens) (Rutala 2008, Therapeutic Goods Administration 2012). In Australia, claims of disinfectant properties are subject to regulation by the Therapeutic Goods Administration (TGA) and approved disinfectants are registered after demonstrating compliance with essential principles for quality, safety and performance (Therapeutic Goods Administration 2012).

This review focuses on the use of modes of disinfection that have emerged or undergone further development for use in healthcare facilities subsequent to the review of evidence for the 2010 Guidelines. Three novel disinfectant technologies are considered in this review: ultra-violet (UV) light, hydrogen peroxide (HP) vapour and electrolysed water. The review examines the effects (including harms) of using each of these interventions compared to using a detergent solution (standard care), sodium hypochlorite (bleach) or both on clinical outcomes. The review also examines the effects of sodium hypochlorite, a widely used disinfectant, compared to using a detergent solution.

Ultra-violet light

Ultra-violet light in the UV-C wavelength range (200 to 270 nanometers) has microbiocidal properties against multiple pathogens, including *Clostridium difficile* and other healthcare associated pathogens. Technologies have been developed for automated (no-touch) disinfection of hospital rooms using UV light, and these have been suggested as an adjunct to manual application of disinfectants. The technologies only disinfect areas directly in the UV light and can only be used when rooms are vacated, partly because of the potentially harmful effects of UV exposure (Leas 2015).

Hydrogen peroxide vapour/mist

Hydrogen peroxide has microbiocidal properties against multiple pathogens, including *Clostridium difficile.* Automated (no touch) systems for producing hydrogen peroxide vapour and hydrogen peroxide dry mist are designed to disinfect by dispersing vapour or mist evenly across a room. As with UV light, the systems can only be used when rooms are vacated (Leas 2015). Rooms and ventilation systems must be sealed to prevent exposure, and hydrogen peroxide must be monitored to ensure safe levels outside the room during disinfection and within the room before re-entering. While hydrogen peroxide has been suggested to have low toxicity, previous reviews found little or no evidence about the safety of no-touch hydrogen-peroxide producing systems (Leas 2015).

Electrolysed water

Electrolysed water systems pass an electric current through tap water with added salt to produce neutral electrolysed water. Electrolysed water has antimicrobial properties that have led to use in other industries (e.g. food production), where advantages are suggested to include not needing hazardous chemicals, ease of handling and low operating costs (Stewart 2014, Leas 2015).

Sodium hypochlorite

Sodium hypochlorite (bleach) is a commonly used chlorine-based disinfectant with broad spectrum antimicrobial properties. Sodium hypochlorite may cause irritation to skin, eyes and other mucous membranes. It can also corrode metals and discolour or stain fabrics (Leas 2015).

2. Objectives

To examine the effect of ultra-violet (UV) light, hydrogen peroxide (HP) vapour and/or electrolysed water on infection rates in high risk population groups compared with standard care (cleaning with detergent, disinfection with sodium hypochlorite, or both) on clinical outcomes.

To examine the effect of disinfection with sodium hypochlorite on infection rates in high risk population groups compared with cleaning with detergent on clinical outcomes.

3. Methods

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

3.1 Criteria for considering studies for this review

3.1.1 Types of participants

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 included, patients in intensive care, oncology, haematology, burns and renal units. Studies set on wards on which there was a known outbreak or in contact precaution rooms were also eligible.

3.1.2 Types of settings

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

3.1.3 Types of interventions

Studies evaluating the effects of 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.

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 surface was eligible including hard nonporous and porous surfaces.

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.

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).

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

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

Adverse effects

Data on adverse effects (harms, safety) was collected and included in our review when the data were reported in included studies that measured at least one of the primary or secondary outcomes (i.e.

infection, colonisation), or in eligible studies that explicitly aimed to examine adverse effects. We considered only patient or health professional health outcomes, not broader impacts on health services delivery.

3.1.6 Types of studies

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

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

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

3.2 Search methods for identification of studies

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

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

3.2.1 Search terms

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

3.2.2 Bibliographic and grey literature databases

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

3.2.3 Other sources

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

3.3 Data collection and analysis

3.3.1 Selection of studies

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

3.3.2 Data extraction and management

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

3.3.3 Assessment of risk of bias of included studies

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

For each study, we report our judgment of risk of bias (low, high, unclear) by domain and provide a rationale for the judgment with supporting information (summarised in the results and reported in full in Technical report, Appendix 5, characteristics of included studies). Summary assessments of risk of bias for each comparison and outcome were used in determining the overall quality of the body of evidence using GRADE.

3.3.4 Measures of treatment effect

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, missing data, assessment of heterogeneity and reporting bias

Where data were published, we re-analysed interrupted time series designs that had been analysed as before after studies (Boyce 2008, Hacek 2010, McMullen 2007, Orenstein 2011) or that had incompletely reported analyses (Haas 2014, Mitchell 2014). The analysis methods are described in the Technical report (section 3.3.5; Appendix 3). For all analyses, we standardised the rates of infection to per 1,000 patient-days.

Methods for dealing with missing data, and assessment of heterogeneity and reporting bias are described in the Technical report (sections 3.3.6, 3.3.7, 3.3.8).

3.3.6 Data synthesis

In line without our protocol, we did not combine effect estimates from studies using non-randomised study designs (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 study characteristics, in tables structured by comparison, outcome, and study design.

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

For each comparison and outcome, we assessed the quality of the evidence using the GRADE approach. In accordance with GRADE guidance (Schunemann 2013), we assessed the following five domains: (1) risk of bias, (2) inconsistency, (3) imprecision, (4) indirectness, and (5) publication bias. A judgement was made about whether there were serious, very serious or no concerns in relation to each domain. While some overall conclusions are drawn across studies, most studies addressed different questions (comparisons, type of pathogen, patient population) or had other important differences that meant synthesis of effects across studies would be uninterpretable. For this reason, we report GRADE assessments for individual studies and describe our approach in the Technical report (section 3.3.10).

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

4. Results

4.1 Results of the search

The searches of Embase, PubMed, Cochrane Trials Register and CINAHL Plus were conducted on 23 August 2016 and retrieved 3388 records. Screening the references considered for the AHRQ report and ClinicalTrials.gov added a further 622 records. After removing duplicates, we screened 3854 records. Figure 1 shows the flow of references through the review. (See Technical report, Appendix 1 for the search results for each source.) The figure includes all studies screened for this review, and the review of antimicrobial surfaces. The full text of 172 papers were screened; from which 161 were excluded from the novel disinfectants review.

The full publication of six studies (five of novel disinfectants; one of antimicrobial surfaces) that were potentially eligible but which were reported only as conference abstracts were searched for separately

in Scopus and PubMed. We also used SCOPUS to conduct forward citation searches for all studies included in the review. The characteristics of the five studies of novel disinfectants that were published only as conference abstracts are described in the "Studies awaiting further assessment" section.

After screening and full-text review, we included nine studies (reported in nine papers and two trial registry entries) in the novel disinfectants review. One of the studies reported in a registry entry is yet to be published so is listed as an ongoing study (Maragakis 2015).

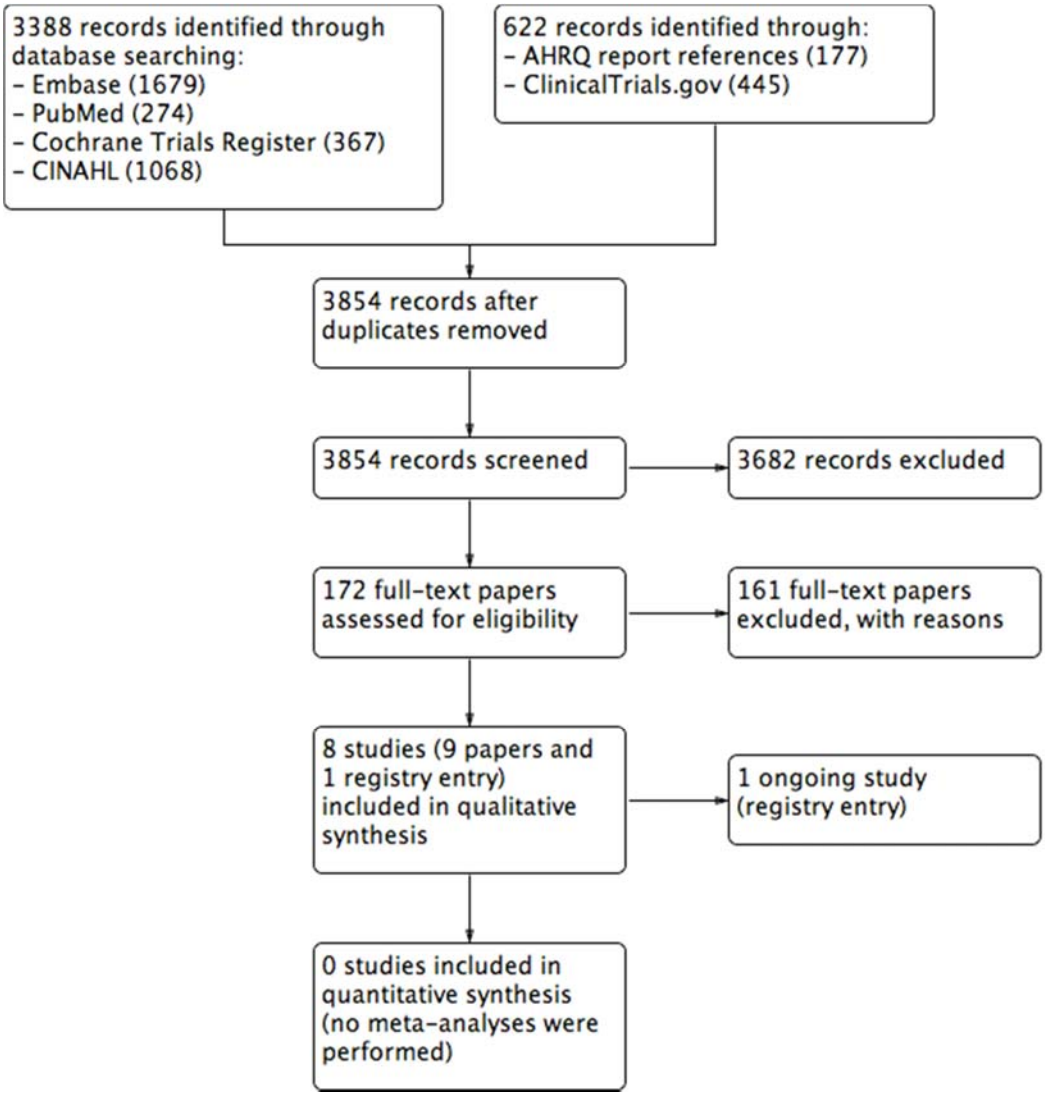


Figure 1: Study flow diagram

4.2 Description of studies

4.2.1 Included studies

Characteristics of the eight included studies are summarised in Table 1 and reported in detail in the Technical report, Appendix 5 (Characteristics of included studies). Seven of the studies were conducted

in the United States (Anderson 2017, Boyce 2008, Haas 2014, Hacek 2010, McMullen 2007, Orenstein 2011, Passaretti 2013) and the eighth was in Australia (Mitchell 2014).

Sodium hypochlorite (bleach)

One randomised trial examined the effects of sodium hypochlorite for terminal room disinfection compared to standard practice (quaternary ammonium) on incidence rates of hospital-acquired MRSA, VRE, and multidrug-resistant *Acinetobacter (Anderson 2017)*. This trial included four comparisons, the other three involving ultra-violet light disinfection (considered separately under 'Ultra-violet light disinfection systems'). Three non-randomised studies examined the effects of sodium hypochlorite compared to standard cleaning/disinfection (quaternary ammonium) on incidence rates of hospital acquired *C. difficile* associated diarrhoea (Hacek 2010, McMullen 2007, Orenstein 2011

Settings and populations. In the randomised trial, interventions were used for terminal disinfection of 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 (for sodium hypochlorite, these were MRSA, VRE, or MDR *Acinetobacter).* Eligible patients were those exposed to a seed room for 24 hours or more (exposed patients). The trial was conducted in nine hospitals (two tertiary, six community, one Veterans Affairs), and included 8074 patients in the sodium hypochlorite comparison. The three non-randomised studies introduced sodium hypochlorite interventions in response to an identified increase in cases of *C. difficile* associated disease (CDAD). All were based in rooms or units with high CDAD incidence, including rooms vacated by patients with CDAD (Hacek 2010), a medical intensive care unit (McMullen 2007), and two units described only as having high CDAD incidence (Orenstein 2011). None of these studies reported information about the size of the study, for example the number of rooms cleaned, the number of room occupations, or the number of cleans.

Intervention protocols and duration. All studies used comparable preparations of sodium hypochlorite but varied as to whether sodium hypochlorite was used for daily clean (McMullen 2007, Orenstein 2011) or discharge/terminal clean only (Anderson 2017, Hacek 2010). In Anderson 2017, terminal room cleaning was performed with commercial sodium hypochlorite wipes (1:10 dilution, equivalent to 0.55% active chlorine) over a 6 month period. In Hacek 2010, sodium hypochlorite cleaning (1:10 dilution with water) was used on discharge over a 24 month period. In McMullen 2007, two different sodium hypochlorite-cleaning protocols were used (both using 1:10 dilution with water). In the first 5 months immediately after the CDAD outbreak, all rooms on the MICU were cleaned with sodium hypochlorite including the nurses' station and other areas not occupied by patients. In the second 24 month period, only rooms vacated by patients with CDAD were cleaned with sodium hypochlorite. In Orenstein 2011, daily sodium hypochlorite cleaning with commercial wipes (0.55% active chlorine) was used over a 12 month period.

Study design and other outcomes. Anderson 2017 was a cluster randomised crossover trial conducted over four consecutive seven-month intervention periods (28 months in total, design and outcomes described under 'Ultra-violet light disinfection systems'). The three non-randomised studies used a before-after design, in which incidence rates of infection in a pre-intervention period were compared to rates after the bleach intervention was introduced. The studies were re-analysed as interrupted times series studies because all three reported time series data for an eligible outcome (infection). Neither Hacek 2010 nor McMullen 2007 reported any other outcomes. In addition to the outcome reported in this review, Orenstein 2011 reported time between hospital-acquired CDAD cases, overall incidence of CDAD (hospital and community acquired, per 10,000 patient days), and cost of the intervention.

Hydrogen peroxide disinfection systems

Three non-randomised studies examined the effects of hydrogen peroxide vapour (HPV) disinfection as an adjunct to standard cleaning compared to standard cleaning/disinfection alone (Boyce 2008, Mitchell 2014, Passaretti 2013). Boyce 2008 examined the effects of HPV on incidence rates of hospital-acquired CDAD. Mitchell 2014 examined the effects of HPV on incidence rates of hospital-acquired MRSA, while Passaretti 2013 examined effects on incidence rates of multiple hospital-acquired MROs (VRE, MRSA, MRGN bacteria) and *C. difficile*, reporting results for individual pathogens and all pathogens combined.

Settings and populations. In Boyce 2008 the HPV intervention was introduced in response to an identified increase in cases of CDAD. The intervention was used in all rooms on five wards with the highest CDAD incidence (number of rooms/cleans not reported). In Mitchell 2014, HPV was used in rooms accommodating patients with MRSA (3629 discharge cleans; 1712 in HP arm). In Passaretti 2013, HPV was used on three high risk units (two ICUs and a surgical unit; 437 room occupations) and compared to standard cleaning/disinfection on three high risk control units (medical, cardiothoracic surgery, surgical oncology; 5913 room occupations).

Intervention protocols. All HPV decontamination occurred in rooms vacated after discharge or transfer of patients. Most studies noted that air conditioning and ventilation ducts were sealed, and HPV levels were monitored outside the room and prior to anyone re-entering the room. The same HPV decontamination system was used in Boyce 2008 and Passaretti 2013 (Bioquell). Mitchell used a dry HPV system (Nocospray) in all single occupancy rooms (1363/1712 (80%) rooms in the HP arm), but used HP solution in double occupancy rooms. Standard cleaning/disinfection varied across studies, involving daily sodium hypochlorite disinfection of rooms occupied by patients with CDAD (Boyce 2008, not reported for other rooms), discharge cleaning twice with pH neutral detergent (Mitchell 2014), or daily and discharge cleaning with quaternary ammonium (Passaretti 2013).

Study design and other outcomes. Boyce 2008 and Mitchell 2014 used a before-after study design, in which incidence rates of infection/colonisation in a pre-intervention period (7 and 46 months respectively) were compared to rates after the HPV intervention was introduced (10 and 38 months respectively). Boyce was re-analysed as an interrupted times series using time series data reported in the paper. Mitchell reported results from time series analyses, but was re-analysed because not all statistics were reported. Passaretti 2013 was categorised as a non-randomised trial, reporting a comparison between concurrent intervention and control groups (18 months duration). In addition to the outcome analysed in this review, Mitchell reported incidence rates of hospital-acquired MRSA bacteraemia. Time series data were not reported in the paper for this outcome, hence it was not re-analysed. All three studies reported data for bacterial contamination of surfaces, but only Mitchell 2014 and Passaretti 2014 had data for both intervention and control periods/arms.

Ultra-violet light disinfection systems

One randomised trial (Anderson 2017) and one non-randomised study (Haas 2014) examined the effects of ultra-violet (UV-C) light disinfection as an adjunct to standard cleaning compared to standard cleaning/disinfection alone. Both studies examined the effect of UV disinfection on incidence rates of hospital-acquired MROs and *C. difficile*.

Settings and populations. Anderson 2017, used UV light for terminal disinfection of 'seed rooms' (previous occupant had proven infection or colonisation with an MRO (MRSA, VRE, MDR *Acinetobacter) or C. difficile*). Outcomes were measured among patients exposed to a seed room for 24 hours or more. In Haas 2014 pulsed xenon UV light disinfection was used on discharge in contact precaution rooms

(patients with *C. difficile* or MROs) and a burns unit, daily in operating rooms, and weekly in a dialysis unit. All units were in one hospital.

Intervention protocols and duration. Anderson 2017 examined the effects of UV light as an adjunct to standard terminal room disinfection, including three comparisons that differed according to target pathogen. For MROs, the comparisons were (1) UV light as an adjunct to standard disinfection (quaternary ammonium) vs standard disinfection (QA) alone (7660 patients), and (2) UV light plus sodium hypochlorite as an adjunct to standard disinfection (QA) versus standard disinfection (QA) alone (8403 patients). For *C. difficile* the comparison was (3) UV light as an adjunct to standard disinfection (sodium hypochlorite) vs standard disinfection alone (sodium hypochlorite) (5177 patients). Intervention protocols required placement of the UV system in the centre of the room, to minimise shadowing (areas not in direct line of UV light) and ensure light was emitted into the adjacent bathroom. In Haas 2014, sodium hypochlorite was used for standard daily and discharge cleaning. Rooms were vacated prior to cleaning, windows were covered, and then all furnishing and fittings were placed in the path of the UV light. No information was reported about the number of rooms or cleans.

Study design and other outcomes. Anderson 2017 used a cluster randomised crossover trial design, in which all nine hospitals received the four interventions in a randomly allocated sequence. Each intervention was used for six months, preceded by a one month wash-in period to prevent effects of the previous intervention carrying-over into the next intervention period. Haas 2014 used a before-after design, in which incidence rates of acquisitions of hospital-acquired MROs and *C. difficile* in a pre-intervention period (30 months) were compared to rates after the HPV intervention was introduced (22 months). The study was re-analysed as an interrupted times series using data reported in the paper.

In addition to the outcomes reported in this review, Anderson et al measured bacterial contamination of surfaces in two hospitals (20-28 randomly selected seed rooms per intervention group, 10 surfaces per room), and the effects of implementing UV disinfection on health service delivery outcomes (room turnover time, emergency room wait time, time on diversion). The registry report for this trial also lists eight secondary outcomes not included in the trial report. Four of these planned outcomes are measures of infection caused by target MROs among exposure patients; these appear eligible for this review but results are yet to be published. In addition to the outcome analysed in this review, Haas 2014 reported incidence rates of all hospital-acquired MROs individually but time series data were not available for these outcomes. Other outcomes included length of stay before CDAD (reported in Nagaraja 2015), additional time for discharge arising from use of UVD, and feasibility of use (based on % of cancellations of UVD).

Electrolysed water

No eligible studies were identified that evaluated the effects of electrolysed water on hospital acquired infection or colonisation with MROs or *C. difficile*.

Table 1. Summary of characteristics of included studies

Study ID	Study design	Intervention (I) and comparison (C)	Duration[a]	Setting	Main outcome (metric)	Pathogen(s)
Sodium hypochlorite (sodium hypochlorite) vs standard cleaning/disinfection						
Anderson 2017[b] USA	Cluster randomised crossover trial	I1. Sodium hypochlorite wipes (1:10 dilution) for terminal room disinfection [see UV light disinfection for I2-4] C. Standard cleaning/disinfection (daily and terminal room disinfection with quaternary ammonimum)	I/C four seven-month periods in randomly allocated sequence (one month wash-in, six month intervention)	'Seed' rooms vacated by patients with confirmed infection or colonisation with an MRO Nine hospitals including two tertiary (853 and 950 bed), six community (148-660 bed), one Veterans Affairs (271 bed).	Infection/colonisation (composite): incidence rate of hospital-acquired MROs among patients exposed to seed rooms (cases per 1,000 exposure days)	VRE, MRSA, MDR *Acinetobacter*
Hacek 2010 USA	Time series (re-analysed)	I. Sodium hypochlorite (on discharge; 1:10 dilution with water) C. Standard cleaning/disinfection (quaternary ammonium)	I. Aug 2005 - Aug 2007 (25 months) C. Oct 2004 - July 2005 (10 months)	Rooms vacated by patients with CDAD (No. rooms/cleans not reported); hospital-wide *C. difficile* outbreak, all sites. Three hospitals in a university health system (~850 beds, 40,000 annual admissions)	Infection: incidence rate of hospital-acquired CDAD (cases per 1,000 patient-days)	*C. difficile*
McMullen 2007[c] USA	Time series (re-analysed)	I1. Sodium hypochlorite (daily, all rooms; 1:10 dilution with water) I2. Sodium hypochlorite (daily, rooms of patients with CDAD; 1:10 dilution with water) C. Standard cleaning/disinfection (quaternary ammonimum)	I1. Aug - Dec 2002 (5 months) I2. Jan 2003 - Dec 2004 (24 months) C1. Jan - July 2002 (7 months; pre-intervention period)	Medical intensive care unit (19 bed), with *C. difficile* outbreak/increased incidence. I1: all rooms (including nursing station, staff restroom, staff conference room, waiting room). I2: rooms vacated by patients with CDAD. (No. cleans not reported) University-affiliated tertiary care facility (1,400-bed)	Infection: incidence rate of hospital-acquired CDAD (cases per 1,000 patient-days)	*C. difficile*
Orenstein 2011[d] USA	Time series (re-analysed)	I. Sodium hypochlorite wipes (daily; 0.55% active chlorine) C. Standard cleaning/disinfection (quaternary ammonimum)	I. Aug 2009 - July 2010 (12 months) C. Aug 2008 - July 2009 (12 months)	Two units with high CDAD incidence; all rooms (No. rooms/cleans not reported). Acute care hospital (1,249-bed)	Infection: incidence rate of hospital-acquired CDAD (cases per 1,000 patient-days)	*C. difficile*
Hydrogen peroxide vapour disinfection as an adjunt to standard cleaning/disinfection vs standard cleaning/disinfection						
Boyce 2008[e] USA	Time series (re-analysed)	I. Hydrogen peroxide vapour room decontamination (Bioquell) C. Standard cleaning/disinfection alone (sodium hypochlorite)	I. June 2005 - Mar 2006 (10 months) C. Nov 2004 - May 2005 (7 months)	5 wards (highest CDAD incidence), all rooms (No. rooms/cleans not reported); hospital-wide *C. difficile* outbreak. University-affiliated hospital (500-bed)	Infection: incidence rate of hospital-acquired CDAD (cases per 1,000 patient-days)	*C. difficile*
Mitchell 2014[d,f] Australia	Time series (re-analysed)	I. Dry hydrogen peroxide vapour room decontamination (single rooms, Nocospray system); hydrogen peroxide solution (shared rooms)	I. Nov 2009 - Dec 2012 (38 months) C. Jan 2006 - Oct 2009 (46 months)	Rooms accommodating MRSA patients (3629 discharge cleans; 1712 in HP arm). HPV used in 1363/1712 rooms (~80%) Public hospital, acute care facilities (300-bed)	Infection/colonisation (composite): incidence rate of hospital-acquired MRSA (cases per 1,000 patient-days)	MRSA

Study ID	Study design	Intervention (I) and comparison (C)	Duration[a]	Setting	Main outcome (metric)	Pathogen(s)
		C. Standard cleaning/disinfection alone (pH neutral detergent)				
Passaretti 2013 USA	Controlled before-after	I. Hydrogen peroxide vapour room decontamination (Bioquell) C. Standard cleaning/disinfection alone (quaternary ammonimum)	I/C (concurrent): Jan 2008 - June 2009 (18 months)	High risk units; 3 intervention units - surgical ICU, neurosurgical ICU, surgical (437 room occupations), 3 control units - medical, cardiothoracic surgery, surgical oncology ICU (5913 room occupations) Tertiary care hospital/referral center (994-bed)	Infection/colonisation (composite): incidence rate of hospital-acquired MROs and CDAD (cases per 1,000 patient-days)	VRE, MRSA, MRGN bacteria, *C. difficile*
Ultra-violet disinfection as an adjunct to standard cleaning/disinfection vs standard cleaning/disinfection						
Anderson 2017[b] USA	Cluster randomised crossover trial	I2. UV-C light (Tru-D Smart system) as an adjunct to terminal room disinfection with QA I3. UV light plus sodium hypochlorite as an adjunct to terminal room disinfection with QA C. Standard cleaning/disinfection (daily and terminal room disinfection with quaternary ammonimum)	I/C four seven-month periods in randomly allocated sequence	'Seed' rooms vacated by patients with confirmed infection or colonisation with MRO or *C difficile* Nine hospitals including two tertiary (853 and 950 bed), six community (148-660 bed), one Veterans Affairs (271 bed).	Infection/colonisation (composite): incidence rate of hospital-acquired MROs among patients exposed to seed rooms (cases per 10,000 exposure days)	VRE, MRSA, MDR *Acinetobacter*
Anderson 2017[b] USA	Cluster randomised crossover trial	I4. UV-C light as an adjunct to terminal room disinfection with sodium hypochlorite C. Standard cleaning/disinfection (daily and terminal room disinfection with sodium hypochlorite wipes (1:10 dilution)	I/C four seven-month periods in randomly allocated sequence	'Seed' rooms vacated by patients with confirmed *C difficile* infection Nine hospitals including two tertiary (853 and 950 bed), six community (148-660 bed), one Veterans Affairs (271 bed).	Infection: incidence rate of hospital-acquired CDAD among patients exposed to seed rooms (cases per 10,000 exposure days)	*C. difficile*
Haas 2014[g] USA	Time series (re-analysed)	I. Pulsed xenon UV-C light room disinfection (Xenex system) C. Standard cleaning/disinfection alone (sodium hypochlorite)	I. July 2011 - Apr 2013 (22 months) C. Jan 2009 - June 2011 (30 months)	Contact precautions rooms (*C. difficile*, MRO), burns unit, operating rooms, dialysis unit. Other units on request. (No. rooms/cleans not reported). Tertiary care hospital (643-bed)	Infection/colonisation (composite): incidence rate of hospital-acquired MROs and CDAD (cases per 1,000 patient-days)	VRE, MRSA, MRGN bacteria, *C. difficile*

a. Intervention period is inclusive (first to last day of the month) unless reported otherwise

b. Anderson 2017 includes four comparisons: sodium hypochlorite vs standard disinfection with QA (MROs only), two of UV light vs standard disinfection with QA (MROs only), and one of UV light vs standard disinfection with sodium hypochlorite (*C. difficile* only).

c. McMullen 2007: data also reported for surgical ICU (sodium hypochlorite clean of rooms vacated by CDAD patients). Intervention period was too-short for time series analysis (2 data collection points).

d. Anderson 2017, Orenstein 2011 and Mitchell 2014: Reported cases per 10,000 days. These were standardised to cases per 1,000 days in reporting or re-analysis to enable comparison across studies.

e. Boyce 2008: Data were reported for a third period, prior to the outbreak and introduction of infection control measures that were used throughout the HPV intervention period.

f. Mitchell 2014: Outcome data were also reported for MRSA bacteraemia, but time series data were not available in the paper for re-analysis (single pre- and post-intervention measure).

g. Haas 2010: Outcome data were also reported for individual pathogens, but time series data were not available in the paper for re-analysis (single pre- and post-intervention measure only).

4.2.2 Ongoing studies

Characteristics of one ongoing study are described in the Technical report, Appendix 6. Maragakis 2015 is a two arm cluster-randomised trial that compares UV light disinfection to standard cleaning/disinfection (details not reported). The study is based in a single hospital in the USA; the type of ward is not reported in the registry entry (11,000 patients). The primary outcome for this trial is incidence rates of acquisitions of MROs or *C. difficile* (colonisation or infection). The estimated completion date of the trial is March 2018. Details of this study are provided to inform future updates of the Guidelines.

4.2.3 Excluded studies

Reasons for excluding the 42 studies that were considered 'near misses' are described in the Technical report, Appendix 7 (Characteristics of excluded studies). These studies are those that evaluated an eligible intervention (or a closely related intervention), and met most other criteria (i.e. could not clearly be excluded without screening all criteria). Of these, two types of studies provide data outside the scope of the current review, but of potential relevance: (1) studies that met all other criteria but used an uncontrolled before-after design, without reporting time series data suitable for re-analysis (9 studies), and (2) studies that met all other criteria but measured bacterial contamination of surfaces without reporting a clinical outcome (4 studies). The two sets of studies are identified in the Technical report, Appendix 7. Studies that examined HPV or UV light disinfection as part of an infection control bundle may also be of importance (3 studies; details in the Technical report Appendix 7). These were excluded because the comparator did not include the bundled intervention components, making it impossible to isolate the effects of the HPV or UV light disinfection. However, in practice, it is likely that concurrent interventions (including increased vigilance in complying with infection control policy) occurred during the study period in most studies. A full list of studies excluded after full text review is provided in the Technical report, Appendix 8. This list includes the 42 near miss studies, and 119 studies that were clearly ineligible for the novel disinfectants review (including 33 papers relevant to the antimicrobial surfaces review).

4.2.4 Studies awaiting assessment

Five studies of novel disinfectants were published only as conference abstracts with insufficient information to confirm their eligibility (Bernard 2015, Mauzey 2015, McMullen 2016, Sampathkumar 2016, Simmons 2013). We did not identify a trial registry entry for any of these studies. All five studies evaluated the effects of UV light disinfection systems. All were set in the USA and were on high risk wards. These wards included units with a known outbreak or isolation rooms (Bernard 2015, McMullen 2016), neonatal intensive care units (Mauzey 2015), and haematology, oncology or medical surgery wards (Sampathkumar 2016, Simmons 2013). Infection or colonisation with *C. difficile* or an MRO was measured in all studies. Insufficient information was reported in the abstracts to confirm the study design used in each of the five studies. All appeared to use uncontrolled before-after designs, for which it was unclear whether time series data would be available. The complexity of interpreting results from time series analyses, and the potential biases in these designs, meant it was not feasible to re-analyse pre-publication data (if requested from authors) or assess risk of bias from the conference abstracts alone.

4.3 Risk of bias in included studies

Our assessment of the risk of bias for the randomised and non-randomised trials is summarised in Table 2 and for the time series studies in Table 3. The complete assessment for each study, including the rationale for the judgement of each domain is reported in Technical report, Appendix 5 (Characteristics of included studies).

4.3.1 Randomised and non-randomised trials

Anderson 2017 is a cluster randomised crossover trial. All hospitals received all interventions, delivered sequentially over four intervention periods. The sequence of interventions was determined by a method of

randomisation judged to the adequate (domain 1). 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 (domain 2). 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 (domain 4). It was not possible to mask patient participants, health professionals and outcome assessors to the intervention. We judged it unlikely that performance bias would occur in delivering the intervention, since controls were in place to monitor compliance. The risk of bias was judged low for measurement of MRO acquisition, since testing appeared to be performed according to hospital protocols for surveillance (domain 3). The risk of bias for measurement of CDAD was judged unclear, since test ordering practices might have altered in response to intervention (domain 3). Additional outcomes were listed in the registry entry. Omission of these from the trial report does not bias effect estimates reported in this review. While these additional outcomes may alter the overall findings about intervention effects, we judged the risk of bias from selective outcome reporting as low (domain 5). The risk of bias arising from baseline imbalance in patient characteristics or outcomes was judged unclear (domain 6). The study was judged to be at low risk of bias arising from contamination (other sites receiving the intervention) and other sources (domain 7).

Passaretti 2013 is a non-randomised study, and the methods by which patients were allocated to intervention or control rooms are not reported (i.e. no random sequence generation; allocation concealment is not possible). Hence, the study is judged to be at risk of selection bias which may lead to systematic differences between the characteristics of patients in the intervention and control groups (baseline imbalance). The study did however report and adjust for characteristics expected to predict the outcome, which increased our confidence in the results of this study. One author is an employee of the manufacturer of the HPV disinfection system tested in the study (Bioquell), and contributed to the design, conduct and reporting of the study. The disinfection services were also provided free of charge. There is no mention of safeguards to protect against the risk of bias from these sources (e.g. prospective study registration or published protocol), so the risk of bias was assessed as high.

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

Bias/Study ID	Anderson 2017	Passaretti 2013
Random sequence generation	Low	High
Allocation concealment	Low	High
Incomplete outcome data addressed	Low	Low
Knowledge of the allocated interventions adequately prevented (masking of participants, personnel and outcome assessors)	Low/Unclear	Low
Selective outcome reporting	Low	Low
Baseline imbalance – participant characteristics (CRT only)	Unclear	Adjusted for
Baseline imbalance – outcomes (CRT only)	Unclear	No concerns
Contamination – (CRT only)	Low	No concerns
Free of other risks of bias?	Low	High

4.3.2 Time series studies

Domain 1 Interventions independent of other changes. All six time series studies considered changes concurrent with the intervention as potential explanations for observed intervention effects. There was considerable variation in the factors considered, and the extent to which claims were supported by data. Two studies concluded that concurrent changes or interventions may have partly explained the observed effects, specifically increased compliance with infection control measures in McMullen 2007 and, in Mitchell 2014, improvements in both cleaning (through monitoring and feedback) and screening/detection of pathogens. In other studies, there were multiple changes during the intervention period that may have contributed, at least in part, to the observed effects. Consequently, all studies were judged to be at high risk of bias for this domain. Specific factors are summarised below and detailed in the Technical report, Appendix 5, Characteristics of included studies.

Changes in antibiotic use over the study period were considered in three studies (Boyce 2008, McMullen 2007, Mitchell 2014). Mitchell 2014 identified changes in the use of two antibiotics (decrease in fluoroquinolone, increase in cephalosporin), which they concluded may have affected MRSA acquisition rates during the study. McMullen 2007 found no changes over time, while Boyce 2008 identified small statistically significant reductions (all antibiotics combined, second generation cephalosporins) that they concluded were "unlikely to explain reduced CDAD incidence during the intervention period" (p728). Boyce 2008 also examined associations between the use of antibiotics and the main outcome (CDAD); observing small, statistically significant associations (all antibiotics combined, fourth generation cephalosporins).

Concurrent changes in compliance with hand hygiene, contact precautions, or interventions to increase compliance were considered in five of six studies (Boyce 2008, McMullen 2007, Hacek 2010, Mitchell 2014, Orenstein 2011). Three studies reported no changes in compliance (Boyce 2008, Hacek 2010, Orenstein 2011), while two reported no changes in the outcome during a hand hygiene intervention (McMullen 2007, Mitchell 2014). Other interventions concurrent with part of the study period included provision of feedback on acquisition rates or cleaning (McMullen and Mitchell 2014 respectively), intensified cleaning/disinfection (Haas 2010), and "limited" use of UV disinfection during the control period (Haas 2010). Most authors concluded that concurrent interventions were unlikely to explain observed effects, either because no changes in the outcome were observed during the period in which the concurrent intervention was used, or because use of the concurrent intervention was limited (e.g. over short time frame, in few units).

Other changes that were considered included: (1) staffing (e.g. change of cleaning contractor pre-intervention, Haas 2010; no changes, Orenstein 2011), (2) patient characteristics (no differences between periods, McMullen 2007 or Orenstein 2011; increase in high risk patients in intervention period, Haas 2010); (3) presence of epidemic strain (no differences in corresponding months in both periods, Boyce 2008), (4) acquisition rates of community acquired pathogens (18% increase during intervention period, Haas 2010), and (5) increased surveillance or new laboratory testing for target pathogens (occurred in Haas 2010, Mitchell 2014).

Domain 2 Shape of the intervention effect pre-specified. All studies had a clearly defined point at which the intervention occurred, and time series analyses were conducted using this point for analysis. As such, all studies were rated at low risk of bias for this domain.

Domains 3 and 4. Although reported separately, both these domains assess whether there were differences in how outcomes were determined between the pre-intervention and intervention periods (detection bias). In this review, some aspects of data collection are relevant to both domains, but were not double counted in our assessment. Concerns relating to each of these domains are as follows.

Intervention unlikely to affect data collection. The interventions themselves were judged as being unlikely to directly affect data collection, as most studies used routinely collected data that was retrospectively audited to measure the outcome. In studies where the intervention was introduced in response to an increase in the rate of pathogen acquisition (outbreak), knowledge of the outbreak may have prompted an increase in screening (Boyce 2008, Hacek 2010, McMullen 2007, Orenstein 2011). In three studies changes to the frequency of pathogen screening/surveillance or methods of laboratory testing in intervention period were also reported (Boyce 2008, Haas 2010, Mitchell 2014). For these reasons, all studies were rated at high risk of bias on this domain.

Knowledge of the allocated interventions adequately prevented (masking of participants, personnel and outcome assessors). It is likely or possible that personnel working on study units were aware of the intervention, however any change in screening practices is accounted for in the domain above. Three studies used audits of routinely collected data in electronic medical records to assess outcomes (Boyce 2008, Haas 2010, Mitchell 2014). While it is unclear whether these outcomes assessors were masked to the intervention period, the risk of bias is low. Three studies did not report methods of outcome assessment; these studies were rated at unclear risk of bias (Hacek 201, McMullen 2007, Orenstein 2011).

Domain 5 Incomplete outcome data adequately addressed. There was no mention of incomplete data in any of the studies, however outcome data were based on routinely collected sources so the risk of bias was judged as low.

Domain 6 Selective outcome reporting. None of the studies were prospectively registered or had published protocols, so selective reporting cannot be completed ruled out. However, results for all outcomes mentioned in the methods were reported as were outcomes likely to be measured, hence risk of bias was judged as low.

Domain 7 Other risks of bias. Two studies had industry or financial ties, and reported no safeguards to protect against risk of bias from these sources (e.g. prospective study registration), so were assessed as being at high risk of bias (Boyce 2008, Orenstein 2011). In Boyce 2008, two study authors were salaried staff of the manufacturer and the intervention services (HPV disinfection) were provided at discount (details not reported). In Orenstein 2011, one study author consulted for the manufacturer and the intervention (sodium hypochlorite wipes) was partially subsidised by the manufacturer. One study did not report a declaration of interests (McMullen 2007), so was at unclear risk of bias.

Table 3. Summary of risk of bias (RoB) assessments for interupted time series studies

Bias/Study ID	Boyce 2008	Haas 2014	Hacek 2010	McMullen 2007	Mitchell 2014	Orenstein 2011
Intervention independent of other changes	High	High	High	High	High	High
Shape of the intervention effect pre-specified	Low	Low	Low	Low	Low	Low
Intervention unlikely to affect data collection	High	High	High	High	High	High
Knowledge of the allocated interventions adequately prevented (outcome assessment)	Low	Low	Unclear	Unclear	Low	Unclear
Incomplete outcome data adequately addressed	Low	Low	Low	Low	Low	Low
Selective outcome reporting	Low	Low	Low	Low	Low	Low
Other risks of bias	High	Low	Low	Unclear	Low	High

4.4 Effects of interventions

4.4.1 Sodium hypochlorite versus standard cleaning/disinfection

One randomised trial and three ITS studies examined the effects of sodium hypochlorite. Anderson 2017 examined the effect of sodium hypochlorite for terminal room disinfection as an adjunct to standard disinfection with quaternary ammonium. Hacek 2010 examined the effect of discharge cleaning with sodium hypochlorite, collecting data over 10 months prior to the intervention and 24 months post. McMullen 2007 examined the effects of daily cleaning with sodium hypochlorite on all rooms (period 2) and rooms vacated by patients with CDAD (period 3), collecting data over three periods, of length 7, 5, and 24 months respectively. Finally, Orenstein 2011, examined the effect of daily cleaning with sodium hypochlorite wipes, collecting data 12 months prior and 12 months post the intervention. Results from the randomised trial are presented in Table 4. Results for the three non-randomised studies from the segmented regression analyses fitted to the monthly CDAD rates (per 1000 patient-days) are presented in Table 5 and described for each study following. Table 6 reports the summary of findings for this comparison, including the GRADE assessment and evidence statement.

Anderson 2017

Sodium hypochlorite for terminal room disinfection had uncertain effects on the incidence of hospital-acquired MROs compared to quaternary ammonium disinfection alone. A small statistically non-significant

reduction of 17% was observed in the incidence rate ratio of the combined outcome - acquisition of all MRO - but the confidence interval included the possibility of a small increase (RR 0.83 (95% CI: 0.64, 1.06; p=0.14); moderate quality evidence) (Table 4). When pathogens were considered individually, acquisitions of VRE were reduced (57%), but the confidence interval was wide and included the possibility of no reduction; results for MRSA were equivocal (0% reduction (95% CI: 18% reduction to 21% increase). One case of MDR *Acinetobacter* occurred in the sodium hypochlorite group and none occurred in the comparator, so the effect of sodium hypochlorite on the incidence of MDR *Acinetobacter* could not be estimated.

Table 4. Incidence rate of MRO acquisition for the comparison sodium hypochlorite as an adjunct to standard terminal room disinfection versus standard disinfection alone (adapted from Anderson 2017)

Pathogen | intervention group	Patients, No.	Acquisitions, No.	Exposure-days, No.	Rate per 1000 exposure-days[b]	Rate ratio (RR)	95% CI	P value
Combined – all MROs (MRSA, VRE, MDR *Acinetobacter*)[a]							
Standard disinfection[d]	3740	97	17195	5.64			
Sodium hypochlorite	4334	83	19211	4.32	0.83	(0.64, 1.06)	0.140
MRSA							
Standard disinfection[d]	3300	73	14524	5.03			
Sodium hypochlorite	3631	74	15343	4.82	1.00	(0.82, 1.21)	0.967
VRE							
Standard disinfection[d]	1055	37	5838	6.34			
Sodium hypochlorite	1468	24	7522	3.19	0.43	(0.19, 1.00)	0.049
MDR *Acinetobacter*							
Standard disinfection[d]	31	0	156	0			
Sodium hypochlorite	28	1	98	10.2	NE[c]	NE	NE

[a] Results from a trial post-hoc analysis reported in supplementary table 3
[b] Reported cases per 10,000 days. These were standardised to cases per 1,000 days to enable comparison across studies.
[c] Not estimated: Only one acquisition of this pathogen occurred across the four study groups.
[d] Standard disinfection involves daily and terminal clean with quaternary ammonium for MROs.

Table 5. Results of segmented regression analyses of sodium hypochlorite for HA CDAD rates (per 1000 patient-days)

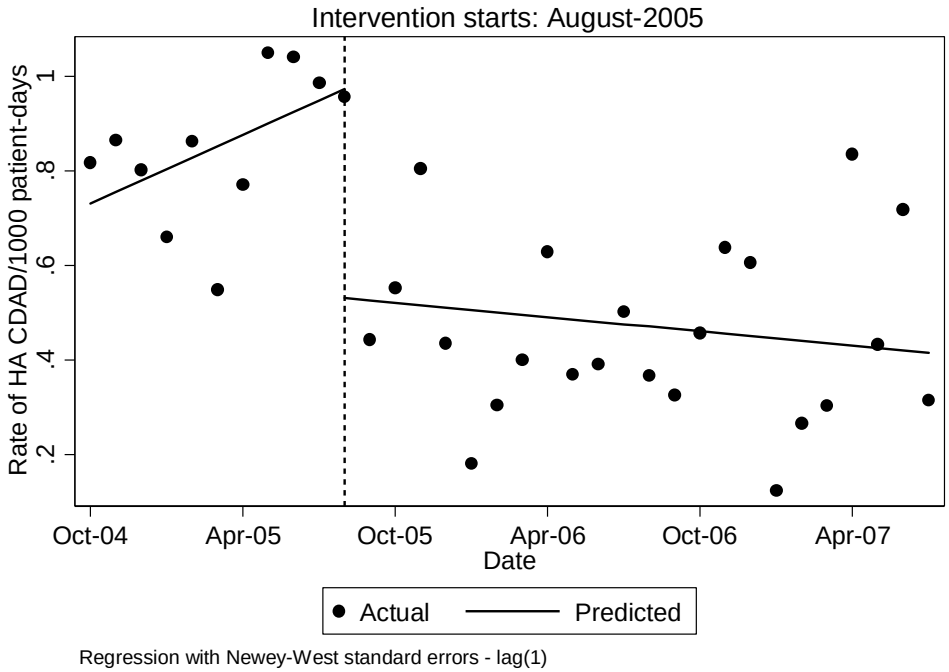
Study	Hacek 2010			McMullen 2007			Orenstein 2011		
Outcome	CDAD			CDAD			CDAD		
Parameter	Est.	95%CI	p-value	Est.	95%CI	p-value	Est.	95%CI	p-value
Period 1 slope	0.02	(-0.00, 0.05)	0.079	2.23	(0.59, 3.87)	0.009	-0.11	(-0.27, 0.05)	0.179
Change in level (P2 – P1)	-0.44	(-0.71, -0.17)	0.002	-15.4	(-22.26, -8.61)	0.000	-1.35	(-3.06, 0.35)	0.113
Period 2 slope	-0.01	(-0.02, 0.01)	0.492	0.84	(0.28, 1.40)	0.005	0.00	(-0.08, 0.09)	0.949
Change in slope (P2 – P1)	-0.03	(-0.06, 0.00)	0.069	-1.39	(-3.09, 0.31)	0.106	0.11	(-0.06, 0.28)	0.198
Change in level (P3 – P2)				-2.17	(-5.49, 1.15)	0.193			
Period 3 slope				-0.10	(-0.28, 0.07)	0.238			
Change in slope (P3 – P2)				-0.95	(-1.54, -0.35)	0.003			

Est. = estimate of parameter (as outline following); 95%CI = 95% Confidence Interval.
Period 1 slope = secular trend, rate per month in the pre-intervention period (P1)
Change in level (P2 – P1) = immediate effect of the first intervention
Period 2 slope = rate per month in the first post-intervention period (P2)
Change in slope (P2 – P1) = gradual effect of the first intervention over time, per month
Change in level (P3 – P2) = immediate effect of the second intervention

Period 3 slope = rate per month in the second post-intervention period (P3)
Change in slope (P3 – P2) = gradual effect of the second intervention over time, per month

Hacek 2010

Prior to the intervention, there was a slight increase in the rate of hospital-acquired CDAD of 0.02/1000



patient-days per month (95%CI: -0.00, 0.05). Post the intervention, there was a slight decrease in the rate of hospital-acquired CDAD of -0.01/1000 patient-days per month (95%CI: -0.00, 0.05). The confidence intervals for these slopes did not exclude the possibility that the slopes were 0. There was evidence of an immediate effect of the intervention, with a reduction in infection rate of -0.44/1000 patient-days (95%CI: -0.71, -0.17), or equivalently, a decrease of 45% (Table 5, Figure 2).

Figure 2. Observed and predicted rates of HA CDAD per 1000 patient-days over time from Hacek 2010.

McMullen 2007

McMullen 2007 consisted of three periods: pre-intervention, sodium hypochlorite clean of all rooms (high-intensity), and sodium hypochlorite clean of rooms vacated by patients with CDAD (low-intensity). In the period prior to the high-intensity intervention, there was an increasing rate of hospital-acquired CDAD of 2.23/1000 patient days per month (95%CI: 0.59, 3.87) (Table 5, Figure 3). There was evidence of an immediate effect of the high-intensity intervention, with a reduction in infection rate of -15.4/1000 patient-days (equivalently, a decrease of 89%) (95%CI: -22.26, -8.61). However, following the introduction of the high-intensity intervention, there was an increase in the infection rate of 0.84/1000 patient-days per month (95%CI: 0.28, 1.40). The immediate effect of the low-intensity intervention reduced the infection rate by -2.17 (equivalently 35%) (95%CI: -5.49, 1.15). Following this reduction, there was a slight decrease in the infection rate of -0.10/1000 patient days per month in the low-intensity period (95%CI: -0.28, 0.07), however, the confidence interval did not exclude a slope of 0. The change in slope between the high-intensity and low-intensity periods was different (p = 0.003). As an example, assuming the trajectory in the high-intervention period continued into the low-intensity period, the infection rate predicted from the model in the high-intervention period, would be 13.5/1000 patient-days (95%CI; 4.6, 22.5) higher than that expected based on the regression model fitted in the low-intensity period at January 2004. However, caution is required in interpreting the above estimates since the first and second periods are based on few data points.

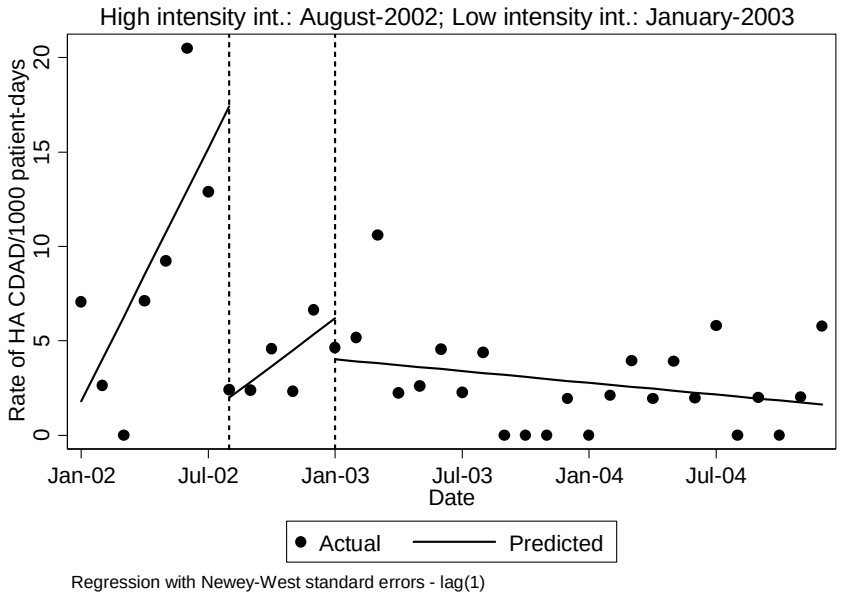


Figure 3. Observed and predicted rates of CDAD per 1000 patient-days over time from McMullen 2007.

Orenstein 2011

Prior to the intervention, there was a decreasing trend in infection rate of -0.11 per 1000 patient-days per month, although a trend of 0 could not be excluded (95% CI: -0.27, 0.05). Post the intervention, the trend in infection rate over time was 0 (95%CI: -0.08, 0.09). The immediate effect of the intervention was a reduction in infection rate of -1.35/1000 patient-days (equivalently, a decrease of 80%), however, the confidence interval did not exclude the possibility of no reduction or a slight increase (Table 5, Figure 4).

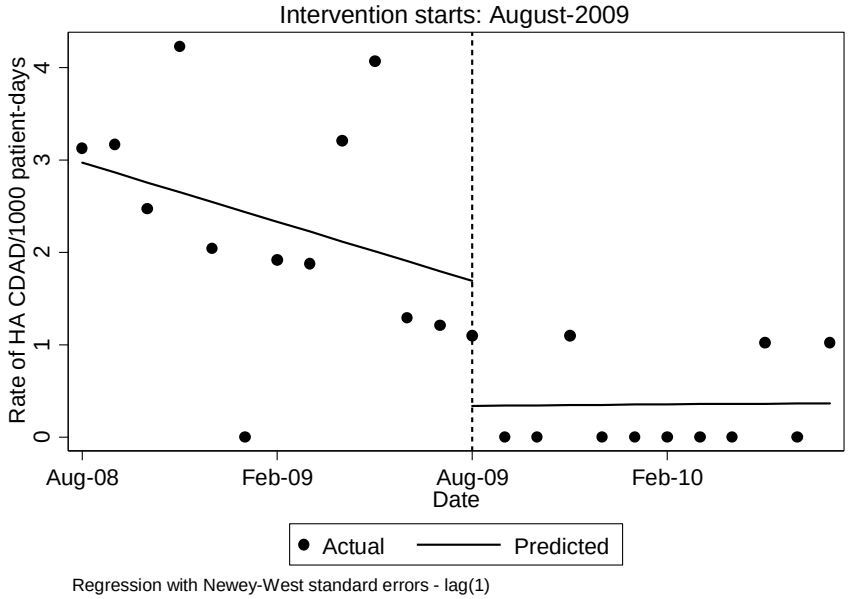


Figure 4. Observed and predicted rates of CDAD per 1000 patient-days over time from Orenstein 2007.

Table 6 Summary of findings and evidence statement: Sodium hypochlorite versus standard cleaning/disinfection

Quality assessment		Summary of findings			
		No of points			
		Int.	Control	Summary of effect (based on single study)	Quality
Sodium hypochlorite for terminal room disinfection vs standard terminal room disinfection (quaternary ammonium)					
Anderson 2017 Infection or colonisation - incidence rate of hospital-acquired MROs (MRSA, VRE, MDR *Acinetobacter*) Outcome importance: Important, but not critical in decision making					
Randomised trial (cluster, cross-over)	Risk of bias: Not serious Inconsistency: Cannot assess Indirectness: Not serious Imprecision: Serious[1] Other considerations: None	4334 patients	3740 patients	The effect of terminal room disinfection with sodium hypochlorite on the incidence rate of hospital acquired MROs is uncertain. Addition of sodium hypochlorite for terminal room disinfection reduced the rate of hospital-acquired MROs by 17% compared to quaternary ammonium disinfection alone (RR 0.83 (95% CI: 0.64, 1.06; p=0.140))[2]. However the confidence interval includes the possibility of a small increase of 6% or a clinically important reduction of 36%.	⊕⊕⊕⊖ Moderate due to serious imprecision. Single study (consistency cannot be assessed).
Hacek 2010 Infection - incidence rate of hospital-acquired CDAD (cases per 1,000 patient-days) Outcome importance: Critical in decision making					
Interrupted time series	Risk of bias: Serious[3] Inconsistency[4]: Cannot assess Indirectness: Not serious Imprecision: Serious[5] Other considerations: None	24 months	10 months	The effect of sodium hypochlorite disinfection on the rate of hospital acquired CDAD is uncertain due to very low quality evidence. Sodium hypochlorite disinfection led to a clinically important, immediate reduction in the rate of hospital acquired CDAD -0.44/1000 patient-days (95%CI: -0.71, -0.17), or equivalently, a decrease of 45%. The effect was maintained long term.	⊕⊖⊖⊖ Very low due to serious risk of bias, imprecision. Single study (consistency cannot be assessed).

[1] Imprecision (-1) the 95%CI includes the possibility of a clinically important reduction or a small reduction.

[2] Results from the trialists' post hoc analysis in which patients exposed to *C. difficile* 'seed' rooms were removed (supplementary table 3). The analyses reported in the main manuscript included patients exposed to rooms previously occupied by a patient with CDAD *(C. difficile* 'seed' rooms) or an MRO (MRO 'seed' rooms). However, these results are difficult to interpret because they combine the comparison for MRO seed rooms (bleach as an adjunct to QA vs QA alone) with the comparison for *C. difficile* seed rooms in which the same intervention was used in both groups (bleach vs bleach). Consequently, this analysis may underestimate the effect of bleach when used as an adjunct to QA.

[3] RoB (-1) due to concerns that the intervention was not independent of other changes, and possible changes to screening in outbreak period (concurrent with intervention).

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

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

Sodium hypochlorite for daily disinfection vs standard cleaning/disinfection (quaternary ammonium)					
McMullen 2007[6] Infection - incidence rate of hospital-acquired CDAD (cases per 1,000 patient-days) Outcome importance: Critical in decision making					
Interrupted time series	Risk of bias: Very serious[7] Inconsistency: Cannot assess Indirectness: Not serious Imprecision: Not serious[8] Other considerations: None	5 months (I1) 24 months (I2)	7 months	The effect of sodium hypochlorite disinfection on the rate of hospital acquired CDAD is uncertain due to very low quality evidence. Sodium hypochlorite disinfection led to a clinically important, immediate reduction in the rate of hospital acquired CDAD -15.4/1000 patient-days (95%CI: -22.26, -8.61), or equivalently, a decrease of 89%. In the first intervention period (sodium hypochlorite clean, all rooms), there was an increase in rate of CDAD. In the second intervention period (sodium hypochlorite clean, rooms of patients with CDAD) the trend in the rate of CDAD was stable.	⊕⊖⊖⊖ Very low due to very serious risk of bias. Single study (consistency cannot be assessed).
Orenstein 2011 Infection - incidence rate of hospital-acquired CDAD (cases per 1,000 patient-days) Outcome importance: Critical in decision making					
Interrupted time series	Risk of bias: Very serious[9] Inconsistency: Cannot assess Indirectness: Not serious Imprecision: Serious[10] Other considerations: None	12 months	12 months	The effect of sodium hypochlorite disinfection on the rate of hospital acquired CDAD is uncertain due to very low quality evidence. Sodium hypochlorite disinfection led to an immediate reduction in the rate of hospital-acquired CDAD -1.35/1000 patient-days, or equivalently, a decrease of 80%, however, the confidence interval did not exclude the possibility of no reduction (95%CI: -3.06, 0.35). During the intervention period the trend in the rate of CDAD was stable. There was no evidence that the trend in the intervention period was different from the secular trend in the pre-intervention period.	⊕⊖⊖⊖ Very low due to very serious risk of bias and serious imprecision. Single study (consistency cannot be assessed).
No studies Adverse effects Outcome importance: Critical for decision making					
None of the included studies reported on adverse effects of sodium hypochlorite.					

[6] McMullen: two intervention periods (1st bleach clean, all rooms; 2nd bleach clean rooms of patients with CDAD). The immediate effect compares the pre-intervention period with the first period.

[7] RoB (-2) due to concerns that the intervention was not independent of other changes, and possible changes to screening during the outbreak period (concurrent with intervention). In addition the pre-intervention period and the first intervention period had few data points, so the observed effects may be biased due to regression to the mean or overfitting.

[8] Based on the immediate effect between the pre-intervention period and the first intervention period.

[9] RoB (-2) due to concerns that the intervention was not independent of other changes, possible changes to screening in the outbreak period (concurrent with intervention), and industry ties.

[10] Imprecision (-1) due to very wide confidence intervals that include both large reduction and an increase in rates of CDAD.

4.4.2 Hydrogen peroxide vapour versus standard cleaning/disinfection

Two ITS studies examined the effects of hydrogen peroxide vapour. Boyce 2008 examined the effects of HP vapour disinfection and standard cleaning/disinfection on wards with a high incidence of *C. difficile*, collecting data over three periods, of length 12, 7, and 10 months respectively. Mitchell 2014 examined the effect of HP vapour in rooms accommodating patients with MRSA, collecting data over 46 months prior to the intervention and 38 months post. One study, Passaretti 2012, examined the effect of HP vapour on MROs and *C. difficile* acquisition, in a non-randomised trial set in high risk units (e.g. ICUs), with three units each allocated to intervention and comparator, respectively. Results from the segmented regression analyses fitted to the monthly infection rates (per 1000 patient-days) are presented in Table 7 and those from the controlled before-after study in Table 8. Table 9 reports the summary of findings for this comparison, including the GRADE assessment and evidence statement.

Table 7. Results of segmented regression analyses of hydrogen peroxide vapour for hospital-acquired CDAD rates or MRSA rates (per 1000 patient-days)

Study	Boyce 2008			Mitchell 2014		
Outcome	CDAD			MRSA		
Parameter	Est.	95%CI	p-value	Est.	95%CI	p-value
Period 1 slope	0.05	(-0.04, 0.13)	0.258	0.00	(-0.02, 0.01)	0.615
Change in level (P2 – P1)	0.52	(-0.53, 1.56)	0.315	-0.09	(-0.55, 0.37)	0.701
Period 2 slope	-0.13	(-0.27, 0.00)	0.048	-0.01	(-0.03, 0.00)	0.097
Change in slope (P2 – P1)	-0.18	(-0.30, -0.06)	0.006	-0.01	(-0.03, 0.01)	0.403
Change in level (P3 – P2)	-0.17	(-0.75, 0.41)	0.544			
Period 3 slope	0.03	(-0.03, 0.10)	0.343			
Change in slope (P3 – P2)	0.16	(0.02, 0.31)	0.031			

Est. = estimate of parameter (as outline following); 95%CI = 95% Confidence Interval.
Period 1 slope = secular trend, rate per month in the pre-intervention period (P1)
Change in level (P2 – P1) = immediate effect of the first intervention
Period 2 slope = rate per month in the first post-intervention period (P2)
Change in slope (P2 – P1) = gradual effect of the first intervention over time, per month
Change in level (P3 – P2) = immediate effect of the second intervention
Period 3 slope = rate per month in the second post-intervention period (P3)
Change in slope (P3 – P2) = gradual effect of the second intervention over time, per month

Boyce 2008

Boyce 2008 consisted of three periods: pre-epidemic period, epidemic period (pre-intervention period) and the intervention period. In the pre-epidemic period, there was a slight increase in the rate of hospital-acquired CDAD of 0.05/1000 patient-days per month, although a trend of 0 over this period could not be excluded (95%CI: -0.04, 0.13). An epidemic emerged in the second period, at which point control measures were implemented. There was a decrease in the infection rate in the second period of -0.13/1000 patient-days per month (95%CI: -0.27, 0.00). The immediate effect of the intervention was small, with a reduction in the infection rate of -0.17/1000 patient-days (equivalently, a decrease of 19%), and the confidence interval included no reduction, and an increase in the infection rate as plausible estimates (95%CI: -0.75, 0.41). There was a slight increase in the rate of infection in the intervention period of 0.03/1000 patient-days per month, but the confidence interval did not exclude a trend of 0 (95%CI:-0.03, 0.10). There was evidence that the slopes in the epidemic and intervention periods differed (p-value = 0.031) (Table 7, Figure 5). Caution is required in interpreting the above estimates since the second period is based on few data points.

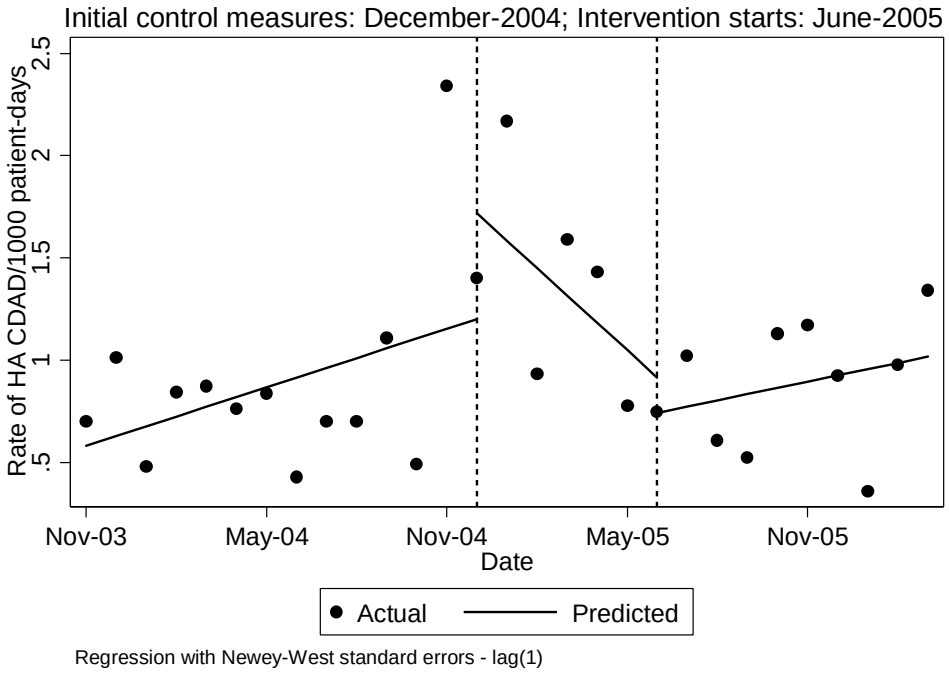


Figure 5. Observed and predicted rates of CDAD per 1000 patient-days over time from Boyce 2008.

Mitchell 2014

Prior to the intervention, there was stability in the trend of hospital-acquired MRSA rates (period 1 slope = 0.00 (95%CI: -0.02, 0.01)). The immediate effect of the intervention was a reduction in infection rate of -0.09/1000 patient-days (equivalently, a decrease of 11%), however, the confidence interval did not exclude the possibility of no reduction or a slight increase (95%CI: -0.55, 0.37). There was stability in the trend of infection rates post intervention (-0.01/1000 patient-days per month (95%CI: -0.03, 0.00), and no evidence that the slopes were different between the pre and post intervention periods (p = 0.403) (Table 7, Figure 6).

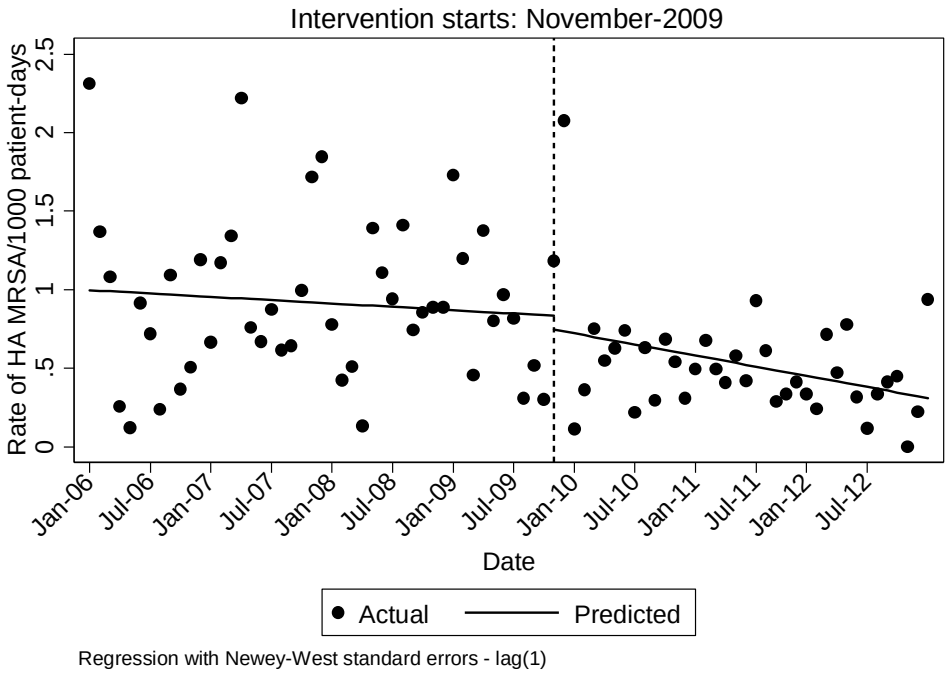


Figure 6. Observed and predicted rates of MRSA per 1000 patient-days over time from Mitchell 2014.

Our results differ to those reported in Mitchell 2014, where the authors' concluded there was a reduction in the MRSA rates between the pre- and post-periods, which they had confirmed using time-series analysis. This difference may have arisen due to a number of reasons, for example, the functional form of the fitted models or the outcome modelled (rate versus count). In regard to the former, we fitted models that allowed for different trends in the pre- and post-intervention periods, and this may have differed to the model fitted in Mitchell 2014.

Passaretti 2013

One non-randomised trial examined the effects of a hydrogen peroxide room decontamination system on the incidence rate of hospital-acquired MROs and *C. difficile* among patients in six high risk medical units (Passaretti 2013). Table 8 presents results as reported for patients admitted to rooms in which a prior occupant had been infected or colonised with an MRO or *C. difficile*. A 64% reduction in the incidence rate of acquisition of all pathogens combined was observed among patients in rooms decontaminated with hydrogen peroxide compared to standard cleaning/disinfection (IRR 0.36 (95%CI: 0.19, 0.70), p<0.01; 1364 participants, low quality evidence). When considered individually, acquisitions of each MRO and *C. difficile* were also reduced, with the largest and only statistically significant reduction shown for VRE (IRR 0.25 (95%CI: 0.10, 0.60), p<0.01; participants, low quality evidence). The authors reported that the observed reduction in incidence rate of acquisitions of all pathogens combined was "mainly driven by the reduced incidence of VRE acquisitions" (p31), suggesting that HPV may have had differential effects on different pathogens.

Table 8. Incidence rate of acquisition of all pathogens combined, and individual pathogens (adapted from Passaretti 2013)

Pathogen | intervention group	Patients, No.	Acquisitions, No.	Patient-days, No.	Crude IR per 1000 patient-days	Adjusted IRR[a]	95% CI	P value
Combined (VRE, MRSA, MRGN, *C. difficile*)							
No HPV	927	98	6228	15.7			
HPV	437	18	2904	6.2	0.36	(0.19, 0.70)	<0.01
VRE							
No HPV	654	53	4566	11.6			
HPV	474	8	3267	2.4	0.25	(0.10, 0.60)	<0.01
MRSA							
No HPV	494	14	3736	3.7			
HPV	557	5	4010	1.2	0.53	(0.16, 1.79)	0.30
MRGN bacterium							
No HPV	1298	23	9928	2.3			
HPV	584	7	4225	1.7	0.55	(0.20, 1.57)	0.26
C. difficile							
No HPV	1253	26	9676	2.7			
HPV	557	4	4029	1.0	0.49	(0.16, 1.47)	0.19

[a] Incidence rate ratios (IRR) were adjusted for potential confounders including unit, age, mortality risk score, HIV status, end stage renal disease status, surveillance compliance of the unit (VRE and MRSA only) and time (using quarterly indicators).

Table 9 Summary of findings and evidence statement: HPV disinfection versus standard cleaning/disinfection

Quality assessment		Summary of findings			
		No of points			
		Int.	Control	Summary of effect (based on single study)	Quality
Hydrogen peroxide vapour disinfection vs standard cleaning/disinfection alone					
Boyce 2008 Infection - incidence rate of hospital-acquired CDAD (cases per 1,000 patient-days) Outcome importance: Critical for decision making					
Interrupted time series	Risk of bias: Very serious[11] Inconsistency: Cannot assess[12] Indirectness: Not serious Imprecision: Serious[13] Other considerations: None	7 months	10 months	The effect of HPV disinfection on the rate of hospital acquired CDAD are uncertain due to very low quality evidence. HPV disinfection led to a small immediate reduction in the rate of hospital-acquired CDAD of -0.17/1000 patient-days (equivalently, a decrease of 19%), but the confidence interval included no reduction, and an increase in CDAD rate as plausible estimates (95%CI: -0.75, 0.41). During the intervention period the trend in the rate of CDAD was stable.	⊕⊖⊖⊖ Very low due to very serious risk of bias and serious imprecision. Single study (consistency cannot be assessed).
Mitchell 2014 Infection or colonisation - incidence rate of hospital-acquired MRSA (cases per 1,000 patient-days) Outcome importance: Important, but not critical in decision making					
Interrupted time series	Risk of bias: Serious[14] Inconsistency: Cannot assess[12] Indirectness: Not serious Imprecision: Serious[15] Other considerations: None	38 months	48 months	The effect of HPV disinfection on the rate of hospital acquired MRSA is uncertain due to very low quality evidence. HPV disinfection led to a small immediate reduction on rate of hospital acquired MRSA -0.09/1000 patient-days (equivalently, a decrease of 11%), however, the confidence interval did not exclude the possibility of no reduction or a slight increase (95%CI: -0.55, 0.37). During both periods the trend in the rate of hospital acquired MRSA was stable.	⊕⊖⊖⊖ Very low due to serious risk of bias and serious imprecision. Single study (consistency cannot be assessed).
Passaretti 2013 Infection or colonisation - incidence rate of hospital-acquired MROs/CDAD (cases per 1,000 patient-days) Outcome importance: Important, but not critical in decision making					
Non-randomised trial	Risk of bias: Serious[16] Inconsistency: Cannot assess[12] Indirectness: Not serious Imprecision: Not serious Other considerations: None	437 patients	927 patients	HPV disinfection may reduce the rate of hospital acquired MROs/CDAD. HPV disinfection led to a large (64%) reduction in the rate of hospital-acquired MROs/CDAD compared to standard cleaning/disinfection (IRR 0.36 (95%CI: 0.19, 0.70)).	⊕⊕⊖⊖ Low due to serious risk of bias. Single study (consistency cannot be assessed).

[11] RoB (-2) due to concerns that the intervention was not independent of other changes, possible changes to screening during the outbreak period (concurrent with intervention), and industry ties. In addition the pre-intervention period (Dec 2004-May2005) had few data points, the observed effects may be biased due to regression to the mean or overfitting.
[12] Inconsistency (-1) for all single non-randomised studies. Two or more studies are required to assess the consistency of effects.
[13] Imprecision (-1) due to wide confidence intervals that include both large reduction and an increase in rates of CDAD.
[14] RoB (-1) due to concerns that the intervention was not independent of other changes, and changes to screening during the intervention.
[15] Imprecision (-1) due to the confidence interval including both a reduction and an increase in rates of MRSA.
[16] RoB (-1) due to the absence of randomisation, allocation concealment and industry ties. Although these concerns are potentially very serious (leading to downgrading by -2), intervention groups characteristics were comparable and differences/confounding adjusted for in the analysis.

Quality assessment	Summary of findings			
	No of points			
	Int.	Control	Summary of effect (based on single study)	Quality
No studies Adverse effects Outcome importance: Critical for decision making				
Boyce 2008 reported that staff did not report any adverse events. Passaretti 2013 reported that no health and safety incidents were reported.				

4.2.3 Ultra-violet light disinfection versus standard cleaning/disinfection

One cluster randomised crossover trial (Anderson 2017) and one ITS study (Hass 2014) examined the effect of ultra-violet light terminal room disinfection on acquisition of MROs and *C. difficile*. In Anderson 2017 hospitals received four interventions (two with UV light) in a randomly allocated sequence over 28 months, with each intervention period lasting seven months (including a one month wash-in). Results for comparisons of UV light to standard disinfection, and UV light plus sodium hypochlorite to standard disinfection, are presented in Table 10 and Y respectively. In Haas 2014 data were collected 12 months prior and 12 months post the intervention. Results are presented in Table 12. Table 13 presents the summary of findings for these studies, including the GRADE assessment and evidence statement.

Anderson 2017

Addition of UV light for terminal room disinfection reduced the incidence rate of hospital-acquired MROs by 37% compared to standard quaternary ammonium disinfection alone; however, the confidence interval includes the possibility that the reduction could be as small as 16% (RR 0.63 (95% CI: 0.47, 0.84; p=0.002); moderate quality evidence) (Table 10). When considered individually, acquisitions of MRSA and VRE were both reduced, but the confidence intervals for these estimates include the possibility of a small increase in incidence rates (Table 10). The effect on MDR *Acinetobacter* could not be estimated because no cases were observed in either the UV light group or the standard disinfection group.

The incidence rate ratio for *C. difficile* was equivocal, with a 0% reduction when UV light was used for terminal disinfection compared to standard sodium hypochlorite disinfection alone (95% CI: 43% reduction to 75% increase; p=0.997; low quality evidence) (Table 10). The very wide confidence interval for this effect estimate includes the possibility of a large reduction or a large increase in CDAD when UV light is used as an adjunct to standard disinfection with sodium hypochlorite, hence the evidence is rated as of low quality.

Table 10. Incidence rate of MRO or CDAD acquisition for the comparison UV light as an adjunct to standard terminal room disinfection versus standard disinfection alone (adapted from Anderson 2017)

Pathogen | intervention group	Patients, No.	Acquisitions, No.	Exposure-days, No.	Rate per 1000 – exposure days[b]	Rate ratio (RR)	95% CI	P value
Combined – all MROs (MRSA, VRE, MDR *Acinetobacter*)[a]							
Standard disinfection	3740	97	17195	5.64			
UV light	3920	56	16915	3.31	0.63	(0.47, 0.84)	0.002
MRSA							
Standard disinfection	3300	73	14524	5.03			
UV light	3451	54	14780	3.65	0.78	(0.58, 1.05)	0.104
VRE							
Standard disinfection	1055	37	5838	6.34			
UV light	1206	17	5780	2.94	0.41	(0.15, 1.13)	0.084
MDR *Acinetobacter*							
Standard disinfection	31	0	156	0			
UV light	47	0	199	0	NE[c]	NE[c]	NE[c]
C. difficile							
Standard disinfection[d]	2499	36	11385	3.16			
UV light	2678	38	12509	3.04	1.00	(0.57, 1.75)	0.997

[a] Results from a trial post-hoc analysis reported in supplementary table 3.

[b] Reported cases per 10,000 days. These were standardised to cases per 1,000 days to enable comparison across studies.

[c] Not estimated: Only one acquisition of this pathogen occurred across the four study groups.

[d] Standard disinfection involves daily and terminal clean with quaternary ammonium for MROs or with sodium hypochlorite for *C. difficile*.

UV light plus sodium hypochlorite for terminal room disinfection led to a small (18%) reduction in the incidence rate of all hospital-acquired MROs combined when compared to standard quaternary ammonium disinfection alone; however, the confidence interval included the possibility of no reduction (RR 0.82 (95% CI: 0.67 to 1.00, p=0.048; moderate quality evidence). When MROs were considered individually, there was a large reduction in incidence rate of VRE acquisitions (64% reduction (95% CI: 30 to 82% reduction; p=0.003), moderate quality evidence) but results for MRSA were equivocal and the effect on MDR *Acinetobacter* could not be estimated (Table 11).

Table 11. Incidence rate of MRO acquisition for the comparison UV light plus sodium hypochlorite as an adjunct to standard terminal room disinfection versus standard disinfection (adapted from Anderson 2017)

Pathogen | intervention group	Patients, No.	Acquisitions, No.	Exposure-days, No.	Rate per 1000 exposure-days[b]	Rate ratio (RR)	95% CI	P value
Combined – all MROs (MRSA, VRE, MDR *Acinetobacter*)[a]							
Standard disinfection[d]	3740	97	17195	5.64			
UV light plus sodium hypochlorite	4663	105	22982	4.57	0.82	(0.67, 1.00)	0.048
MRSA							
Standard disinfection[d]	3300	73	14524	5.03			
UV light plus sodium hypochlorite	3848	89	18960	4.69	0.97	(0.78, 1.22)	0.819
VRE							
Standard disinfection[d]	1055	37	5838	6.34			
UV light plus sodium hypochlorite	1753	37	9488	3.90	0.36	(0.18, 0.70)	0.003
MDR *Acinetobacter*							
Standard disinfection[d]	31	0	156	0			
UV light plus sodium hypochlorite	62	0	244	0	NE[c]	NE[c]	NE[c]

[a] Results from a trial post-hoc analysis reported in supplementary table 3

[b] Reported cases per 10,000 days. These were standardised to cases per 1,000 days to enable comparison across studies.

[c] Not estimated: Only one acquisition of this pathogen occurred across the four study groups.

[d] Standard disinfection involves daily and terminal clean with quaternary ammonium for MROs.

Hass 2014

Prior to the intervention, there was stability in the trend of hospital-acquired MROs and CDAD rates (period 1 slope = 0.02 (95%CI: -0.03, 0.06)). The immediate effect of the intervention was a reduction in infection rate of -0.35/1000 patient days (equivalently, a decrease of 30%), but the confidence interval did not exclude the possibility of no reduction (95%CI -0.73, 0.04). There was stability in the trend of infection rates post intervention (0.00/1000 patient-days per month (95%CI: -0.04, 0.04), and no important difference between the pre and post intervention period slopes (p-value = 0.688) (Table 12, Figure 7).

Table 12. Results of segmented regression analyses of ultra-violet light disinfection for hospital-acquired MROs and CDAD rates (per 1000 patient-days)

Study	Hass 2014		
Outcome	MROs and CDAD		
Parameter	Est.	95%CI	p-value
Period 1 slope	0.02	(-0.03, 0.06)	0.459
Change in level (P2 – P1)	-0.35	(-0.73, 0.04)	0.073
Period 2 slope	0.00	(-0.04, 0.04)	0.896
Change in slope (P2 – P1)	-0.01	(-0.08, 0.06)	0.688

Est. = estimate of parameter (as outline following); 95%CI = 95% Confidence Interval.
Period 1 slope = secular trend, rate per month in the pre-intervention period (P1)
Change in level (P2 – P1) = immediate effect of the first intervention
Period 2 slope = rate per month in the first post-intervention period (P2)
Change in slope (P2 – P1) = gradual effect of the first intervention over time, per month

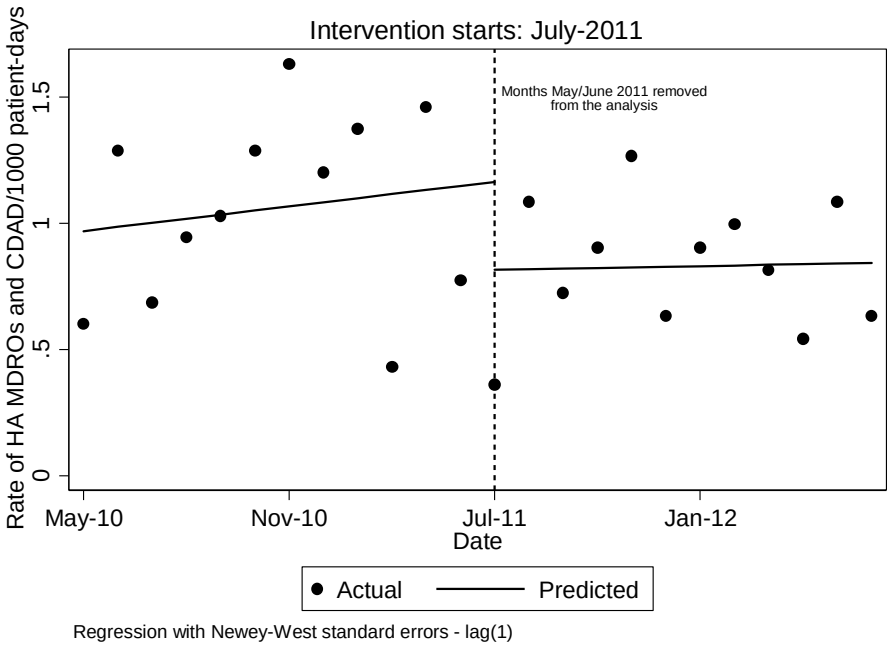


Figure 7. Observed and predicted rates of MROs and CDAD per 1000 patient-days over time Hass 2014.

Table 13 Summary of findings and evidence statement: UV light disinfection versus standard cleaning/disinfection alone

Quality assessment		Summary of findings			
		No of patients or points		Summary of effect (based on single study)	Quality
		Int.	Control		
Ultraviolet light for terminal room disinfection vs standard terminal room disinfection (sodium hypochlorite)					
Anderson 2017 Infection - incidence rate of hospital-acquired CDAD Outcome importance: Critical in decision making					
Randomised trial (cluster, cross-over)	Risk of bias: Not serious Inconsistency: Cannot assess[17] Indirectness: Not serious Imprecision: Very serious[18] Other considerations: None	2678 patients	2499 patients	Terminal room disinfection with UV light may have little or no effect on the incidence of hospital-acquired CDAD compared to using sodium hypochlorite alone. However further research is likely to have an important impact on our confidence in the effect estimate and may change the estimate. Addition of UV light for terminal room disinfection did not reduce the rate of hospital-acquired CDAD compared to sodium hypochlorite disinfection alone (RR 1.0, equivalently a decrease of 0% (95% CI: 0.57, 1.75; p=0.997)).	⊕⊕⊖⊖ Low due to very serious imprecision. Single study (consistency cannot be assessed).
Haas 2014 Infection or colonisation - incidence rate of hospital-acquired MROs/CDAD (cases per 1,000 patient-days) Outcome importance: Important, but not critical in decision making					
Interrupted time series	Risk of bias: Serious[19] Inconsistency: Cannot assess[20] Indirectness: Not serious Imprecision: Very serious[21] Other considerations: None	12 months	12 months	The effect of UV disinfection on the rate of hospital acquired MROs/CDAD is uncertain due to very low quality evidence. UV disinfection led to an immediate reduction in the rate of hospital-acquired MROs/CDAD of 0.35/1000 patient days (equivalently, a decrease of 30%), but the confidence interval did not exclude the possibility of no reduction (95%CI -0.73, 0.04). During both periods the trend in the rate of hospital acquired MRSA was stable.	⊕⊖⊖⊖ Very low due to serious risk of bias and very serious imprecision. Single study (consistency cannot be assessed).

[17] Inconsistency. This is a single RT, so it is not possible to assess consistency. Although the quality of evidence was not downgraded for inconsistency, studies in other contexts are required to determine whether the observed effect can be replicated.
[18] Imprecision (-2) the 95%CI includes the possibility of clinically important benefits (a large reduction in CDAD rates) or harms (a large increase in CDAD rates), leading to conflicting interpretation of effects.
[19] RoB (-1) due to concerns that the intervention was not independent of other changes, and changes to screening in intervention period.
[20] Inconsistency (-1) for all single non-randomised studies. Two or more studies are required to assess the consistency of effects.
[21] Imprecision (-2) the 95%CI includes the possibility of a large reduction or a small increase, leading to conflicting interpretation of effects.

Quality assessment		Summary of findings			
		No of patients or points		Summary of effect (based on single study)	Quality
		Int.	Control		
Ultraviolet light for terminal room disinfection vs standard terminal room disinfection (quaternary ammonium)					
Anderson 2017 Infection or colonisation - incidence rate of hospital-acquired MROs (MRSA, VRE, MDR *Acinetobacter*) Outcome importance: Important, but not critical in decision making					
Randomised trial (cluster, cross-over)	Risk of bias: Not serious Inconsistency: Cannot assess[20] Indirectness: Not serious Imprecision: Serious[22] Other considerations: None	3920 patients	3740 patients	Terminal room disinfection with UV light may lead to clinically important reductions in the incidence of hospital-acquired MROs. Addition of UV light for terminal room disinfection reduced the rate of hospital-acquired MROs by 37% compared to quaternary ammonium disinfection alone (RR 0.63 (95% CI: 0.47, 0.84; p=0.002))[23]. However the confidence interval includes the possibility of a small, clinically unimportant reduction of 16%.	⊕⊕⊕⊖ Moderate due to serious imprecision. Single study (consistency cannot be assessed).
Ultraviolet light plus sodium hypochlorite for terminal room disinfection vs standard terminal room disinfection (quaternary ammonium)					
Anderson 2017 Infection or colonisation - incidence rate of hospital-acquired MROs (MRSA, VRE, MDR *Acinetobacter*) Outcome importance: Important, but not critical in decision making					
Randomised trial (cluster, cross-over)	Risk of bias: Not serious Inconsistency: Cannot assess[24] Indirectness: Not serious Imprecision: Serious[25] Other considerations: None	4663 patients	3740 patients	The effect of terminal room disinfection with UV light plus sodium hypochlorite on the incidence of hospital-acquired MROs is uncertain. Addition of UV light plus sodium hypochlorite for terminal room disinfection reduced the rate of hospital-acquired MROs by 18% compared to quaternary ammonium disinfection alone (RR 0.82, (95% CI 0.67, 1.00; p=0.048))[26]. However the confidence interval includes the possibility of clinically important reduction of 33% reduction or no reduction.	⊕⊕⊕⊖ Moderate due to serious imprecision. Single study (consistency cannot be assessed).
No studies Adverse effects Outcome importance: Critical for decision making					
Anderson 2017 reported one accidental exposure to ultra-violet light in which a health professional entered a room while the disinfection system was operating. The person reported headaches and seeing sun spots, but no long term effects.					

[22] Imprecision (-1) the 95%CI includes the possibility of a clinically important reduction or a small reduction.

[23] Results from the trialists' post hoc analysis, which excluded patients exposed to *C. difficile* 'seed' *rooms* (supplementary table 3). The analysis reported in the main manuscript (Table 2) included patients exposed to rooms previously occupied by a patient with CDAD *(C. difficile* 'seed' rooms) or an MRO (MRO 'seed' rooms). These results are difficult to interpret because they combine two comparisons: (1) UV as an adjunct to bleach vs bleach (used in *C. difficile* 'seed' *rooms*) and (2) UV as an adjunct to QA vs QA (used in MRO 'seed' rooms).

[24] Inconsistency. This is a single RT, so it is not possible to assess consistency. Although the quality of evidence was not downgraded for inconsistency, additional studies are required to determine whether the observed effect can be replicated.

[25] Imprecision (-1) the 95%CI includes the possibility of a clinically important reduction or no reduction.

[26] Results from the trialists' post hoc analysis, which excluded patients exposed to *C. difficile* 'seed' *rooms* (supplementary table 3). The analysis reported in the main manuscript (Table 2) included patients exposed to rooms previously occupied by a patient with CDAD *(C. difficile* 'seed' rooms) or an MRO (MRO 'seed' rooms). These results are difficult to interpret because they combine two comparisons: (1) UV as an adjunct to bleach vs bleach (used in *C. difficile* 'seed' *rooms*) and (2) UV as an adjunct to QA vs QA (used in MRO 'seed' rooms).

5.0 Discussion

5.1 Summary of main results

This review included eight completed studies and one ongoing study of novel disinfectants. Results of the latter are yet to be reported by the study investigators, but the study examines the effects of ultraviolet light disinfection (Maragakis 2015). Of the eight completed studies, four studies evaluated the effects of sodium hypochlorite disinfection compared to standard cleaning/disinfection (one on MROs, and three on *C. difficile* associated diarrhoea); three evaluated the effects of hydrogen peroxide vapour disinfection as an adjunct to standard cleaning/disinfection (each on different pathogens); and two evaluated the effects of ultra-violet light disinfection on multiple MROs and *C. difficile*. One study evaluated both sodium hypochlorite and ultra-violet light disinfection, hence it contributes evidence on both interventions.

One randomised trial (Anderson 2017) provided inconclusive evidence about the effects of sodium hypochlorite for terminal cleaning of contact precaution rooms on acquisition of MROs (moderate quality evidence). Two interrupted time series studies provided very low quality evidence that sodium hypochlorite may lead to a clinically important, immediate reduction in rates of hospital-acquired CDAD, when used to control outbreaks (Hacek 2010, McMullen 2007; data not pooled). The effects appeared to be sustained over 12 months. A third time series study of sodium hypochlorite wipes was inconclusive (Orenstein 2011, very low quality evidence).

One non-randomised trial provided low quality evidence that hydrogen peroxide vapour disinfection may lead to clinically important reduction in hospital-acquired MROs or *C. difficile* (combined outcome) (Passarreti 2013). Although the study was at high risk of bias, the observed intervention effects were large. Two interrupted time series studies on the effects of HP vapour, showed small immediate reductions in hospital-acquired CDAD and MRSA respectively, and the confidence intervals for these studies did not exclude the possibility that the intervention had no effect.

One randomised trial (Anderson 2017) provided moderate quality evidence that UV light for terminal cleaning of contact precautions rooms may lead to clinically important reductions of hospital-acquired MROs when compared to standard disinfection with quaternary ammonium. When used in contact precaution rooms where the previous patient had a confirmed *C. difficile* infection, the effect of UV light on *C. difficile* acquisition was inconclusive compared to standard disinfection with sodium hypochlorite (low quality evidence). Finally, one interrupted time series study on the effects of ultraviolet light disinfection on MRO and *C. difficile* acquisition was inconclusive (very low quality evidence).

5.2 Overall completeness and applicability of the evidence

Evidence about the effects of sodium hypochlorite, hydrogen peroxide vapour, and ultra-violet light disinfection on clinical outcomes remains sparse despite recent publication of a large randomised trial (Anderson 2017). No studies of electrolysed water were identified that were eligible for this review.

Three of four studies that examined the effects of sodium hypochlorite were set in wards where sodium hypochlorite disinfection was introduced to control an outbreak or increase in the rate of CDAD (one involving an outbreak across three hospitals, Hacek 2010). Only one of these studies involved patients in other high risk groups (i.e. not solely high risk because of CDAD status), being set in a medical intensive care unit (McMullen 2007). Only one study, a randomised trial, examined the use of sodium hypochlorite disinfection for controlling acquisition of any of the multi-drug resistant organisms eligible for inclusion in this review (MRSA, VRE, *Actinetobacter* spp., CPE, ESBL producing organisms). This trial focussed on patients admitted to contact precaution rooms where the previous occupant had a confirmed MRO (for sodium hypochlorite vs standard disinfection comparison), rather than specific high risk groups. There are, therefore, important gaps in the evidence about the effects of sodium hypochlorite among specific high-risk groups, and on acquisition and infection arising from multi-drug resistant organisms.

The three studies of hydrogen peroxide vapour disinfection examined effects on different pathogens (CDAD, MRSA, multiple MROs (VRE, MRSA, MRGN bacteria) and *C. difficile*). One of these studies was set on high risk wards (three intensive care units, two surgical units, one medical ward), one on wards with high rates of CDAD, and one in rooms that had accommodated patients with MRSA (Pasaretti 2013, Boyce 2008, and Mitchell 2014 respectively).

The large trial of ultra-violet light disinfection examined acquisition of MROs or *C.difficile* among patients admitted to contact precaution rooms where the previous occupant had a confirmed MRO or *C.difficile.* The trial provides important evidence about the potential of terminal room disinfection with UV light to decrease the risk of MRO acquisition. These findings require replication in other contexts, and data for high risk groups are needed. Findings for *C. difficile* acquisition were inconclusive, with further studies required to determine if addition of ultra-violet light disinfection offers any benefit over sodium hypochlorite alone. The main finding of the time series study of ultra-violet light disinfection were consistent with those of the trial (Haas 2014, Nagaraja 2015). In addition to contact precaution rooms, ultraviolet light disinfection was used in multiple high risk units (burns, dialysis, operating theatres). In a second paper arising from the study, the authors examined effects on *C. difficile* outcomes (incidence rate of CDAD, length of stay before acquiring CDAD), but the data were not suitable for re-analysis in this review.

There was particularly sparse evidence about the effects of novel disinfectants among high risk groups, such as transplant patients, haematology-oncology patients and those in intensive care. Multiresistant organisms may be acquired by uncolonised patients by three routes – endogenously (via antibiotic selection pressure); directly on the hands of healthcare workers; or indirectly via contamination of the environment. The interventions considered in this review are only likely to impact on one of these routes. Cross transmission is thought to be an important mode of acquisition for MROs and *C difficile*. High risk groups are important in that they are more likely to get infection (vs colonization); but also get more antibiotics, so the relative contribution of cross-transmission in this group may be different to lower risk groups.

None of the non-randomised studies reported adverse effects or safety as an outcome, although two studies noted that there were no reports of adverse effects from staff (Boyce 2008, Passaretti 2013). Anderson 2017 reported one accidental exposure to ultra-violet light in which a health professional entered a room while the disinfection system was operating. The person reported headaches and seeing sun spots, but no long term effects. Although little evidence of adverse effects was identified in this review, different review methods are required to ensure studies of adverse effects are identified. Non-reporting of adverse events in the included studies should, therefore, not be interpreted as the absence of any evidence on adverse effects, nor that there are not adverse events.

Finally, the evidence base is almost entirely derived from hospitals in the United States; seven of the eight completed studies and the one ongoing study. The remaining study was in Australia. While the results of the studies in the USA are applicable to an Australian context, replication in a more diverse range of settings is desirable.

5.3 Quality of the evidence

The single randomised trial contributing to this review provides moderate quality evidence about the effects of UV disinfection for reducing MRO incidence. However, overall the evidence contributing to this review is of low to very low quality. This is due to the small number of studies addressing each question (so consistency of findings cannot be assessed) and the high risk of bias arising from the study designs. The evidence contributing to the review derives almost entirely from interrupted time series studies. This analysis approach enables evaluation of the effects of an intervention, by making use of longitudinal data (time series) to account for important pre-intervention trends in the outcome of interest (Kontopantelis 2015). However, the approach relies on there being no concurrent changes in the intervention period that might affect the outcome. Multiple concurrent changes were documented in all studies, making it impossible attribute observed effects solely to the intervention. The analysis also relies on there being sufficient data points to

ensure pre-intervention trends can be estimated. Short pre-intervention series are prone to regression to the mean and overfitting, which leads to poorly estimated trends; causal conclusions rely heavily on projections from the pre-intervention trend (Huitema 2011). Several studies had few data points which means there are important caveats around their results. Finally, we were unable to combine effect estimates across studies which reduces certainty around our assessment of the effects.

The small number of studies, most showing effects that favour intervention, suggest that publication bias may be also a concern (Guyatt 2011). Several of the studies had industry ties (employees of the manufacturer were included as authors, interventions subsidised by the manufacturer), without safeguards to protect against potential bias such as pre-registration of the study. This raises further concerns about the potential for selective reporting of studies that show effects that favour the interventions.

5.4 Potential biases in the review process

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

First, we relied on the AHRQ report for the majority of studies published between 2006 and February 2015. While the searches from that report were appraised and appeared comprehensive, it is possible that some studies may have been missed. However additional screening of reference lists for related reviews, and our independent search of all records in clinicaltrials.gov identified no additional studies that were eligible for the AHRQ report. We combined all citations from that report with our updated search, and independently screened these without cross reference to their decisions during the screening process. After final inclusion decisions were made, we verified our list against the AHRQ report and found no discrepancies. We did not search grey literature, or approach study authors or manufacturers about whether they were aware of unpublished studies.

Second, we did not contact authors for further information or data (with one exception, as documented in the methods). This meant we may have missed subsequent publications of some studies published only as conference abstracts. It also meant we relied on published data for our assessment of study design, risk of bias and for re-analysis of time series studies.

For all time-series studies (with one exception) we only had access to rates (extracted from figures) and not counts. Modelling counts would have been preferable. In addition, did not adjust for seasonality in the models, which could mean that in some studies which span different seasons, the observed effects may be partially explained by seasonal differences.

6.0 Authors' conclusions

6.1 Implications for practice

We found that there is currently limited evidence to support the use of routine sodium hypochlorite cleaning, the use of UV light disinfection or hydrogen peroxide vapour to prevent infections with multi-resistant organisms. Low quality evidence supports the use of routine sodium hypochlorite cleaning, compared to standard cleaning with detergents, in terminating outbreaks of *Clostridium difficile*. There is immature evidence to support the use of HPV, in addition to routine cleaning, to prevent a range of MROs. Moderate quality evidence suggests that addition of UV light for terminal room disinfection may reduce the risk of MRO acquisition compared to standard cleaning with quaternary ammonium disinfectants. The results of ongoing studies of UV light disinfection are awaited to determine if these findings can be replicated in other contexts.

The effectiveness of all these interventions has not been conclusively established, so the cost effectiveness of these interventions is unknown. Whether an effect size is clinically significant is likely to depend on the baseline risk of MRO acquisition. For example, some studies reported a baseline MRO acquisition of up to 10%, where a 50% reduction equates to a "number needed to treat" of 20; where the baseline risk is 2%, a similar reduction equates to a "number needed to treat" of 100.

6.2 Implications for research

We found few well-designed studies suited to establishing the effects of novel disinfectants on clinical outcomes. The inclusion of infection and colonisation outcomes in future studies is key to determining whether these interventions have a clinically important impact; this is an important gap in existing research which has largely focussed on whether novel disinfectants reduce bacterial contamination. Studies among high-risk populations are also needed (e.g. oncology, burns), as investment in novel disinfectant modalities is expensive and their use is therefore likely to be prioritised in areas of highest risk.

The optimal design to assess the causal effects of an intervention is one which involves random allocation of individuals or clusters of individuals to treatment groups. Individually randomised trials are unlikely to be possible in this setting because of the risk of contamination between treatment groups. For example, patients allocated to control rooms may be moved to intervention rooms during the course of their admission. Cluster randomisation by ward may reduce contamination between treatment groups, but will not resolve the issue completely because of movement of patients between wards. Therefore, the optimal design would be a cluster randomised trial where clusters were hospitals (as was the case in Anderson 2017).

Interrupted time series designs are more prone to bias than randomised trials, and therefore it is more difficult to ascribe observed treatment effects to the treatment. However, they are an important design that may be useful when a randomised trial is not possible. ITS designs can be strengthened by including a long series, both pre and post intervention (allowing for investigation of seasonal effects and minimising issues of regression to the mean and overfitting) (Huitema 2011); including a sufficient number of observations at each time-point (Wagner 2002); collection of potential confounding factors over time (such as changes to the composition of the population that may explain the outcome); documentation of co-interventions (e.g. when they occurred, what they involved); consistent methods for data collection in the pre and post intervention periods; and, masking of outcome assessment. Further, collection of 'control' outcomes not expected to respond to the intervention (e.g. urinary tract infections, Methicillin-sensitive *Staphylococcus aureus*) over time, or the inclusion of control sites, may provide more confidence in ascribing observed treatment effects to the treatment if no changes are observed in the control outcomes or sites.

References

References to studies included in this review

Anderson 2017

Anderson DJ, Chen LF, Weber DJ, Moehring RW, Lewis SS, Triplett PF, Blocker M, Becherer P, Schwab JC, Knelson LP et al: Enhanced terminal room disinfection and acquisition and infection caused by multidrug-resistant organisms and *Clostridium difficile* (the Benefits of Enhanced Terminal Room Disinfection study): a cluster-randomised, multicentre, crossover study. The Lancet 2017, e-publication ahead of print.

A Four-arm Prospective, Multicenter Study to Assess the Efficacy, Effectiveness, and Feasibility of Enhanced Terminal Room Disinfection With Chlorine and UV Light Using Clinical and Microbiologic Outcomes. 2015. NCT01579370

Boyce 2008

Boyce, J. M., N. L. Havill, J. A. Otter, L. C. McDonald, N. M. Adams, T. Cooper, A. Thompson, L. Wiggs, G. Killgore, A. Tauman and J. Noble-Wang (2008). Impact of hydrogen peroxide vapor room decontamination on Clostridium difficile environmental contamination and transmission in a healthcare setting. Infect Control Hosp Epidemiol 29(8): 723-729.

Haas 2014

Haas, J. P., J. Menz, S. Dusza and M. A. Montecalvo (2014). Implementation and impact of ultraviolet environmental disinfection in an acute care setting. Am J Infect Control 42(6): 586-590.

Nagaraja, A., P. Visintainer, J. P. Haas, J. Menz, G. P. Wormser and M. A. Montecalvo (2015). Clostridium difficile infections before and during use of ultraviolet disinfection. American Journal of Infection Control 43(9): 940-945.

Hacek 2010

Hacek, D. M., A. M. Ogle, A. Fisher, A. Robicsek and L. R. Peterson (2010). Significant impact of terminal room cleaning with bleach on reducing nosocomial Clostridium difficile. Am J Infect Control 38(5): 350-353.

McMullen 2007

McMullen, K. M., J. Zack, C. M. Coopersmith, M. Kollef, E. Dubberke and D. K. Warren (2007). Use of hypochlorite solution to decrease rates of Clostridium difficile-associated diarrhea. Infect Control Hosp Epidemiol 28(2): 205-207.

Mitchell 2014

Mitchell, B. G., W. Digney, P. Locket and S. J. Dancer (2014). Controlling methicillin-resistant Staphylococcus aureus (MRSA) in a hospital and the role of hydrogen peroxide decontamination: an interrupted time series analysis. BMJ Open 4(4): e004522.

Orenstein 2011

Orenstein, R., K. C. Aronhalt, J. E. McManus, Jr. and L. A. Fedraw (2011). A targeted strategy to wipe out Clostridium difficile. Infect Control Hosp Epidemiol 32(11): 1137-1139.

Passaretti 2013

Passaretti, C. L., J. A. Otter, N. G. Reich, J. Myers, J. Shepard, T. Ross, K. C. Carroll, P. Lipsett and T. M.

Perl (2013). An evaluation of environmental decontamination with hydrogen peroxide vapor for reducing the risk of patient acquisition of multidrug-resistant organisms. Clin Infect Dis 56(1): 27-35.

References to ongoing studies

Maragakis 2015

Maragakis. Ultra Violet-C Light Evaluation as an Adjunct to Removing Multi-Drug Resistant Organisms (UVCLEAR-MDRO). 2015. NCT02605499

References to studies awaiting further assessment

Bernard 2015

Bernard, H. and J. Little (2015). The Impact of Ultraviolet (UV) Disinfection System Coupled with Evidence-based Interventions on the Incidence of Hospital Onset Clostridium Difficile (HO-C-Diff). 42nd Annual Conference Abstracts, APIC 2015, Nashville, TN June 2015. American Journal of Infection Control 43: S27-S27.

Mauzey 2015

Mauzey, S. (2015). Coming to the Light: Impact of Ultraviolet Technology on Incidence of Pseudomonas in a Neonatal Intensive Care Unit...42nd Annual Conference Abstracts, APIC 2015, Nashville, TN June 2015. American Journal of Infection Control 43: S21-S21.

McMullen 2016

McMullen, K., G. Dunn, R. Wade and A. Siddiqui (2016). 9-199 - Impact of No-touch Ultraviolet-C Light Room Disinfection System on Hospital Acquired Infection Rates. American Journal of Infection Control 44: S93-S93.

Sampathkumar 2016

Sampathkumar, P., L. Nation, C. Folkert, J. E. Wentink and K. W. Zavaleta (2016). A Trial of pulsed xenon ultraviolet disinfection to reduce C. Difficile Infection. American Journal of Infection Control 44(6): S32-S33.

Simmons 2013

Simmons, S. E., J. Stachowiak, M. Stibich, S. Martin, S. Reich, K. Sams and L. Courtney (2013). Results from a trial of a pulsed xenon ultraviolet disinfection device: Reducing the burden of hospital associated infections. American Journal of Infection Control 41(6 SUPPL. 1): S35.

Other references

Armstrong, R., E. Waters and J. Doyle (2011). Reviews in health promotion and public health. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). J. Higgins and S. Green, The Cochrane Collaboration.

Australian Commission on Safety and Quality in Health Care (2013). Implementation guide for surveillance of *Clostridium difficile* infection. Canberra, Commonwealth of Australia

Brennan, S., S. McDonald, A. Cheng, S. Green and J. McKenzie (2016). Novel disinfection methods to reduce infection rates in high risk hospitalised populations. Protocol for a systematic review. Prepared by Cochrane Australia for the National Health and Medical Research Council. September 2016. Monash University, Melbourne, Australia

Department of Health and Human Services Victoria (2015). Victorian guideline on carbapenemase-producing Enterobacteriaceae. Melbourne https://www2.health.vic.gov.au/Api/downloadmedia/%7B8ED077BE-4006-4854-83DA-5A0606ADD242%7D

Effective Practice and Organisation of Care (2013). Summary assessments of the risk of bias. EPOC Resources for review authors. Oslo, Norwegian Knowledge Centre for the Health Services Available at: http://epoc.cochrane.org/epoc-specific-resources-review-author

Effective Practice and Organisation of Care (2013). What study designs should be included in an EPOC review? EPOC Resources for review authors. Oslo, Norwegian Knowledge Centre for the Health Services Available at: http://epoc.cochrane.org/epoc-specific-resources-review-author

Effective Practice and Organisation of Care (2015). Suggested risk of bias criteria for EPOC reviews. EPOC Resources for review authors. Oslo, Norwegian Knowledge Centre for the Health Services Available at: http://epoc.cochrane.org/epoc-specific-resources-review-author

Effective Practice and Organisation of Care (EPOC) (2015). EPOC Resources for review authors. Oslo: Norwegian Knowledge Centre for the Health Services. Available at: http://epoc.cochrane.org/epoc-specific-resources-review-authors

Falagas, M. E. and D. E. Karageorgopoulos (2009). "Extended-spectrum β -lactamase-producing organisms." Journal of Hospital Infection **73**(4): 345-354.

Guh, A. Y., S. N. Bulens, Y. Mu, J. T. Jacob, J. Reno, J. Scott, L. E. Wilson, E. Vaeth, R. Lynfield, K. M. Shaw, P. M. Vagnone, W. M. Bamberg, S. J. Janelle, G. Dumyati, C. Concannon, Z. Beldavs, M. Cunningham, P. M. Cassidy, E. C. Phipps, N. Kenslow, T. Travis, D. Lonsway, J. K. Rasheed, B. M. Limbago and A. J. Kallen (2015). "Epidemiology of Carbapenem-Resistant Enterobacteriaceae in 7 US Communities, 2012-2013." JAMA **314**(14): 1479-1487.

Guyatt, G. H., A. D. Oxman, V. Montori, G. Vist, R. Kunz, J. Brozek, P. Alonso-Coello, B. Djulbegovic, D. Atkins, Y. Falck-Ytter, J. W. Williams, J. Meerpohl, S. L. Norris, E. A. Akl and H. J. Schünemann (2011). "GRADE guidelines: 5. Rating the quality of evidence—publication bias." Journal of Clinical Epidemiology **64**(12): 1277-1282.

Higgins, J. and S. Green, Eds. (2011). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration.

Hoffmann, T., P. Glasziou, V. Barbour and H. Macdonald (2014). "Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide." BMJ **1687**: 1 - 13.

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

Kontopantelis, E., T. Doran, D. A. Springate, I. Buchan and D. Reeves (2015). "Regression based quasi-experimental approach when randomisation is not an option: interrupted time series analysis." BMJ **350**: h2750.

Leas, B., N. Sullivan, J. Han, D. Pegues, J. Kaczmarek and C. Umscheid (2015). Environmental Cleaning for the Prevention of Healthcare-Associated Infections (HAI) Technical Brief No 22 (Prepared by the ECRI Institute – Penn Medicine Evidence-based Practice Center under Contract No 290-2012-00011-I) AHRQ Publication No 15-EHC020-EF. Rockville, MD, Agency for Healthcare Research and Quality**:** 121 http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=2103&pageaction=displayproduct

Lewis, S. R., A. R. Butler, D. J. W. Evans, P. Alderson and A. F. Smith (2016). "Chlorhexidine bathing of the critically ill for the prevention of hospital-acquired infection." Cochrane Database of Systematic Reviews(6).

Liberati, A., D. G. Altman, J. Tetzlaff, C. Mulrow, P. C. Gotzsche, J. P. A. Ioannidis, M. Clarke, P. J. Devereaux, J. Kleijnen and D. Moher (2009). "The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration." BMJ **339**(jul21_1): b2700-.

McLaws, M. L., A. C. Pantle, K. R. Fitzpatrick and C. F. Hughes (2009). "More than hand hygiene is needed to affect methicillin-resistant Staphylococcus aureus clinical indicator rates: clean hands save lives, part IV." Med J Aust **191**(8 Suppl): S26-31.

Moher, D., A. Liberati, J. Tetzlaff and D. Altman (2009). "Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement." PLoS Medicine **6**(7): 1 - 6.

National Health and Medical Research Council (2010). Australian guidelines for the prevention and control of infection in healthcare. Canberra, Commonwealth of Australia

Public Health England. (2014). "Acute trust toolkit for the early detection, management and control of carbapenemase-producing Enterobacteriaceae." Retrieved 13 July, 2016, from https://www.gov.uk/government/publications/carbapenemase-producing-enterobacteriaceae-non-acute-and-community-toolkit.

Rutala, W. A., D. J. Weber and the Healthcare Infection Control Practices Advisory Committe (HICPAC) (2008). Guideline for disinfection and sterilization in healthcare facilities. Atlanta, CDC, Department of Health and Human Services

Schunemann, H. J., J. Brozek, G. Guyatt and A. D. Oxman, Eds. (2013). Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. Accessed 5 July 2016. Hamilton, Canada, McMaster University.

Slimings, C., P. Armstrong, W. D. Beckingham, A. L. Bull, L. Hall, K. J. Kennedy, J. Marquess, R. McCann, A. Menzies, B. G. Mitchell, M. J. Richards, P. C. Smollen, L. Tracey, I. J. Wilkinson, F. L. Wilson, L. J. Worth and T. V. Riley (2014). "Increasing incidence of Clostridium difficile infection, Australia, 2011-2012." Med J Aust **200**(5): 272-276.

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.

Therapeutic Goods Administration. (2012). "The regulation of disinfectants and sterilants." Retrieved 11 July, 2016, from https://www.tga.gov.au/disinfectants-sterilants.

Wagner, A., S. Soumerai, F. Zhang and D. Ross-Degnan (2002). "Segmented regression analysis of interrupted time series studies in medication use research." Journal of clinical pharmacy and therapeutics. **27**(4): 299-309.

Weber, D. J., D. Anderson and W. A. Rutala (2013). "The role of the surface environment in healthcare-associated infections." Curr Opin Infect Dis **26**(4): 338-344.