

**Advancing evidence-based hospital infection control: a critical analysis
based on systematic reviews of non-pharmacological interventions**

Jesús López Alcalde

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UAB

Universitat Autònoma de Barcelona

Faculty of Medicine

Department of Paediatrics, Obstetrics, Gynaecology and Preventive Medicine and Public Health

PhD in Methodology of Biomedical Research and Public Health

Advancing evidence-based hospital infection control: a critical analysis based on systematic reviews of non-pharmacological interventions

Doctoral Thesis

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December 2025

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Thesis presented by Jesús López Alcalde to obtain the degree of Doctor of Medicine with International Mention from *Universitat Autònoma de Barcelona* and carried out under the direction of Dr. Xavier Bonfill Cosp and Dr. Javier Zamora Romero.

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“Life is what happens when you're busy making other plans”, such as a PhD

Adapted from John Lennon

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Abstract

Advancing evidence-based hospital infection control: a critical analysis based on systematic reviews of non-pharmacological interventions

Background

Hospital-acquired infections (HAIs) represent a threat to the sustainability of healthcare systems. Systematic reviews (SRs) evaluating the impact of infection control interventions face methodological challenges. This thesis aims to critically analyse and synthesise research evidence on non-pharmacological interventions to reduce the transmission of microorganisms within hospital settings.

Objectives

The specific objectives of the thesis align with each of the studies included in the PhD project.

- I. To assess the effects of decontaminating hospital environmental surfaces on HAIs.
- II. To assess the effects of using gloves, gowns or masks when contact is anticipated with a hospitalised patient with Methicillin-resistant *Staphylococcus aureus* (MRSA) or with the patient's immediate environment.
- III. To assess the consideration of sex and gender in Cochrane reviews of interventions for preventing HAIs.
- IV. To assess the consideration of non-randomised studies of interventions (NRSIs) in Cochrane reviews of interventions for preventing HAIs.
- V. To identify methodological challenges in SRs of interventions aimed at reducing the transmission of microorganisms in the hospital setting.
- VI. To formulate recommendations for the design of randomised controlled trials (RCTs) of interventions aimed at reducing the transmission of microorganisms in the hospital setting.

Methods

The thesis employs diverse methods, including two SRs following Cochrane and GRADE, a methodological appraisal of 113 Cochrane reviews using the *Sex and Gender Appraisal Tool-Systematic Reviews* (SGAT-SR), and a cross-sectional descriptive study of the consideration of NRSIs in these SRs. An integrative descriptive synthesis was employed for studies V and VI.

Results

Study I. The SR included eleven RCTs and four ongoing trials. Meta-analysis was not possible (no more than one RCT contributed data per outcome). The certainty of evidence for hospital environmental surface decontamination in reducing HAIs was very low.

Study II. This was an empty review. The SR identified no eligible studies, completed or ongoing. It was not possible to assess the effect of gloves, gowns, or masks on MRSA transmission.

Study III. Sex and gender considerations were virtually absent in the 113 Cochrane reviews. 50% met no SGAT-SR criteria, and none defined sex/gender terms. Only 3% performed disaggregated analyses by sex/gender, and 3% addressed sex/gender in their conclusions.

Study IV. Among the 113 Cochrane reviews, 49% considered at least one type of NRSI as eligible. Only 7 reviews provided a rationale, of which 3 followed Cochrane guidance. The most frequent label for NRSIs was the “quasi-randomised controlled trial” (87%). 67% of SRs admitting NRSIs used design labels without describing their methodological features.

Study V. SRs of infection control interventions face methodological challenges, such as the inclusion of non-conventional RCTs, lack of tailored risk-of-bias tools, and the assessment of complex interventions and their integrity.

Study VI. Future RCTs should prioritise patient-centred outcomes over indirect microbial measures, adopt core outcome sets, and use appropriate statistical models for cluster designs and infection outcomes.

Conclusions

The impact of hospital environmental surfaces decontamination and the use of gloves, gowns or masks on HAI prevention is uncertain. This uncertainty should not be interpreted as evidence of no effect. Sex and gender considerations are largely absent from Cochrane reviews on HAI prevention, and the characterisation of non-randomised studies shows room for improvement.

Advancing infection control research requires a patient-centred approach that incorporates gender and sex perspectives and synthesises evidence from both randomised and non-randomised studies. Future review authors and trialists must be equipped to address the methodological complexities inherent to this field.

Resumen

Avanzando en el control de infecciones hospitalarias basado en evidencia: un análisis crítico basado en revisiones sistemáticas de intervenciones no farmacológicas

Antecedentes

Las infecciones asociadas a la atención hospitalaria (IH) representan una amenaza para la sostenibilidad del sistema sanitario. Las revisiones sistemáticas (RS) que evalúan el impacto de las intervenciones de control de infecciones presentan retos metodológicos. Esta tesis pretende analizar críticamente y sintetizar la evidencia científica sobre intervenciones no farmacológicas para reducir la transmisión de microorganismos en entornos hospitalarios.

Objetivos

Los objetivos específicos de la tesis se alinean con los estudios del proyecto de doctorado.

- I. Evaluar los efectos de la limpieza de superficies ambientales hospitalarias sobre las IH.
- II. Evaluar los efectos del uso de guantes, batas o mascarillas ante pacientes hospitalizados con *Staphylococcus aureus* resistente a la meticilina (SARM) o su entorno inmediato.
- III. Evaluar la consideración del sexo y del género en las revisiones Cochrane sobre intervenciones para prevenir la IH.
- IV. Evaluar la consideración de los estudios no aleatorizados de intervención (ENAls) en las revisiones Cochrane sobre intervenciones para prevenir la IH.
- V. Identificar retos metodológicos en las RS de intervención para reducir la transmisión de microorganismos en el hospital.
- VI. Formular recomendaciones para el diseño de ensayos clínicos aleatorizados (ECAs) de intervenciones para reducir la transmisión de microorganismos en el hospital.

Métodos

La tesis emplea diversos métodos, incluyendo dos RS con metodología Cochrane y GRADE, una evaluación metodológica de 113 revisiones Cochrane utilizando la herramienta Sex and Gender Appraisal Tool-Systematic Reviews (SGAT-SR), y un

estudio descriptivo transversal sobre la consideración de ENAI en estas RS. Los estudios V y VI emplearon una síntesis descriptiva integrativa.

Resultados

I. La RS incluyó once ECAs y cuatro ECAs en curso. No se pudo metaanalizar (como máximo, un ECA aportó datos por desenlace). La certeza de la evidencia de la limpieza sobre las IH fue muy baja.

II. RS vacía: la RS no identificó estudios elegibles, finalizados o en curso. No fue posible evaluar el efecto de los guantes, batas o mascarillas sobre la transmisión de SARM.

III. La consideración del sexo y género fue prácticamente inexistente en las 113 revisiones Cochrane. El 50% no cumplió ningún criterio de la SGAT-SR y ninguna definió sexo/género. Solo el 3% realizó análisis desagregados por sexo/género y el 3% abordó el sexo/género en sus conclusiones.

IV. El 49% de las 113 revisiones consideró elegible al menos un tipo de ENAI. Solo 7 revisiones justificaron la inclusión de ENAI, de las cuales 3 siguieron las directrices de Cochrane. La etiqueta más frecuente para ENAI fue “ensayo controlado cuasi-aleatorio” (87%). El 67% de las RS que admitieron ENAI utilizó etiquetas de diseño sin describir sus características metodológicas.

V. Las RS de intervenciones de control de infecciones enfrentan desafíos metodológicos, como la inclusión de ECAs no convencionales, la falta de herramientas de sesgo adaptadas y la evaluación de intervenciones complejas y de su integridad.

VI. Los futuros ECAs deben priorizar desenlaces centrados en el paciente sobre medidas microbianas indirectas, adoptar “core outcomes sets” y utilizar modelos estadísticos adecuados para diseños por conglomerados y desenlaces de infección.

Conclusiones

El impacto de la limpieza de superficies hospitalarias y el uso de guantes, batas o mascarillas en la prevención de IH es incierto. Esta incertidumbre no debe interpretarse como evidencia de la ausencia de efecto. Las revisiones Cochrane sobre prevención de IH rara vez abordan el sexo y el género, y la caracterización de estudios no aleatorizados revela oportunidades de mejora.

Para avanzar en la investigación sobre el control de infecciones, se necesita un enfoque centrado en el paciente que integre las dimensiones de sexo y género y que sintetice la evidencia de estudios aleatorizados y no aleatorizados. Las futuras investigaciones deben abordar las complejidades metodológicas mediante la capacitación específica para revisores y autores.

Resum

Avançant en el control d'infeccions hospitalàries basat en l'evidència: una anàlisi crítica basada en revisions sistemàtiques d'intervencions no farmacològiques

Antecedents

Les infeccions associades a latència hospitalària (IH) representen una amenaça per a la sostenibilitat del sistema sanitari. Les revisions sistemàtiques (RS) que avaluen l'impacte de les intervencions de control d'infeccions s'enfronten a reptes metodològics. Aquesta tesi pretén analitzar críticament i sintetitzar l'evidència científica sobre intervencions no farmacològiques per reduir la transmissió de microorganismes en entorns hospitalaris.

Objectius

Els objectius específics de la tesi s'alineen amb els estudis del projecte de doctorat.

- I. Avaluar els efectes de la neteja de superfícies ambientals hospitalàries sobre les IH.
- II. Avaluar els efectes de l'ús de guants, bates o màscares en el contacte amb pacients hospitalitzats amb *Staphylococcus aureus* resistent a la meticil·lina (SARM) o el seu entorn immediat.
- III. Avaluar la consideració del sexe i el gènere a les revisions Cochrane d'intervencions per prevenir IH.
- IV. Avaluar la consideració dels estudis no aleatoritzats sobre intervencions (ENAI) a les revisions Cochrane d'intervencions per prevenir IH.
- V. Identificar reptes metodològics a les revisions sistemàtiques d'intervencions per reduir la transmissió de microorganismes en l'àmbit hospitalari.
- VI. Formular recomanacions per dissenyar assaigs clínics aleatoritzats (ACAs) d'intervencions per reduir la transmissió de microorganismes en l'àmbit hospitalari.

Mètodes

La tesi empra diversos mètodes, incloent-hi dos RS amb metodologia Cochrane i GRADE, una avaluació metodològica de 113 revisions Cochrane utilitzant l'eina Sex and Gender Appraisal Tool-Systematic Reviews (SGAT-SR), i un estudi descriptiu transversal sobre la consideració d'ENAI en aquestes RS. Els estudis V i VI van emprar una síntesi descriptiva integrativa.

Resultats

I. La RS va incloure onze ACAs i quatre més en curs. No va ser possible metaanalitzar els estudis (com a màxim un ACA va aportar dades a cada variable de resultat). La certesa de l'evidència sobre la descontaminació de les superfícies ambientals hospitalàries sobre les IRAS va ser molt baixa.

II. Aquesta va ser una RS buida: no va identificar estudis elegibles, finalitzats o en curs. No va ser possible avaluar l'efecte dels guants, bates o màscares sobre la transmissió de SARM.

III. La consideració del sexe i gènere va ser pràcticament inexistent en les 113 revisions Cochrane. El 50% no va complir cap criteri de la SGAT-SR i cap no va definir termes sobre sexe/gènere. Només el 3% va fer anàlisis desagregades per sexe/gènere i el 3% va abordar el sexe/gènere en les seves conclusions.

IV. El 49% de les 113 revisions va considerar elegible com a mínim un tipus d'ENAI. Només 7 revisions van justificar la inclusió d'ENAI, de les quals 3 van seguir les directrius Cochrane. La denominació més freqüent per a ENAI va ser "assaig controlat quasi-aleatoritzat" (87%). El 67% de les RS que van incloure ENAI va utilitzar denominacions de dissenys d'estudi sense descriure'n les característiques metodològiques.

V. Les RS d'intervencions de control d'infeccions enfronten reptes metodològics, com ara la inclusió d'ACAs no convencionals, la manca d'eines d'avaluació del risc de biaix adaptades i l'avaluació d'intervencions complexes i de la seva integritat.

VI. Els futurs ACAs han de prioritzar variables de resultats centrats en el pacient en comptes de mesures microbianes indirectes, adoptar conjunts bàsics de variables de resultat (core outcomes sets) i utilitzar models estadístics adequats per a dissenys per conglomerats i variables de resultat d'infecció.

Conclusions

L'impacte de la neteja de superfícies hospitalàries i l'ús de guants, bates o màscares sobre la prevenció d'IRAS és incert. Aquesta incertesa no s'ha d'interpretar com a evidència de no tenir cap efecte. Les revisions Cochrane sobre prevenció d'IRAS vegades amb prou feines aborden el sexe i el gènere, i la caracterització d'estudis no aleatoritzats mostra oportunitats de millora. Per avançar en la investigació sobre el control d'infeccions, cal un enfocament centrat en el pacient que integri les dimensions de sexe i gènere i sintetitzi evidència d'estudis aleatoritzats i no aleatoritzats. En el futur s'ha de poder disposar d'eines per abordar les complexitats metodològiques inherents a aquest camp.

1. Introduction

1.1. Hospital-acquired infections: A global threat

1.1.1. Healthcare-associated infections and hospital-acquired infections: Definitions

Healthcare-associated infections are defined as infections acquired during the provision of healthcare, and therefore, not present or incubating at the time of the patient's admission to a healthcare facility. For most bacterial pathogens, this typically implies that clinical symptoms manifest 48 hours or more after admission—the average incubation period. However, because incubation periods vary depending on the specific pathogen and, to some extent, the patient's underlying health status, each case must be evaluated individually^{1, 2}.

Healthcare-associated infections extend beyond the hospital and also include infections acquired in other healthcare environments, as well as occupational infections among healthcare personnel. Consequently, the term *healthcare-associated infection* has replaced earlier terms such as **nosocomial infections** or **hospital infections** to better reflect this broader scope^{3, 4}.

Hospital-acquired infections—abbreviated from now as **HAIs**—specifically refer to infections contracted during hospital stays. These are particularly prevalent, as hospitalised patients often present with multiple risk factors that increase their susceptibility to infection⁵.

1.1.2. HAIs are frequent worldwide

On any given day, approximately **1 in 31 hospitalised patients has at least one HAI** in the United States⁶. Although standard surveillance methods are still needed⁷, HAIs are recognised as a global concern, affecting countries regardless of income level. In high-income countries, HAI prevalence typically remains below 10%, with reported rates of 3% in China⁸, 3.2% in the U.S.⁶, 6.5% in Europe⁹, 8% in Canada¹⁰, and 10% in Australia¹¹. Available data—though fragmented—indicate that prevalence in low- and middle-income countries (LMIC) is often higher, frequently exceeding 20%^{7, 12}.

Prevalence also varies by type of hospital setting. In Europe, for example, the proportion of patients with at least one HAI ranges from 4.4% in primary hospitals to 7.7% in tertiary hospitals⁹. The highest burden is observed in intensive care units (ICUs), where the prevalence reaches 20.5%, compared to 6.4% across other hospital departments combined⁹.

According to the 2022–2023 point prevalence survey conducted in European acute care hospitals⁹, respiratory tract infections accounted for the largest proportion of HAIs (29.3% of all HAIs), including pneumonia (19.0%), COVID-19 (7.0%), and other lower respiratory tract infections (3.3%). These were followed by urinary tract infections (19.2%), surgical site infections (16.1%), bloodstream infections (BSIs) (11.9%), and gastrointestinal infections (9.5%)⁹.

HAIs are caused by a range of microorganisms, predominantly bacteria, but also viruses and fungi. The same European survey identified the most frequently isolated pathogens from HAIs as *Escherichia coli* (12.7%), *Klebsiella* spp. (11.7%), *Enterococcus* spp. (10.0%), SARS-CoV-2 (9.5%), *Staphylococcus aureus* (9.0%), *Clostridioides difficile* (8.0%), *Pseudomonas aeruginosa* (7.9%), coagulase-negative staphylococci (5.8%), *Candida* spp. (4.7%), *Proteus* spp. (3.2%), *Acinetobacter* spp. (3.2%), and *Enterobacter* spp. (3.0%)⁹.

1.1.3. HAIs increase morbidity, mortality, disability, and healthcare costs

HAIs constitute a global threat to patient safety and healthcare quality. They are associated with increased morbidity and mortality, and poorer clinical outcomes¹³⁻¹⁶. Moreover, HAIs contribute to long-term disability. Bordino *et al.* estimated that HAIs accounted for 424,657 disability-adjusted life-years (DALYs) in Italy, equivalent to approximately 703 DALYs per 100,000 individuals, with BSIs and healthcare-associated pneumonia responsible for 59% and 29% of this burden, respectively¹⁷.

In addition to their clinical impact, HAIs impose a substantial financial burden on healthcare systems. They are consistently linked to prolonged length of hospital stays (LOS), increased demand for medical care, and higher costs, many of which are not reimbursed¹⁴. In Germany, for instance, HAIs were associated with an average increase of 8.45 days in LOS per case in general hospital wards¹⁸. In the United States, the direct annual costs of managing HAIs were estimated between \$9.8 and \$33.8 billion¹⁹⁻²¹. Similarly, a study conducted at an Italian university hospital reported that each HAI episode resulted in an additional €3,335 to €4,695 in direct costs per patient²². The financial impact is further exemplified by an outbreak of carbapenemase-producing *Enterobacteriaceae*, which incurred an estimated cost of €1.1 million over ten months²³.

1.1.4. Antimicrobial resistance is a global threat

A high proportion of HAIs are caused by drug-resistant and multidrug-resistant organisms (MDROs). According to the *European Centre for Disease Prevention and Control* (ECDC), approximately 32% of HAIs in Europe exhibit resistance to

antimicrobials⁹. Antimicrobial resistance is a global health concern, with high but regionally variable prevalence. The increasing resistance observed among Gram-negative bacteria is particularly alarming and represents a growing threat to public health²⁴.

Antimicrobial resistance in the context of HAIs further constrains treatment options, complicating clinical management and outcomes^{9, 25}. Infections caused by MDROs are associated with substantially higher healthcare costs compared to those caused by drug-susceptible strains. For example, in Australia, BSIs caused by third-generation cephalosporin-resistant *Klebsiella pneumoniae* and methicillin-resistant *Staphylococcus aureus* (MRSA) resulted in extended hospital stays of 4.6 and 2.9 days, respectively²⁶. In Switzerland, HAIs caused by antibiotic-resistant bacteria are estimated to account for 3.28 attributable deaths and 87.8 DALYs per 100,000 individuals²⁷.

The spread of resistant pathogens poses a threat to patient safety and has economic implications. It is estimated that the global economic burden of antimicrobial resistance could equal or exceed the financial impact of the 2008 global financial crisis^{24, 28}. Consequently, implementing interventions to prevent HAIs, particularly those involving drug-resistant organisms, has the potential to substantially reduce healthcare expenditures and contribute to health system sustainability²⁹.

1.1.5. Role of sex and gender in HAIs transmission and outcomes

Sex and gender differences in infectious diseases have received limited attention³⁰. Yet, both can influence disease incidence, duration, severity, and mortality through various biological and social pathways³⁰.

Sex-based biological differences play a role in shaping how infectious diseases impact patients. For instance, females are more prone to catheter-associated urinary tract infections due to anatomical factors that facilitate the bacterial contamination of the catheter³⁰. On the other hand, the immunological response also varies by sex. For instance, pre-menopausal women may have better survival in sepsis, potentially linked to sex steroids that modulate immune function, gene expression, and behaviour³¹⁻³³. Still, evidence on sex-specific sepsis outcomes remains inconclusive³⁴. On the other hand, male patients may experience higher rates of HAIs, as well as increased 30-day and one-year mortality³⁵.

Gender differences in behaviors, exposure risks, healthcare access, and decision-making can also shape transmission and outcomes for different HAIs³⁰. For example,

women are less likely than men to receive antibiotics within three hours of a sepsis diagnosis³⁶.

1.2. Non-pharmacological interventions to prevent HAIs

Various strategies exist to control the transmission of microorganisms in hospitals. Most institutions implement a combination of these strategies^{5, 37, 38}, which include the following, among others: 1) Antimicrobial stewardship (rational antibiotic use); 2) Hand hygiene; 3) Early detection of pathogen carriers (e.g., laboratory surveillance and screening for MRSA); 4) Decolonisation therapy to eliminate microorganisms from colonised people; 5) Isolation of colonised or infected patients to stop the transmission; 6) The use of contact precautions, also known as barrier precautions, such as masks, gloves, or gowns; 7) Bundled interventions for device insertion and manipulation; and 8) Decontamination of the environment and equipment.

This PhD focuses on two major categories of non-pharmacological interventions used in hospitals to prevent HAIs: a) Decontamination of environmental surfaces and b) The use of contact precautions, particularly gloves, gowns and masks.

1.2.1. Decontamination of hospital environmental surfaces

1.2.1.1. Description of the intervention

Hospital environmental surfaces are those surfaces in hospitals that typically do not come into direct contact with patients. They include medical equipment (e.g., haemodialysis knobs) and housekeeping surfaces (e.g., floors and keyboards). They can have minimal or frequent hand contact ("high-touch surfaces")³⁹.

Decontamination of hospital environmental surfaces is a process that removes or destroys soil and pathogenic microorganisms from the surfaces. The levels of decontamination are the following.

- **Cleaning** is the removal, usually with detergent and water or enzyme cleaner and water, of adherent visible soil, blood, protein substances, microorganisms and other debris from the surfaces, serrations, joints, and lumens of instruments, devices, and equipment. Cleaning employs a manual or mechanical process that prepares the items for safe handling, further decontamination or both³⁹.
- **Disinfection** is the thermal or chemical destruction of pathogenic and other types of microorganisms. It refers to the elimination of many or most microorganisms. It is less lethal than sterilisation because it destroys most recognised pathogenic microorganisms but not necessarily all microbial forms (e.g., bacterial spores)⁴⁰.

Examples of chemical disinfectants include quaternary ammonium compounds (QACs) and bleach (sodium hypochlorite)⁴¹.

- **Sterilisation** is the validated process used to render a product free of all forms of viable microorganisms. In a sterilisation process, the presence of microorganisms on any individual item can be expressed in terms of probability. Although this probability can be reduced to a very low number, it can never be reduced to zero⁴⁰. Sterilisation is reserved for medical instruments³⁹.

Cleaning alone can be adequate for routine decontamination, that is, measures developed for use in the usual care of all patients. **Enhanced cleaning** uses additional interventions for routine cleaning, such as increased frequency, or automated equipment, such as floor scrubbers. **Terminal decontamination** is performed in a room between occupying patients, and is normally augmented with a disinfectant to ensure that any potential contamination is removed before use by another patient³⁹.

In addition, **physical disinfection** is an emerging area of research. Examples include no-touch disinfection methods based on ultraviolet light C (UV-C) radiation or hydrogen peroxide vapour (HPV). Self-disinfecting surfaces coated with silver or copper have also received attention^{40, 42}.

1.2.1.2. How decontamination of hospital environmental surfaces might work

The decontamination of environmental surfaces in hospitals is implemented as a routine activity or when infection rates are increasing or exceed a recognised benchmark (for example, during outbreaks)⁵. Environmental surfaces play a documented role as persistent sources of pathogen transmission in healthcare settings, which makes effective environmental hygiene essential for the prevention and control of HAIs^{43, 44}.

Common HAI pathogens, including MRSA, Vancomycin-resistant *Enterococci* (VRE), *Acinetobacter*, *Norovirus*, and *Clostridium difficile*, are isolated from a variety of hospital surfaces^{45, 46}. High-touch areas, such as bed rails, supply carts, and intravenous pumps, carry greater bioburden⁴⁷, but pathogens also persist on less frequently touched surfaces, such as floors, curtains, and sinks^{48, 49}.

Microorganisms can survive for prolonged periods—days to months—on dry surfaces⁵⁰⁻⁵². *C. difficile* spores, for example, may persist for up to five months⁵². Additionally, surface bioburden often rebounds rapidly after cleaning⁵³. Finally, the transfer of MDROs between patients and the environment can occur early in the admission, which suggests that standard terminal room disinfection at the end of a patient's stay may not be sufficient to prevent acquisition of MDROs from the environment⁵⁴.

Although difficult to quantify, the role of environmental surfaces in microbial transmission in hospitals has been documented by multiple types of evidence, including transmission models, microbiologic investigations, outbreak reports, and intervention trials^{51, 55-58}. Furthermore, higher microbial loads on surfaces have been linked to increased HAI risk, reinforcing the importance of environmental decontamination to prevent pathogen transmission in the healthcare setting^{51, 59, 60}.

Environmental surfaces are a significant source of contamination, as evidenced by the detection of genetically similar strains on patients, healthcare staff, and environmental surfaces—suggesting bidirectional transmission⁶¹. It is estimated that bacterial transfer from contaminated surfaces occurs during approximately one in five patient interactions⁵⁴. Furthermore, healthcare workers' hands and gloves can become contaminated after contact with surfaces, but hand hygiene compliance is often lower after environmental contact than after direct patient contact^{62, 63}. This suggests that healthcare workers often underestimate the role of environmental surfaces in the transmission of HAIs. As a result, healthcare workers may subsequently touch patients, increasing the risk of onward transmission^{64, 65}. In addition, healthcare professionals' improper glove disposal practices can lead to the contamination of surrounding surfaces and floors⁶⁶.

Patients themselves can also acquire pathogens through contact with contaminated surfaces, which may explain why admission to a room previously occupied by a patient colonised or infected with a specific pathogen increases the risk of HAI with the same organism in subsequent occupants⁶⁷⁻⁷¹. A meta-analysis reported that prior room occupancy by a patient carrying an MDRO was associated with an odds ratio (OR) of 2.14 (95% confidence interval [CI]: 1.65–2.77) for MDRO acquisition⁶⁷.

1.2.2. The use of contact precautions: Gloves, gowns and masks

1.2.2.1. Description of the intervention

According to the *Centres for Disease Control and Prevention* (CDC), there are two levels of precautions to prevent the transmission of infectious agents in healthcare settings: standard precautions and transmission-based precautions^{39, 72}.

Standard precautions are the primary strategy to prevent HAIs and apply to the care of all patients, regardless of suspected or confirmed infection status. These practices include hand hygiene; appropriate use of personal protective equipment (PPE) such as gloves, gowns, masks, eye protection, or face shields based on anticipated exposure; and safe injection practices^{39, 72}.

Transmission-based precautions are used in addition to standard precautions for patients known or suspected to be infected or colonised with certain pathogens requiring additional control measures. As the causative agent is often unknown at admission, these precautions are initially applied empirically based on clinical presentation and adjusted once the pathogen is identified or ruled out. There are three categories of transmission-based precautions^{39, 72}.

- **Contact precautions:** Prevent transmission of infectious agents which are spread by direct or indirect contact with the patient or the patient's environment. Healthcare personnel caring for patients on contact precautions wear gowns and gloves for all interactions involving patient contact or contaminated surfaces in the patient's environment.
- **Droplet precautions:** Prevent transmission via respiratory droplets (through close respiratory or mucous membrane contact with respiratory secretions). A surgical mask (a respirator is not necessary) is worn for close contact with an infectious patient and should be donned entering the room.
- **Airborne precautions:** Prevent transmission of pathogens that remain infectious over long distances in the air (e.g., measles, chickenpox, tuberculosis, SARS-CoV-2). Healthcare personnel wear a respirator or mask as appropriate, depending on the disease-specific recommendations, donned before entering the room.

Gloves, gowns, and masks are used as protective barriers to limit the spread of pathogens in healthcare settings. In many instances, especially during patient contact or when entering contaminated environments such as rooms or operating theatres, these may be the only physical safeguards available to healthcare workers⁷³.

Isolation refers to the physical separation of patients who are colonised or infected with a microorganism (such as MRSA) or those awaiting screening results, to reduce the risk of transmission to other patients. Isolation strategies vary in intensity and typically involve the use of PPE, including disposable gloves, gowns, and, in some cases, masks. These strategies can be broadly categorised as follows^{39, 74}.

- **Placement of patients in an isolation unit or ward**, which may involve either a purpose-built facility or an improvised area designated for positive patients.
- **Nurse cohorting**, that is, assigning designated staff to care exclusively for colonised or infected patients, physically segregated from patients without the

microorganism within the same ward. These staff do not care for non-positive patients during the same shift.

- **Single-room isolation**, which implies housing individual patients in separate rooms to prevent cross-transmission.
- **Patient cohorting without dedicated staff**, that is, grouping positive patients without restricting nursing staff to their care only.
- **Use of PPE (gloves, gowns, and sometimes masks)**, which represents a fundamental barrier method of infection control, particularly in situations where other forms of physical segregation are not feasible.

Following we provide the definitions provided by the U.S. Food and Drug Administration (FDA)^{75, 76} for different barrier precautions available at the hospital setting.

Medical gloves are disposable medical devices made from natural rubber latex or synthetic materials, designed to be worn on the hands as a barrier against potentially infectious materials and other contaminants. Medical gloves are used during tasks involving contact with patients or bodily fluids and are intended for single use only. Medical gloves include patient examination gloves, surgical gloves, and gloves specifically designed for handling chemotherapy agents. Surgical gloves, in particular, are worn by operating room personnel to protect surgical wounds from contamination.

Gowns are protective garments made of impervious materials, worn to shield the wearer's clothing from microorganisms and exposure to blood, body fluids, secretions, and excretions. Gowns should be used once per patient and either discarded or laundered as appropriate⁷³. There are two main types: isolation gowns and surgical gowns. **Isolation gowns** are typically non-sterile and are designed primarily to prevent microbial transfer and exposure to small volumes of body fluids. In contrast, **surgical gowns** are either supplied sterile or intended for sterilisation, and are made from fluid-resistant materials to minimise the transfer of body fluids. Some are disposable, while others are reusable and constructed from washable fabric.

Masks refer broadly to items worn over the nose and mouth to reduce the risk of inhaling or transmitting infectious agents. Several types exist. **Procedure masks** are intended for use in general patient care. **Surgical masks** are worn in operating theatres to protect both the patient and surgical staff from microbial and fluid exposure. **Particulate respirators**, such as the N95 respirator, are personal protective devices used by healthcare personnel to protect against airborne pathogens $\leq 5 \mu\text{m}$ in size. These include droplet nuclei from infectious patients (e.g., *Mycobacterium tuberculosis*) and airborne

particles containing fungal spores (e.g., *Aspergillus* spp.). The N95 disposable particulate respirator is the most commonly used type in healthcare settings⁵.

1.2.2.2. How gloving, masking and gowning might work to prevent the transmission of MRSA

This section focuses on MRSA, the target pathogen evaluated in one of the PhD studies.

MRSA transmission within hospitals is well documented through molecular typing techniques⁷⁷. Colonised or infected patients serve as the primary reservoir of MRSA^{78, 79}, which typically spreads between patients via transient contamination of healthcare workers' hands, clothing, or equipment. Routine patient care activities can also expose healthcare workers to MRSA⁸⁰. The organism can also persist on environmental surfaces and be transmitted indirectly to patients, often via healthcare workers⁸¹.

While gowns and gloves are the focus of most MDRO research, the use of masks for MRSA remains an underdeveloped area of research. Standard infection control theory considers that *S. aureus* is too large for sustained airborne transmission. Still, some studies also suggest that healthcare personnel with persistent nasal colonisation may contribute to MRSA spread through droplet transmission, leading to contaminated surfaces throughout a room⁸².

Glove use during routine procedures has been shown to prevent hand contamination by various pathogens⁸³ and may be as effective as isolation of patients with MDROs, particularly when isolation is not feasible⁸⁴⁻⁸⁶. Similarly, gowns can reduce transient contamination of healthcare workers' clothing⁸⁷, and masks worn during close contact with colonised patients may lower the risk of nasal colonisation among staff⁸⁸.

In summary, MRSA affects a substantial proportion of hospitalised patients and can be transmitted via direct and indirect contact. Evidence suggests that the use of PPE, that is, gloves, gowns, and masks, can reduce MRSA transmission in both outbreak and non-outbreak settings^{89, 90}. Accordingly, it is hypothesised that the use of such protective measures by healthcare personnel and visitors during interactions with MRSA-positive patients or their immediate environment may help prevent MRSA transmission.

1.3. Systematic reviews: A pillar of evidence-based healthcare

1.3.1. Evidence synthesis and systematic reviews: Definition of concepts

Evidence synthesis, also referred to as knowledge synthesis, involves contextualising and integrating findings from individual research studies within the broader body of knowledge on a given topic⁹¹. Practically, it entails combining information from a variety of sources using explicit and transparent methodologies, to inform decision-making on specific issues⁹².

A **systematic review (SR)** is a type of evidence synthesis that aims to comprehensively identify, appraise, and synthesise all relevant research studies meeting predefined eligibility criteria to address a specific research question. SRs employ explicit, systematic methodologies to minimise bias and enhance the reliability of findings, thereby supporting well-informed decision-making. The methodology is characterised by a structured, transparent, and reproducible approach, including: the a priori formulation of a research question; clear definition of the review scope and inclusion criteria; exhaustive efforts to identify all pertinent studies; critical assessment of potential biases; and synthesis of findings in an impartial and objective manner^{93, 94}.

SRs that evaluate the effects of health interventions, specifically their potential benefits and harms, are central to evidence-based practice. As outlined by Haynes *et al.*⁹⁵, evidence-based healthcare is the process of taking informed decisions integrating the information provided by four key elements, considered in the following sequence: 1) The patient's clinical and physical circumstances; 2) The best available research evidence regarding the efficacy, effectiveness, and efficiency of the available options; 3) The patient's preferences and likely actions, including their willingness and capacity to accept specific interventions; and 4) The clinical expertise of the healthcare professional, which is essential to consider the previous elements and recommend a course of treatment that aligns with the patient's values and is clinically appropriate.

1.3.2. Systematic reviews are essential for informing healthcare decision-making

SRs evaluating the effects of health interventions are essential for informing the second component of evidence-based decision-making. SRs are the best available research evidence on the efficacy, effectiveness, and efficiency of the available options.

Rigorous and up-to-date SRs are fundamental to informing clinical recommendations within evidence-based guidelines⁹⁶⁻⁹⁸. Clinical practice guidelines provide evidence-based recommendations to clinicians and other healthcare professionals for the management of specific clinical conditions⁹⁹. They serve as critical tools for healthcare

providers, patients, and policymakers by supporting evidence-informed decision-making, minimising the use of ineffective or potentially harmful interventions, and promoting optimal patient outcomes at an acceptable cost¹⁰⁰.

1.3.3. Consideration of sex and gender in Cochrane reviews

Sex- and Gender-Based Analysis (SGBA) is an analytical approach that integrates a sex and gender perspective into the development of health research, policies and programmes, as well as health planning and decision-making processes. It helps to identify and clarify the differences between women and men and boys and girls, and demonstrates how these differences affect health status, access to, and interaction with, the health care system^{101, 102}

The incorporation of sex/gender analysis into clinical research has enabled advancements across many disciplines¹⁰³⁻¹⁰⁵. For example, understanding the genetic and hormone-mediated basis of sex differences in immunity promises valuable insights into novel cancer immunotherapies¹⁰⁶.

Integrating SGBA into SRs is essential for generating evidence that is inclusive and applicable to diverse populations. *Cochrane* is an international organisation that produces SRs to support informed decision-making in health care⁹⁸. As a leading evidence synthesis organisation, it promotes the integration of sex and gender in SRs through the *Campbell and Cochrane Equity Methods Group*¹⁰⁷. This group advocates for the systematic consideration of sex and gender throughout the entire SR process. To support researchers, targeted resources have been developed¹⁰⁸, including topic-specific briefing notes and the *Sex and Gender Appraisal Tool for Systematic Reviews* (SGAT-SR)¹⁰⁹, along with its updated version, SGAT-SR-2¹¹⁰. These tools provide guidance on key approaches, such as formulating gender-sensitive research questions, disaggregating data, and conducting subgroup analyses.

1.4. Justification of this PhD

1.4.1. The dissertation premise

This PhD dissertation is grounded in a critical premise: non-pharmacological interventions aimed at reducing the transmission of microorganisms in hospital settings should be evaluated with methodological rigour comparable to that required for pharmacological interventions. This premise has direct implications for how we should conduct SRs, assess the certainty of evidence, and ultimately support evidence-based practice in infection prevention and control. The specific aims of this dissertation systematically address gaps in the current landscape of evidence synthesis for HAIs prevention interventions. This pretension has also been raised in other areas in which randomised controlled trials (RCTs) are also challenging, such as in quality improvement studies¹¹¹.

1.4.2. The need for sound evaluations of infection control interventions

Historically, infection control interventions have been implemented on the basis of medical and scientific rationale (biological plausibility), urgency, or tradition, often without the level of rigour expected for drug therapies^{2, 74, 112, 113}. Evaluation of infection control interventions is frequently based on uncontrolled study designs, as indicated by Alsaggaf *et al.*, who reported that 83% of quasi-experimental studies addressing infection control and antibiotic resistance lacked a control group¹¹⁴. Another review highlighted that the evidence is mostly based on pre/post studies¹¹⁵, a common design for quality improvement initiatives in health systems, but that is prone to a high risk of bias¹¹¹.

Consequently, most recommendations in infection control guidelines are based on evidence from descriptive studies, expert opinion and low-quality evidence¹¹⁶. This low or inconclusive evidence likely explains the heterogeneity of practices in hospital settings¹¹⁷, despite the system-wide implications of these measures for patients, healthcare workers, and health systems.

Furthermore, studies evaluating infection control interventions have frequently employed statistical methods that assume independence of infection or colonisation outcomes, such as the Chi-squared test¹¹⁸. However, this assumption is inappropriate in this context, as the outcome in one patient is often influenced by the status of other patients. Methods that ignore this correlation may produce misleading results and false conclusions. In particular, failing to account for correlation can lead to overestimation of precision and artificially narrow 95% CI^{113, 114, 118, 119}.

1.4.3. Infection control interventions are applied as bundles, but the evaluation of their individual interventions is still needed

Another factor that makes the evaluation of infection control interventions challenging is that they are complex interventions implemented as bundles^{120, 121}. The concept of care bundle was introduced in 2001 as “A small set of evidence-based interventions for a defined patient segment/population and care setting that, when implemented together, will result in significantly better outcomes than when implemented individually”¹²². This implies that infection control interventions are implemented as multimodal strategies that combine multiple evidence-based interventions, such as education, PPE, physical distance, hand hygiene and surveillance and feedback. When implemented collectively and reliably as a group, the bundle can improve patient outcomes¹²³.

The 2024 WHO guideline on COVID-19 infection prevention cautions against evaluating individual interventions from established care bundles, as this may overlook their synergistic effects¹²¹. Measures such as gloves, gowns and masks, and the decontamination of hospital environmental surfaces are designed to work as an integrated package; isolating components not only risks reduced effectiveness but may also raise ethical concerns, as withholding proven elements could endanger patients and staff. Evidence suggests that full adherence to all the components is essential to minimise infection risk. For instance, partial adherence to a surgical care bundle resulted in infection rates of 4.0%, compared to 0.3% with full adherence¹²⁴.

This PhD project acknowledges that evaluating the effects of specific infection control measures, that is, decontamination of hospital environmental surfaces, or the use of gloves, gowns or masks, on HAIs, should not be the only source of evidence to inform decisions about infection control interventions, particularly in complex healthcare settings with multiple transmission pathways^{125, 126}. Still, the PhD premise aligns with Ioannidis’s views, who considers that a rigorous evaluation of each intervention in the bundle offers valuable insights for practice¹²⁷. Therefore, we attempted to disentangle the effectiveness of these interventions.

First, it is essential to determine whether the individual components of an intervention bundle are evidence-based^{122, 127}. This standalone assessment can clarify the relative contribution of each component to overall infection control and inform evidence-based decision-making. Notably, a key function of RCTs is to disentangle the effects of multicomponent interventions, helping determine whether improved outcomes are attributable to the bundle as a whole or to specific elements within it¹²⁷.

Second, evaluating individual interventions lays the foundation for comparative effectiveness analyses among available infection control interventions. This, in turn, supports informed clinical decisions and can help reduce unnecessary variability in clinical practice¹²⁸. The determination of the role of a particular infection control intervention is relevant, as it allows the most effective and safe interventions to be identified, and provides evidence-based information to implement the minimum interventions needed to reduce transmission of micro-organisms in hospitals¹²⁹.

Third, given that implementing contact precautions and decontamination of surfaces often requires considerable resources¹³⁰, which may be limited in hospital settings, assessing the effectiveness of each component is critical for informing cost-effectiveness evaluations.

Fourth, considering the challenges healthcare professionals face in consistently adhering to infection control measures¹³¹, identifying the most effective ones is vital. This allows for the prioritisation of a minimal yet effective set of measures to prevent transmission.

Finally, the lower methodological standards often used to evaluate infection control interventions are avoidable. Rigorous study designs, such as cluster-randomised and stepped-wedge trials, are both feasible and increasingly used in this field^{132, 133}.

1.4.4. The general context in which this PhD project was developed

1.4.4.1. Patient safety as a strategic priority in Spain

At the outset of this PhD, patient safety was a core priority for health ministries and the WHO, as harm resulting from unsafe care undermines health outcomes, erodes public trust, and increases healthcare costs¹³⁴. In this context, the collaboration between the Spanish Ministry of Health and the Iberoamerican Cochrane Centre on patient safety was formalised through the National Health System Quality Plan and the Patient Safety Strategy. The Iberoamerican Cochrane Centre played a key role in patient safety by coordinating clinical practice guidelines¹³⁵, leading the bulletin of the Iberoamerican Group of Systematic Reviews on Patient Safety¹³⁴, and developing Cochrane reviews of interventions aimed at improving patient safety. These activities supported the Ministry in the production of evidence, the dissemination of SRs on patient safety, and training healthcare professionals in safe practices. The two SRs included in this PhD were funded under the framework of the National Health System Quality Plan.

1.4.4.2. Commitment to integrating sex and gender in health research

In recent years, there has been growing attention in Spain to the integration of sex and gender perspectives in health research. This shift has been largely driven by initiatives supported by the *Institute of Health Carlos III*, under the Ministry of Economy, Industry, and Competitiveness. One such initiative is the SEXCOMPLEX project—coordinated by Hospital Ramón y Cajal and funded by ISCIII—which specifically examined the influence of sex/gender differences and sex hormones on chronic diseases of complex aetiology.

At the time this PhD was initiated, only one study, conducted by Doull *et al.*, had assessed the incorporation of sex and gender in Cochrane reviews¹³⁶. Their analysis of a random sample of 38 reviews on cardiovascular health, published prior to April 2007, found that SGBA was largely absent. Thus, despite Cochrane's ongoing efforts, SGBA seemed to be insufficiently addressed in many published reviews, often confined to descriptive baseline characteristics rather than rigorous analytical approaches.

Study III of this PhD was developed within the framework of a SEXCOMPLEX work package focused on methodological standards in SRs. This study aligned with ISCIII and Cochrane's strategic objectives to promote equity in evidence synthesis, contributing to more informed decision-making and enhancing the relevance and applicability of evidence across diverse population groups.

1.4.4.3. The COVID-19 pandemic

The need for rigorous evaluation frameworks for infection control interventions has become essential, particularly since the COVID-19 pandemic. A notable example is the Cochrane review *Physical interventions to interrupt or reduce the spread of respiratory viruses*, which assessed the effectiveness of face masks and other measures to prevent respiratory virus transmission¹³⁷. The review received intense public attention, especially after the media framed its findings as evidence that “masks don't work”¹³⁸. In response, Cochrane issued a statement clarifying that this interpretation was misleading, noting that the review's findings were inconclusive: due to limitations in the primary studies, it could not determine whether mask-wearing reduces transmission risk.

The review's widespread uptake—reflected in a high *Altmetric* score placing it in the top 5% of all research outputs—underscores the importance of rigorous, transparent methods for evaluating infection control interventions. The surrounding debate illustrates how methodological weaknesses in the evidence base can lead to public misinterpretation with relevant health consequences.

The Cochrane reaction underscores an important point: evaluating non-pharmacological interventions using similar methodological frameworks to those applied to pharmacological interventions can guide transparent discussion of issues such as intervention adherence, intervention intensity, and what trials can realistically answer¹³⁸. Producing rigorous, up-to-date and transparent SRs of infection control interventions that assess the certainty of evidence using the *Grading of Recommendations Assessment, Development and Evaluation* (GRADE)¹⁴ approach is a critical step toward strengthening evidence-based practice in this field, including situations of public health emergencies, during which insufficiently evaluated infection-control measures can be adopted^{139, 140}.

2. Aim of the PhD project

2.1. General aim

The general aim of this thesis is to critically appraise and synthesise research evidence of non-pharmacological interventions intended to reduce the transmission of microorganisms within hospitals.

2.2. Specific aims and objectives

The specific aims and objectives of this thesis align with each of the studies included in the PhD project. See Table 1.

Although this PhD project consists of six distinct studies, it is designed as a single, integrated work. Beyond addressing specific research questions, the thesis aims to explore how evidence on non-pharmacological infection control interventions is generated, synthesised, and interpreted, with each study providing complementary methodological insights.

Table 1. Specific aims and objectives of the PhD project

Specific aims	PhD study	Specific objectives
Aim I. To assess the effects of hospital surface decontamination, through cleaning, disinfection, or both, on HAIs	Study I: Decontamination of environmental surfaces in hospitals to reduce HAIs: SR	I.1. To evaluate potential benefits I.2. To evaluate potential harms
Aim II. To assess the effects of wearing gloves, a gown or a mask when contact is anticipated with a hospitalised patient colonised or infected with MRSA or with the patient's immediate environment	Study II: Gloves, gowns and masks for reducing the transmission of MRSA in the hospital setting: SR	II.1. To evaluate potential benefits II.2. To evaluate potential harms
Aim III. To assess the consideration of sex and gender in Cochrane reviews of interventions for preventing HAIs	Study III: Consideration of sex and gender in Cochrane reviews of interventions for preventing HAIs: methodology study	III.1. To describe and assess the terminology and definitions used for sex and gender III.2. To determine the content of the reviews about sex and gender III.3. To describe the sex and gender based analysis implemented in the reviews III.4. To assess whether the review conclusions considered the sex- and gender-related findings
Aim IV. To assess the consideration of NRSIs in Cochrane reviews of interventions for preventing HAIs	Study IV: Consideration of NRSIs in Cochrane reviews of interventions for preventing HAIs: cross-sectional descriptive observational study	IV.1. To determine the number of Cochrane reviews of interventions to prevent HAIs admitting NRSIs IV.2. To describe and assess the justification provided for admitting NRSIs IV.3. To describe the study design labels used for NRSIs IV.4. To assess how the NRSIs were defined
Aim V. To identify methodological challenges in SRs of interventions aimed at reducing the transmission of microorganisms in the hospital setting	Study V: Methodological challenges in SRs of hospital infection control interventions: an integrative descriptive synthesis	To systematically identify and categorise methodological challenges in SRs of hospital infection control interventions, with particular attention to areas requiring further methodological research and development.
Aim VI. To formulate recommendations for the design of RCTs of interventions aimed at reducing the transmission of microorganisms in the hospital setting	Study VI: Design recommendations for RCTs of hospital infection control interventions: an integrative descriptive synthesis	To formulate study design recommendations that are broadly applicable to hospital infection control interventions, with specific emphasis on environmental surface decontamination and the use of gloves, gowns, and masks.
Abbreviations: HAIs: hospital-acquired infections. MRSA: Methicillin-resistant <i>Staphylococcus aureus</i> . NRSIs: non-randomised studies of interventions. RCTs: randomised controlled clinical trials. SRs: Systematic reviews		

3. Methods

This section outlines the rationale for each study of this thesis and its methods. Collectively, these studies address key gaps in the evaluation, synthesis, and reporting of non-pharmacological interventions for HAI prevention in SRs. Taken together, they position this dissertation as a comprehensive contribution to enhancing the methodological rigour, transparency, and equity of evidence synthesis in the field of infection control.

Studies I and II were both SRs conducted in accordance with Cochrane methodology as applicable at the time of manuscript submission. Study I adhered to the most recent version of the *Cochrane Handbook for Systematic Reviews of Interventions* (version 6.4, updated August 2024)¹⁴¹. Study II, published in 2015, followed the *Cochrane Handbook for Systematic Reviews of Interventions*, Version 5.1.0 (updated March 2011)¹⁴².

During the preparation of this work I used ChatGPT, Perplexity and Grammarly in order to improve language and readability. After using these tools, the author reviewed and edited the content as needed and takes full responsibility for the content of the publication.

The publications resulting from this thesis are listed in Annex 1.

3.1. Methods for study I: SR on decontamination

3.1.1. Justification of the study

Despite their widespread adoption, hospital surface decontamination faces challenges including inadequate cleaning, rapid re-contamination, unforeseen transmission risks, and poor hand hygiene after surface contact¹⁴³⁻¹⁴⁵. Evidence comparing decontamination strategies is limited, which may explain the heterogeneous practices across centres^{117, 146}. Moreover, reducing the surface microbial burden does not necessarily lead to fewer infections, leaving the clinical impact of decontamination uncertain¹²⁵. Finally, disinfectants can harm health and the environment, and promote antimicrobial resistance¹⁴⁷⁻¹⁴⁹.

Given the clinical and economic burdens of HAIs, there is an urgent need for effective, safe, and sustainable decontamination strategies, particularly in the post-COVID-19 era¹⁵. The SR aimed to assess the effects of hospital surface decontamination, through cleaning, disinfection, or both, on HAIs.

3.1.2. Study design

This SR follows a pre-published Cochrane protocol¹⁵⁰. Deviations from the protocol reflected updated SR methods (see Annex 2.1). We followed Cochrane¹⁴¹ and GRADE methods¹⁵¹ and the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) reporting guidelines¹⁵².

3.1.3. Criteria for considering studies for this review

3.1.3.1. Types of studies

This review included the following designs, irrespective of their publication status, language or statistical analysis.

- Parallel RCTs with individual (i-RCT) or cluster (cl-RCT) allocation
- Quasi-RCTs with allocation to interventions at the individual (i-QRCT) or group-level (cl-QRCT)
- Cross-over RCTs with individual (iXO-RCT) or cluster (CRXO-RCT) allocation with at least two intervention and control sites
- Stepped-wedge RCTs with individual (iSW-RCT) or cluster (SW-cl-RCT) allocation

We admitted CRXO-RCTs and SW-cl-RCTs with a cross-sectional, cohort or mixed design¹⁵³. The stepped-wedge RCT was eligible because it is increasingly used to evaluate patient safety interventions. This design is especially relevant when the intervention is expected to do more good than harm and/or when logistical, practical, or financial constraints prevent simultaneous delivery to all participants¹³³.

We considered explicit study design features—not just design labels—to define eligible study types and determine inclusion. See Table 2 below.

Table 2. Study designs features and labels for trials

Study design features	Study design labels							
	i-RCT	ci-RCT	i-QRCT	ci-QRCT	ixO-RCT	CRXO-RCT	iSW-RCT	SW-ci-RCT
Type of design	Parallel ^a				Cross-over ^b		Stepped-wedge ^c	
Allocation unit	Individual	Group	Individual	Group	Individual	Group	Individual	Group
Sequence generation method	Random ^d		Quasi-random ^e		Random ^d			
Allocation concealment	Not an inclusion criterion							
Type of design	Cohort ^f					Cohort ^f Cross-sectional ^g Mixed ^h	Cohort ^f	Cohort ^f Cross-sectional ^g Mixed ^h
Minimum number of clusters per arm	NA	>1 ⁱ	NA	>1 ⁱ	NA	Not an inclusion criteria	NA	Not an inclusion criteria
Wash-out period	NA				Not an inclusion criteria ^j			
Timing of baseline assessment & intervention allocation	Prospective							
Timing of outcome assessment	Prospective							
Analysis population (ITT / PP population)	Not an inclusion criteria							
Consideration of data correlation in the analysis	Not an inclusion criteria							

Abbreviations:

cl-RCT: cluster parallel RCT. **SW-cl-RCT:** stepped-wedge cluster RCT. **CRXO-RCT:** cluster cross-over RCT. **ITT:** intention-to-treat. **ixO-RCT:** individual cross-over RCT. **i-RCT:** individual parallel RCT. **iSW-RCT:** individual stepped-wedge RCT. **NA:** not applicable. **PP:** per-protocol. **RCT:** randomised controlled trial. **SW-cl-RCT:** stepped-wedge cluster RCT.

Footnotes:

^a **Parallel trial:** each unit was assigned to a single arm and received only one option (experimental or control) throughout the entire study period. ^b **Cross-over trial:** each unit was assigned to a single sequence to receive both the experimental and control interventions. ^c **Stepped-wedge trial:** each unit was assigned to a sequence, receiving the control intervention first, followed by the experimental intervention, with the sequence rolled out to all trial units over multiple periods. ^d **Random sequence generation:** allocation process which theoretically ensures that the intervention and the control group differ only in the exposure to the treatment. Examples: use of software for random number generation or coin flips. ^e **Quasi-random sequence generation:** allocation process that attempts but does not achieve true randomisation (e.g., alternation or week days). ^f **Cohort:** same set of participants is followed over time. ^g **Cross-sectional:** different set of participants measured at each new measurement. In a CRXO cross-sectional design, each cluster-period contains a cross-section of different individuals. A cluster-period is a grouping of observations by the time of measurement and cluster ¹⁵⁴. ^h **Mixed:** each cluster-period contains a repeated-cross-section of the same or different individuals. ⁱ In cluster-designs with only one intervention or control site, the intervention (or comparison) is confounded by the study site, making it challenging to attribute any observed differences to the intervention rather than to another site-specific variable ¹⁵⁵. ^j We included cross-over RCTs independently if they had a wash-out period.

3.1.3.2. Types of participants

We included studies involving any of the following participants irrespective of their age, sex, or gender identity (participant was defined as the person in whom the outcome is measured): a) Patients in the hospital: inpatients or outpatients of any age, sex and gender; b) Any other person who could be responsible for the transmission of microorganisms in hospitals: hospital staff (healthcare or non-healthcare professionals) or patients' carers or visitors.

We included studies considering the hospital setting, that is, an institution with an organised medical staff which provides medical care to patients¹⁵⁶. Hospital outpatient clinics were also eligible. We excluded other healthcare facilities, such as, ambulatory care facilities, rehabilitation centres, residential facilities or nursing homes. See definitions in glossary.

We excluded performance decontamination studies, that is, studies aiming to establish documented evidence that a decontamination process removes or inactivates pathogens from inanimate objects (*in-vitro* or *in-situ* studies not involving humans).

3.1.3.3. Types of interventions

Experimental intervention: decontamination of hospital environmental surfaces

Decontamination is a process that removes or destroys contamination so that infectious agents or other contaminants cannot reach a susceptible site in sufficient quantities to initiate infection or any other harmful response³⁹.

Eligible decontamination levels for this review were either cleaning alone or cleaning followed by disinfection. We admitted any decontamination method for hard surfaces, irrespective of type, technique, substance, concentration, area, timing, equipment, frequency or duration. Decontamination could be implemented as a routine activity or in response to increasing infection rates (e.g., during outbreaks).

Hospital environmental surfaces are those that generally do not come into direct contact with patients during care. They can be further divided into medical equipment surfaces, such as knobs on haemodialysis machines or instrument carts, and housekeeping surfaces, such as floors, walls, or computer keyboards^{39, 65}. Decontamination of carpeting (for example, by vacuuming or steam cleaning), curtains and bed screens was eligible.

Multi-component interventions were eligible only if decontamination was the primary component and co-interventions were balanced across groups: decontamination must be

the prominent component and the co-interventions similar across groups so that decontamination effects can be disentangled.

We excluded the following interventions.

- Sterilisation (as it is not used for decontaminating hospital environmental surfaces)
- Decontamination of instruments or devices that come into direct contact with patients during care, particularly non-critical, semi-critical, and critical items³⁹. Examples of 'non-critical' items are cuffs, stethoscopes, tourniquets, ophthalmoscopes or reflex hammers
- Decontamination of body surfaces (such as skin or prostheses), areas used for manipulating toxic substances (e.g., chemotherapy), and bedding or clothing
- Air decontamination (such as with ultraviolet air steriliser or laminar airflow systems)
- Antimicrobial treatment of textiles (e.g., clothing or bed linens)
- Water decontamination
- Monitoring environmental cleanliness, such as through microbiological testing or standardised checklists to assess adherence to cleaning procedures
- Education or training of cleaning staff
- Workforce factors, such as the externalisation of cleaning services
- Impact of placing single-use cleaning/disinfecting wipes

Control interventions

The comparator should consist of one of the following elements: a) No intervention or sham procedure for decontamination of environmental surfaces; b) Standard practice for decontamination of environmental surfaces; c) Any other active intervention for decontaminating hospital environmental surfaces; or d) Any infection control intervention which does not include decontamination of hospital environmental surfaces.

3.1.3.4. Types of outcome measures

If otherwise not stated, we considered outcomes measured in humans. Therefore, we excluded studies assessing surface contamination exclusively. We did not exclude studies solely on the basis of the reporting of the outcome data, since this might have introduced bias due to selective outcome reporting¹⁵⁷. See definitions in Table 3.

Table 3. Decontamination systematic review: outcomes definition

Review outcomes	Comments
Primary outcomes	
a. Outcomes measured in patients	
Hospital-acquired colonisation	- Colonisation is the presence of microorganisms (on skin, mucous membranes, in open wounds, or in excretions or secretions) that are not causing adverse clinical signs or symptoms. Hospital-acquired colonisation is a colonisation that was not present at the time of admission to the hospital¹. - We included colonisations only in studies reporting an existing screening policy at admission for the microorganism of interest. Without such a policy, colonisation data would likely be incomplete due to missed detection of asymptomatic carriers⁷⁴. - We admitted studies evaluating the effects of decontamination on colonisation by a target microorganism, such as MRSA, since routine practice typically focuses on specific microorganisms.
HAI	- Infection acquired in the hospital as a result of the delivery of healthcare. Therefore, it was not present or incubating at the time of admission to the healthcare facility. For most bacterial infections, this means that the infection usually becomes evident 48 hours (the typical incubation period) or more after admission. However, because the incubation period varies with the type of pathogen and, to some extent, with the patient's underlying condition, each infection must be assessed individually¹. - We excluded HAIs focused on a specific microorganism (e.g., MRSA) or specific infections (e.g., pneumonia), except for bloodstream infections (BSIs). Decontamination is a horizontal intervention that can prevent infections from multiple organisms¹⁵⁸. Classifying it as a vertical intervention (targeting specific pathogens) may misrepresent its broader effects. - We excluded composite outcomes combining infections from different target organisms (e.g., MRSA, VRE, or both) or mixed endpoints (e.g., 'colonisation, infection, or both'), as these combine biologically distinct outcomes and are not informative¹⁵⁹.
Adverse effects in patients	As considered by the study investigators to be related to the decontamination process
b. Outcomes measured in hospital staff, patients' caregivers or visitors	
HAI in staff	HAI in any staff working in the hospital setting (healthcare professionals or not)
HAI in carers or visitors	
Adverse effects on staff	As considered by the study investigators to be related to the decontamination process
Adverse effects on carers or visitors	As considered by the study investigators to be related to the decontamination process
Secondary outcomes	
BSI	- Presence of live pathogens in the blood, causing an infection¹⁶⁰ - BSIs could be of any origin, such as primary or secondary to a catheter
All-cause mortality	
HAI-related mortality	
Length of hospital stay	
Resistance to antibiotics	Proportion or rate of isolates of a specific pathogen resistant to a specified antibiotic
Resistance to disinfectants	Proportion or rate of isolates of a specific pathogen resistant to a specified disinfectant
Abbreviations: BSI: bloodstream infection. HAI: hospital-acquired infection. MRSA: methicillin-resistant <i>Staphylococcus aureus</i> . VRE: vancomycin-resistant <i>Enterococci</i> .	

We accepted any definitions of HAIs and colonisation used by the study authors, as standardised definitions may not have been available at the time of publication⁴. For example, definitions based exclusively on temporal categorisation ('hospital-onset infections') were admitted, as well as those considering the patient's clinical history ('nosocomial infections').

We also accepted any metric for measuring healthcare-associated acquisition, including incidence (dichotomous data) and incidence density rate (rate data), and any follow-up period after the intervention began. When multiple follow-ups were reported, we planned to select the longest.

3.1.4. Search methods for identification of studies

See full search strategies in Annex 2.2.

3.1.4.1. Electronic searches

Information specialists searched MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL, ProQuest Dissertations & Theses Global until February 24, 2025, Web of Science (March 3, 2025), the British Nursing Index and Archive via ProQuest (February 29, 2012), and OpenGrey (December 10, 2020). No language, date, or setting restrictions were applied. We searched ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) for ongoing or unpublished studies (March 3, 2025).

3.1.4.2. Searching other resources

We screened reference lists of the included studies, relevant reviews, and conference proceedings (2008–2024). We contacted the authors of key papers for additional studies. We tracked included studies and relevant reviews in the ISI Science Citation Index. Retraction and errata were checked on article pages and in PubPeer and Retraction Watch. No separate searches for adverse effects were performed.

3.1.5. Selection of studies

We removed duplicates in EndNote¹⁶¹ and imported unique records into Covidence¹⁶² for further deduplication and screening. Two reviewers (JL-A and MM-M, AEG-V, LOC, EJT, or SCN) independently screened titles/abstracts and full texts, resolving disagreements by consensus or a third reviewer (IS or LOC). Trialists were contacted to clarify eligibility. For the excluded full texts, we recorded the main exclusion reason. We collated multiple reports of the same included study; the most complete and recent report was the primary reference and the main source for data extraction. We completed a PRISMA flow chart

and a table of characteristics of excluded studies. We were not blinded to the authors' names of the publications, or their institutions, journals or results during the selection process.

3.1.6. Data extraction and management

We prepared a data extraction form based on methodological and relevant reporting guidelines^{113, 163-167}. We piloted the form for usability. We used EPPI-Reviewer¹⁶⁸ to extract data from each included study on the following characteristics: study design features¹⁶⁹, conflict of interests, sample size estimations, optimal information sizes, observed sample sizes, participants, setting, intervention and control, co-interventions, outcomes¹⁷⁰, risk of bias, and results. We populated a characteristics of included studies table, which summarises the characteristics of each included study providing outcome data per review comparison.

One reviewer extracted data (JL-A), and another checked it (SCN, MM-M, ES, EJT or GV). We resolved discrepancies by consensus or a third reviewer (IS or GV). We contacted authors for clarification of missing or unclear information, checked for retractions or errata, verified numeric accuracy, and attempted to convert composite outcomes into eligible non-composite outcomes.

3.1.7. Assessment of risk of bias in included studies

JLA and another person (GV or SCN) independently evaluated each study's risk of bias using the Cochrane RoB 2 tools for individually-allocated, parallel-group RCTs and cluster RCTs^{171, 172}. We resolved disagreements by consensus and by consulting a third review author (IS or GV), if necessary. We obtained the information from the reports and contacted the authors for clarification. If we did not clarify the issue, we decided based on the available information.

RoB 2 allows assessment from two perspectives: (1) the effect of assignment to interventions at baseline, regardless of adherence ("intention-to-treat effect"), and (2) the effect of adherence to interventions ("per-protocol effect"). We assessed benefits using the intention-to-treat effect and harms using the per-protocol effect. When study data were re-analysed, the risk of bias assessment was applied to the re-analysed results.

To assess attrition bias, we estimated pessimistic and optimistic scenarios for missing participant data to challenge the primary analysis^{173, 174}. We avoided the best- and worst-case scenarios as they are not plausible. Although blinding can be challenging for non-pharmacological interventions¹⁷⁵, we assessed the risk of bias due to lack of blinding. We

did not assess unit-of-analysis errors or conflicts of interest as part of the risk of bias evaluation.

In addition to the standard RoB 2 domains, we assessed review-specific methodological aspects: seasonality, contamination, and carry-over effects.

Seasonality (seasonal bias) was considered under the risk of bias domain *imbalances in baseline characteristics*. It can confound observed intervention effects; for example, increased winter admissions of elderly patients may lead to higher MRSA cases unrelated to the intervention^{74, 113}.

Contamination was assessed under the domain *deviations from intended interventions*. It occurs when the intervention is unintentionally delivered to control participants or vice versa, diluting group differences and biasing results toward the null¹⁷². We judged contamination risk as high when cleaning areas were not clearly separated, especially in individually randomised trials, but not in cluster trials.

Carry-over effects were assessed in cluster randomised crossover trials (CRXO-RCTs) with a cross-sectional design under *deviations from intended interventions*. Although the potential for carry-over is more limited in CRXO-RCTs than in CRXO longitudinal designs, it may still be present due to the microorganisms' survival on environmental surfaces. We defined a minimum wash-out period of seven days to prevent the carry-over effect.

3.1.7.1. Overall assessment of the risk of bias and incorporation into analyses

For each effect estimate and domain, we rated the 'signalling questions' to determine a **low**, **some concerns**, or **high risk of bias**, using the algorithms in the RoB 2 Excel tools^{171, 172}. We considered all RoB 2 domains as key and included them in the overall assessment. Thus, if any domain was judged at high risk of bias, the effect estimate was classified as high risk of bias.

We summarised the RoB for each effect estimate in two different ways: within each study and across studies to assess the certainty of the evidence¹⁷⁶. We planned to explore the impact of the risk of bias by sensitivity analyses, but we were unable to do so due to the insufficient number of included studies. See details in Table 4.

Table 4. Interpretation of risk of bias

Risk of bias	Interpretation	Risk of bias for each effect estimate	
		Within study across domains	Across studies
Low	Plausible bias unlikely to seriously alter the results	Low risk of bias for all key domains	Most information is from studies at low risk of bias
Some concerns	Plausible bias that raises some doubt about the results	Some concerns of risk of bias for at least one key domain (and no domain rated as high risk)	Most information is from studies at low risk of bias or with some concerns
High	Plausible bias that seriously weakens confidence in the results	High risk of bias for at least one key domain or some concerns for multiple domains in a way that substantially lowers confidence in the result	The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of results

We describe our risk of bias assessments in the results section. We used the risk of bias assessment across studies for each effect estimate as part of our determination of the certainty of the evidence using the GRADE system. We planned to note the level of risk of bias in the review text, the forest plots, figures, and the summary of findings tables. We planned to meta-analyse studies regardless of their risk of bias ratings.

3.1.8. Measures of treatment effect

We present results as risk ratios (RRs), odds ratios (ORs), incidence rate ratios (IRRs) or mean differences (MDs) with their 95% CIs, calculated using RevMan Web¹⁷⁷ or OpenEpi¹⁷⁸. We report both the relative and absolute effects. Absolute effects per 1,000 patients or per 1,000 patient-days were calculated using GRADEpro¹⁷⁹ or MS Excel¹⁸⁰

Following recent GRADE guidance¹⁸¹⁻¹⁸³, we interpreted the absolute effect estimates using predefined thresholds and different baseline scenarios (populations with low, moderate, and high basal risks).

3.1.8.1. Process to calculate absolute effects

First step: definition of assumed controls

We assumed controls for three scenarios (low, moderate, and high risk) for each effect estimate using either external peer-reviewed sources or control group data from the included studies. The absolute difference, its magnitude and its precision, were calculated and judged solely based on the moderate-risk scenario.

We considered the thresholds independently of the comparator used; that is, we applied them to comparisons involving either an inactive or an active comparator. This decision

was based on the understanding that, in infection control, it is not plausible to assume the comparator would be inactive. Typically, at least routine practice is applied.

Second step: approach used to define the thresholds for the absolute effects

To our knowledge, no accepted thresholds exist for our review outcomes, particularly for HAIs or colonisations. Their absence likely reflects that the importance of an effect depends on context, including infection type, baseline risk, patient mix, severity, and resource implications. We implemented the following process to define the thresholds.

HAIs and colonisations (dichotomous data)

First, we set equal thresholds for the absolute risk difference (ARD) for HAIs and BSIs.

Second, we extrapolated the ARD in HAIs to hospital-acquired colonisations by assuming that 22% of colonised patients develop an infection. This estimate was taken from a recent umbrella review on multidrug-resistant gram-negative bacteria, which reported a pooled incidence of infection after colonisation of 22%¹⁸⁴. We recognise that this is a pragmatic assumption and that the risk can vary by setting (ICU versus general ward), patient mix, follow-up duration, and surveillance intensity or site.

HAIs and colonisations (rate data)

For HAIs, we obtained thresholds for absolute rate differences (ARaD) per 1,000 patient-days by converting the ARD threshold (infections prevented per 1,000 patients) to an ARaD threshold (infections prevented per 1,000 patient-days). We divided the ARD by the average (LOS, in days): $ARaD = ARD / LOS$, that is $LOS = 8$ days, based on the reported European mean of 8.1 days⁹. This calculation assumes a near-constant infection risk over time and similar LOS across groups. Caution is warranted, as HAI risk often increases with longer stays and interventions may themselves affect LOS. As in some contexts the LOS may be lower, we decided to make the conversion based on a LOS of 5 days.

For hospital-acquired colonisations, we extrapolated the ARaD thresholds for HAIs to hospital-acquired colonisations by assuming that 22% of colonised patients develop an infection (see above).

Third step: Calculation of the absolute difference from the assumed control on the moderate-risk scenario

Dichotomous data

We computed ARDs per 1,000 patients using the GRADEpro calculator¹⁷⁹. GRADEpro derives the absolute effect by applying the relative effect (RR or OR) to the ACR to obtain the intervention risk. ORs are first converted to RRs using the ACR. The ARD per 1,000 is calculated as the difference between the intervention and control risks, multiplied by 1,000. The 95% CI is obtained by applying the same transformation to the confidence limits of the relative effect.

- ARD central effect estimate: $ACR * (RR - 1) * 1,000$
- ARD Lower CI limit: $ACR * (Lower\ limit\ RR - 1) * 1,000$
- ARD Upper CI limit: $ACR * (Upper\ limit\ RR - 1) * 1,000$

Incidence rate data

We calculated ARaDs externally as GRADEpro does not compute them. We expressed rates as cases per 1,000 patient-days. The central estimate of the ARD was obtained by subtracting the rate in the control group from the rate in the intervention group. The 95% CI was derived by applying the confidence limits of the rate ratio to the control rate:

- ARaD central effect estimate: $ACRa * (Relative\ rate - 1)$
- ARaD Lower CI limit: $ACRa * (Lower\ limit\ Relative\ Rate - 1)$
- ARaD Upper CI limit: $ACRa * (Upper\ limit\ Relative\ Rate - 1)$

3.1.8.2. Definition of thresholds to judge the magnitude of absolute effects

We used a pragmatic approach to define thresholds for the outcomes with data included in our review. We tried to anchor these thresholds to peer-reviewed data, as we found no universally accepted thresholds, particularly for HAIs or colonisations.

We defined thresholds for ARaD per 1,000 patient-days by converting the absolute risk reduction thresholds (infections prevented per 1,000 patients) into an ARaD (infections prevented per 1,000 patient-days). This was done by dividing the absolute risk reduction by the average LOS (in days): $IRD = ARR / LOS$. We used a LOS of 8 days, based on the reported European mean of 8.1 days⁹. This calculation assumes a near-constant infection risk over time and similar LOS across groups. Caution is warranted, as HAI risk often increases with longer stays and interventions may themselves affect LOS. See Table 5.

Table 5. Thresholds to determine the magnitude of the absolute effect

Outcome	Context	Basal scenarios %; cases per 1,000 patient-days	Thresholds for absolute difference in the moderate basal scenario:			
			Trivial or no effect	Small effect	Moderate	Large
Hospital-acquired colonisations (MRSA)	ICU	Low: 50‰ ^a				
		Moderate: 150‰ ^a High: 300‰ ^a	< 23‰ ^b	23‰ ^b	45‰ ^b	91‰ ^b
Hospital-acquired colonisations (VRE)	Ward	Low: 6 cases ^c				
		Moderate: 18 cases ^c High: 30 cases ^c	< 5 cases ^b	5 cases ^b	9 cases ^b	18 cases ^b
Hospital-acquired colonisations (C. difficile)	Ward	Low: 2 cases ⁴				
		Moderate: 10 cases ^d High: 20 cases ^d	< 5 cases ^b	5 cases ^b	9 cases ^b	18 cases ^b
Hospital-acquired infections	ICU	Low: 80‰ ^e				
		Moderate: 240‰ ^e High: 480‰ ^e	< 5‰	5‰	10‰	20‰
	Ward	Low: 20‰ ^f ; 13 cases ^g				
		Moderate: 40‰ ^f ; 17 cases ^g High: 120‰ ^f ; 42 cases ^g	< 5‰	5‰	10‰	20‰
Bloodstream infections	ICU	Low: 40‰ ⁱ				
		Moderate: 80‰ ⁱ High: 240‰ ⁱ	< 5‰	5‰	10‰	20‰
	Ward	Low: 2‰ ^j				
		Moderate: 4.4‰ ^j High: 13‰ ^j	< 5‰	5‰	10‰	20‰
All-cause mortality	ICU	Low: 80‰ ^k				
		Moderate: 150‰ ^k High: 300‰ ^k	< 2‰	2‰	5‰	10‰
Length of hospital stay	ICU	Low: 3 days ^l				
		Moderate: 5 days ^l High: 10 days ^l	1 day	1 day	2 days	3 days
Adverse effects in patients	Any	Low: 16‰ ^m				
		Moderate: 33‰ ^m High: 100‰ ^m	5‰	5‰	10‰	20‰
Adverse effects in staff	Any	Low: 50‰ ⁿ				
		Moderate: 100‰ ⁿ High: 300‰ ⁿ	5‰	5‰	10‰	20‰

Abbreviations:

ACR: assumed control risk; **ARD:** absolute risk difference; **C. difficile:** *Clostridium difficile*; **CI:** confidence interval; **ICU:** intensive care unit; **IRD:** incidence rate difference; **LOS:** length of hospital stay; **MRSA:** Methicillin-Resistant *Staphylococcus aureus*; **OR:** odds ratio; **RR:** relative risk; **VRE:** Vancomycin-Resistant *Enterococcus*.

Footnotes:

^a Control risk scenario for hospital-acquired colonisations (MRSA) scenario: estimates from Bloemendaal *et al.*¹⁸⁵ and Kalligeros *et al.*¹⁸⁶.

^b We extrapolated the absolute difference in hospital-acquired infections to hospital-acquired colonisations by assuming that 22% of colonised patients develop an infection. This estimate was taken from an umbrella review on multidrug-resistant gram-negative bacteria, which reported a pooled incidence of infection after colonisation of 22%¹⁸⁴. We recognise that this is a pragmatic assumption and that the risk can vary by setting (ICU versus general ward), patient mix, follow-up duration, and surveillance intensity or site.

^c Control incidence rate scenario for hospital-acquired colonisations (VRE): low-risk baseline scenario derived from the control group in Rock *et al.*¹⁸⁷. Moderate- and high-risk scenarios were extrapolated by multiplying this baseline by three and five, respectively.

^d Control incidence rate scenario for hospital-acquired colonisations (*C. difficile*) scenario: low-risk baseline scenario derived from the control group in Rock *et al.*¹⁸⁷. Moderate- and high-risk scenarios were extrapolated by multiplying this baseline by five and ten, respectively.

^e Control risk scenario for HAIs at the ICU: 20.5% of patients admitted to ICUs in the EU had at least one HAI⁹. We considered 8%, present in countries like Ireland, as a low-risk scenario. The pooled global worldwide HAI incidence in ICUs was 34.7 per 100 patients (95% CI: 23.6–47.7%)¹⁸⁸. Data from low-resource countries were limited. We defined moderate- and high-risk ICU scenarios using the lower and upper bounds of the 95% CI.

^f Control risk scenario for HAIs at the hospital ward: we defined the moderate- and high-risk scenarios using the lower and upper bounds of the 95% CI, respectively. The country-weighted EU/EEA incidence estimate of HAIs was 6.5% (95% CI 4.7–8.7%), ranging from 2.1% (Norway) to 8.9% (Portugal)⁹. We considered a 2% incidence a low-risk scenario representative of high-resource settings. In developing countries, the pooled incidence of overall HAIs was 7.4 per 100 patients (95% CI: 4.4–12.2%)¹⁸⁸.

^g Control incidence rate scenario for HAIs at the hospital ward: we defined 13; 17; and 42 cases per 1,000 patient-days as representative low-, moderate-, and high-risk scenarios, respectively. HAI incidence density was 17.0 per 1,000 patient-days (95% CI, 14.2–19.8) in high-income countries and 42.7 per 1,000 patient-days (95% CI, 34.8–50.5) in low- and middle-income countries³.

^h We derived thresholds for absolute incidence rate differences by converting absolute risk reductions (cases prevented per 1,000 patients) into cases prevented per 1,000 patient-days, dividing the incidence rate by the average EU length of stay (8 days)⁹. We used absolute risk thresholds of small (5 cases), moderate (10 cases), and large (20 cases) per 1,000 patients. Accordingly, we considered ≥5 cases per 1,000 patients the minimal important difference.

ⁱ Control risk scenario for BSIs at the ICU: 3.7% of ICU patients staying more than two days developed at least one BSI (pooled incidence from 14 European countries, excluding Germany)¹⁸⁹. We considered a 3% incidence a low-risk scenario, representative of high-resource settings. Moderate- and high-risk scenarios were defined as 2 and 6 times the low-risk level, respectively.

^j Control risk scenario for BSIs at the ward: BSIs represent 10.8% of all HAIs in Europe (EU and EEA)¹⁹⁰. We applied this proportion to the incidence of HAIs.

^k Control risk scenario for mortality at the ICU: ICU mortality in European countries ranged from 8.5% (Luxembourg) to 25.3% (Slovakia)¹⁸⁹. We used this range to define the low-, moderate-, and high-risk mortality scenarios.

^l Control risk scenario for LOS: three different scenarios suggested by the median LOS and its interquartile range described in a cohort study¹⁹¹: median: 5 days; Q1: 3 days; Q3: 10 days.

^m Control risk scenario for AEs in patients: we found no evidence on the risk of AEs in patients related to cleaning and decontamination. We assumed the patient risk to be one-third that of the staff AE risk.

ⁿ Control risk scenario for AEs in staff: we defined baseline risk scenarios based on Delclos *et al.*¹⁹². Reported asthma prevalence was 4.2% among physicians, 7.3% among nurses, 5.6% among respiratory therapists, and 4.5% among occupational therapists. Overall weighted prevalences were 6.6% for asthma and 27.2% for bronchial hyperresponsiveness symptoms.

3.1.9. Unit-of-analysis issues

We looked and tried to correct for 'unit of analysis errors' (UAEs) in the following circumstances.

3.1.9.1. Statistical approaches for infection or colonisation outcomes

We examined the statistical methods used to analyse infection and colonisation outcomes. In communicable outcomes, a patient's risk of colonisation or infection depends on the status of other patients. Thus, assuming data independence (e.g., using a Chi² test or linear regression) can underestimate variability and overstate precision. Therefore, methods that account for data correlation, such as those appropriate for HAls, should be used^{113, 118, 119}.

We assessed the statistical approaches applied in the included studies but could not re-analyse the data due to the lack of individual-level information.

3.1.9.2. Parallel cluster-allocated designs

Parallel cluster-RCTs that allocate clusters (e.g., wards) but do not account for clustering in the analysis may have UAEs, leading to artificially extreme P values and overly narrow 95% CI¹⁹³. We planned to consider analyses in parallel cluster-RCTs free of UAEs if they were conducted at the cluster or, if conducted at the individual level with appropriate statistical adjustment for clustering. For analyses in cluster-RCTs with UAEs, we planned to perform an 'approximately correct analysis'. If this was not possible, we would have reported only the point estimate, without P values, 95% CIs, or inclusion in the meta-analysis¹⁹⁴. Our review did not include any parallel cluster-RCTs, so no corrections for UAEs were needed in these cases.

3.1.9.3. Cluster cross-over designs

Analyses in CRXO designs should account for both the within-cluster within-period correlation (WPC) and the within-cluster between-period correlation (BPC). We acknowledge that there is limited methodological research on CRXO analyses^{153, 195}, but we attempted to perform an 'approximately correct analysis' to correct this UAE. We multiplied the standard error (SE) of the effect estimate with the UAE by the square root of the design effect (DE)¹⁹⁵. $DE = [1 + (M - 1) \times WPC] - (M \times BPC)$, being M the average cluster size. When WPC and BPC values were unavailable, we used estimates from similar studies (see Table 6).

Table 6. Correlation coefficients

Review outcome with data	Reported in the study?		Review coefficients (source)		Effect _{UAE}	Effect _{AA}
	WPC	BPC	WPC	BPC		
Hospital-associated colonisations	No	No	Not used	Not used	NA	NA
HAIs	No	No	0.19 ¹⁹⁶	0.152 *	RR 1.12 (0.94 to 1.35) ¹⁹⁷ RaR 1.10 (0.94, 1.29) ¹⁹⁸	RR 1.13 (0.57 to 2.24) ¹⁹⁷ RaR 1.10 (0.48, 2.51) ¹⁹⁸
Adverse effects on patients	No	No	0.19 ¹⁹⁶	0.152 *	NA	NA
Adverse effects on staff	No	No	0.19 ¹⁹⁶	0.152 *	NA	NA
Bloodstream infections	No	No	0.19 ¹⁹⁶	0.152 *	NA	NA
All-cause mortality	No	No	0.010 ¹⁹⁵	0.007 ¹⁹⁵	NA	NA
Length of hospital stay	No	No	0.038 ¹⁹⁵	0.032 ¹⁹⁵	NA	NA

Abbreviations:

* Estimated by the reviewers

BPC: within-cluster between-period correlation. **BSI:** bloodstream infection. **Effect_{AA}:** effect estimate with approximate analysis. **Effect_{UAE}:** effect estimate with UAE. **HAI:** hospital-acquired infection. **RaR:** Rate ratio. **RR:** Relative Risk. **WPC:** within-cluster within-period correlation.

Assumptions:

- Over short periods, or in clusters with stable environments and patient characteristics, changes over time are likely to be small, resulting in similar WPC and BPC values. However, if this assumption is incorrect and BPC is lower than WPC, calculating the sample size under the assumption of equal correlations will result in an underpowered study¹⁹⁵. Thus, we assumed BPC to be lower than WPC, specifically setting BPC at 80% of WPC¹⁹⁹.
- We assumed that the correlations' estimates would be similar in the ICU, operating room and the hospital ward.
- For healthcare-associated colonisations, HAIs, BSIs and adverse effects, we considered WPC=0.19 and BPC=0.152 (0.8 x WPC)¹⁹⁹.
- For all-cause mortality and LOS, we planned to use the WPC and BPC as provided in Arnup 2017¹⁵³, which were estimated from the Australia and New Zealand Intensive Care Society – Adult Patient Database (ANZICS-APD)¹⁹⁵.
- We found the following intracluster correlation coefficients (ICCs): 30-day surgical site infection rate: 0.005²⁰⁰; glove and gown contamination in MDRAB rooms: 0.19¹⁹⁶; glove and gown contamination in MRSA rooms: 0.06¹⁹⁶; and prevalence of antibiotic resistance: 0.01²⁰¹.

CRXO trials may have additional UAEs when there is no wash-out period. We did not re-analyse these trials and used the reported effect estimates because all included CRXO-RCTs were cross-sectional. In this design, each cluster-period groups observations by time and cluster, with each cluster-period including different participants¹⁵⁴. Thus, we considered that the absence of a wash-out period was likely less relevant. We also considered this UAE conservative, as it tends to bias results toward the null, making its impact less concerning.

3.1.9.4. Outcome of interest is an event that may re-occur in the same participant

If the outcome of interest could re-occur (e.g., HAIs), we assessed whether count data were incorrectly analysed as dichotomous²⁰². If such a UAE was identified, we planned to reanalyse the data.

3.1.9.5. Handling multi-arm trials

We planned to follow the *Cochrane Handbook* to avoid UAEs in meta-analyses of multi-arm studies, ensuring that the same group of participants was not included more than once in the same analysis²⁰². Our approach was as follows: first, we identified the study arms relevant to our review; second, we selected pairs of interventions and included each pair in the appropriate comparison. If more than two arms from the same study were relevant to a single analysis—which did not occur in this review—we planned to combine compatible arms into one group to avoid duplication.

3.1.9.6. Repeated observations on participants

In long-term studies, results are often reported at multiple follow-up points (e.g., 6 months, 1 year, 2 years). Including more than one time point per study in a standard meta-analysis can cause a unit-of-analysis error²⁰². This was not an issue in our review, as the studies reported effect measures that combined all time points, such as incidence rates.

3.1.10. Dealing with missing data

We assessed missing participant data (MPD) to judge the risk of attrition bias for each effect estimate. See definitions in Table 7.

For efficacy outcomes, our primary analysis strategy was the available-case analysis (ACA) of the intention-to-treat (ITT) population²⁰³. We planned to re-include the exclusions made by the authors²⁰⁴. When the ITT principle was not possible, we planned to use the per-protocol (PP) instead of the 'as treated' analysis. **For adverse effects**, the ACA analysis of the PP population was our first choice as the ITT population may be inappropriate: it is wrong to attribute harm to a treatment that somebody did not receive. Besides, ITT analysis tends to bias the results towards no difference^{171, 203}.

If relevant summary data were missing (e.g., standard deviation (sd)), we planned to calculate them from the statistics of other reports. If this was not possible, we contacted the primary authors or imputed the data¹⁷¹. We did not exclude studies with a high risk of attrition bias from the analyses. However, we planned to evaluate the impact of this decision by sensitivity analysis^{173, 174}.

Table 7. Concepts related to missing data

Concept	Definition
Missing participant data (MPD)	Outcome data of a participant trial that is not available for the review authors and, thus, cannot be analysed for a review effect estimate^{173, 174, 205}. MPD is specific to each effect estimate.
Available-case analysis (ACA)	- Analysis strategy that excludes participants with MPD. This analysis includes data on only those whose results are known, using as a denominator the total number of people who had data recorded for the particular outcome in question²⁰³. - ACA may be biased depending on the missing data mechanism and the amount of MPD. - Sometimes called complete case analysis (CCA) or 'modified intention-to-treat' (mITT) analysis.
As treated analysis (ATA)	Analysis strategy in which participants are analysed according to the intervention they actually received, even if their randomised allocation was to a different treatment group²⁰⁶.
Intention-to-treat (ITT) analysis	- Analysis strategy that meets the following principles^{171, 203 206, 207}: a) To analyse participants in the intervention groups to which they were randomised, regardless of the intervention they received, the interventions were implemented as intended, and the adherence to the intervention; b) To include all randomised participants in the analysis; and c) To measure outcome data on all participants. Thus, all randomised participants must be included in the analysis, and analysed in the arm to which they were allocated^{206, 208}. - Advantages of ITT analysis: a) allows determining the effect of the assignment to the intervention; b) ensures that the benefits of randomisation (similar groups concerning measured and unmeasured prognostic factors) are maintained¹⁷¹.
Modified intention-to-treat' (mITT) analysis	- The phrase mITT is used in different ways²⁰⁹. - Our use of the term refers to missing data rather than to adherence to the intervention. - It may also refer to an analysis that excludes participants who did not receive a specified minimum amount of the intended intervention.
Per-protocol (PP) analysis	Analysis strategy that excludes participants who did not receive the intended intervention in accordance with the protocol¹⁷¹.
Naïve PP analysis	Analysis strategy that is restricted to individuals who adhered to their assigned interventions²⁰⁶.

3.1.11. Data synthesis

3.1.11.1. Definition of review comparisons

Based on a preliminary, non-systematic overview conducted before data extraction, we classified the evaluated aspects of decontamination in the included studies using categories adapted from the 'WASTE' scheme¹²⁸: Workforce, Area, Substance, Technique, and Equipment. Our SR did not assess the effect of the workforce involved in decontamination. Two additional factors were added: frequency and timing of decontamination. See below Table 8.

3.1.11.2. Meta-analysis

Study characteristics were summarised in tables and a narrative synthesis, with descriptive statistics generated in MS Excel. Because few studies were available providing data for each review outcome, we could not perform meta-analyses, assess heterogeneity or publication bias, or perform subgroup or sensitivity analyses.

3.1.11.3. Assessment of the certainty of the evidence

We followed GRADE¹⁵¹ to assess the certainty of a body of evidence for each outcome effect estimate. Two review authors (JLA and GV) assessed the certainty of the evidence. The initially high-certainty RCT evidence was downgraded based on risk of bias, inconsistency, indirectness, imprecision, and risk of publication bias. For judging imprecision, we assessed the compatibility of the 95% CI of the absolute risk difference (ARD) in the moderate risk scenario with predefined thresholds (see above 3.1.8. Measures of treatment effect)¹⁸¹⁻¹⁸³. We communicated the findings following GRADE wording²¹⁰.

We used GRADEpro GDT¹⁷⁹ to create 'Summary of findings' tables for comparisons with data for at least one critical outcome. Relative and absolute effects (and the 95% CI) for each outcome in three basal risk scenarios are presented to reflect the substantial outcome variability across countries and regions.

Table 8. Aspects on decontamination interventions

Technique ^a	Substance ^b	Area		Timing	Equipment ^c	Frequency	Duration
		Level of contamination	Patients' infection status				
Manual decontamination^d	Detergents (cleaning)^e	Non-targeted decontamination	Non-targeted decontamination	Daily decontamination ^f	Standard mop or cloth (cotton)	Standard frequency	
	Manual disinfectants: 1. <i>Surface-active agents (surfactants):</i> • QACS • QAC plus alcohol. • 3-aminopropyl dodecylamine 2. <i>Halogen-releasing agents:</i> • Sodium hypochlorite (bleach) • Chlorine dioxide iodine and iodophor disinfectants • Sodium dichloroisocyanurate • Chlorine-releasing agents 3. <i>Alcohols:</i> • Ethyl alcohol • Isopropyl alcohol-propanol. 4. <i>Oxidisers: PA, HP, IHP, PA, HP</i> 5. <i>Phenolics: phenol</i> 6. <i>Electrolysed water</i> 7. <i>Probiotic disinfectants</i> 8. <i>Disinfectants with phages</i> 9. <i>Copper-based biocidal disinfectants</i> 10. <i>Silver-based biocidal disinfectants</i>	Enhanced decontamination targeting 'high-touch' surfaces	Enhanced decontamination targeting rooms with colonised or infected patients (e.g., rooms of patients with MDRO)	Terminal decontamination ^g	New materials for applying liquid disinfectants ^{211, 212} : • Microfiber • Ultramicrofiber	Same liquid decontamination strategy but with increased number of times	
No-touch decontamination^h	No-touch disinfectants (automated disinfectants): 1. <i>UV light-emitting devices</i> • UV-C radiation: mercury bulbs to produce UV light (normally used for terminal room decontamination) • PX-UV: doesn't use mercury bulbs to produce UV light (normally used for terminal room decontamination) • Handheld UV devices (normally used for spot surface decontamination) 2. <i>HP systems</i> • HPV (30–35% aqueous H ₂ O ₂): normally used for terminal room decontamination • Aerosolised HP systems: pressure-generated aerosol 3–7% H ₂ O ₂ with or without silver ions: normally used for terminal room decontamination • Low dose continuous HP (continuous room decontamination)				Machine for no-touch decontamination		

3. *HINS-light (continuous room decontamination)*
4. *Steam cleaning (spot surface decontamination)*
5. *Chlorine dioxide*
6. *Ozone*
7. *Cold atmospheric pressure plasma*

Antimicrobial surfacesⁱ	1. Surfaces with a heavy metal: copper, silver, zinc 2. Surfaces with a germicide: triclosan, QACs, bacteriophages. 3. Surfaces with cationic nanoparticles 4. Surfaces with light-activated antimicrobial coatings: titanium oxide, polyethylene glycol. 5. Surfaces with altered topography^j 6. Anti-adhesive surfaces^k
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Footnotes:

^a Technique: method (modality) to apply the decontamination substance - by a person (manual decontamination) or a machine (non-touch decontamination).

^b Chemical product used.

^c Tool used to effectuate decontamination.

^d Manual application of the decontamination agent to the surface.

^e The components lift grease but don't impact microbes.

^f Daily decontamination without terminal decontamination.

^g Decontamination of a room between occupying patients. Also called 'deep' decontamination.

^h No-touch decontamination: also called 'automated decontamination', a stand-alone machine applies the chemical agents, instead of the manual application.

ⁱ Antimicrobial surfaces: surfaces with components that may protect them against bacterial contamination, also called self-disinfecting surfaces.

^j Surfaces with altered topography: surfaces designed to inhibit microbial colonisation of surfaces.

^k Anti-adhesive surfaces: surfaces designed to reduce the adhesion force between bacteria and a solid surface to enable the easy removal of bacteria before a biofilm layer is formed^{213, 214}.

Abbreviations:

HINS: high-intensity narrow-spectrum. **HP:** hydrogen peroxide. **HPV:** hydrogen peroxide vapour. **IHP:** improved hydrogen peroxide. **MDRO:** multiple-drug resistant organisms. **PA:** peracetic acid. **PX-UV:** pulsed Xenon UV light. **QACs:** quaternary ammonium compounds. **UV:** ultraviolet. **UV-C:** ultraviolet C light.

3.2. Methods for study II: SR on gloves, gowns and masks

3.2.1. Justification of the study

Evidence on the effectiveness of gloves, gowns, and masks in reducing MRSA transmission in hospitals is mixed. While some studies report positive effects²¹⁵, others suggest that gloving and gowning do not significantly reduce HAIs^{90, 216, 217}, or that MRSA can be controlled without these barriers^{218, 219}.

The Veterans Affairs initiative for MRSA prevention is often cited as a success story for contact precautions. Between 2007 and 2017, hospitals reported a 66% reduction in MRSA infections after implementing a bundle of universal screening, contact precautions, and hand hygiene²²⁰. However, critics argue that the observed decline may reflect concurrent improvements in hand hygiene (20–30%) and enhanced environmental cleaning, rather than the use of gowns and gloves alone²²¹. The suspension of these measures during the COVID-19 pandemic was linked to increased MRSA HAIs in both ICUs and non-ICUs²²².

To determine the effects of using gloves, gowns, and masks to reduce MRSA transmission is needed. SRs have evaluated infection control strategies^{74, 129, 137, 223-229}, but none have isolated the specific effects of gloves, gowns, or masks when contact with MRSA-infected patients or their environment is expected.

Guidelines vary in their recommendations for controlling MRSA in hospital settings^{37, 77, 230}. The UK's *Healthcare Infection Society and Infection Prevention Society*²³⁰ recommends standard precautions for all patients to reduce MRSA transmission and suggest using contact precautions (gloves and gowns/aprons) primarily during direct physical contact with the patient or their immediate environment. This reflects a shift from a 'room-entry' to an 'activity-based' approach. However, these guidelines do not address the use of masks for preventing MRSA transmission.

The 2022 *Society for Healthcare Epidemiology of America Practice Recommendation* continues to recommend contact precautions for MRSA based on the moderate quality of evidence derived from observational data and the success of bundles that included isolation as a core component^{77, 220}. In fact, these guidelines recommend the use of gowns and gloves when providing care to or entering the room of all adult ICU patients, regardless of MRSA colonisation status⁷⁷. However, they do not provide specific recommendations on the use of masks. Moreover, the role of masks in MRSA control remains controversial, as highlighted in several studies^{231, 232}.

On the other hand, although current evidence does not conclusively demonstrate that contact precautions increase adverse events^{77, 230}, concerns remain regarding their potential harms. These measures may reduce patient autonomy, elevate psychological distress, and lower satisfaction with care. Moreover, several studies have pointed out that contact precautions can compromise care quality due to decreased staff contact and reduced adherence to hand hygiene^{85, 231, 233-240}. Inappropriate glove use may also contribute to pathogen transmission²⁴¹. However, the BUGG trial found that a universal gown and glove policy increased hand hygiene at room exits²⁴².

Finally, given the resource demands and challenges with their adherence^{130, 131}, it is essential to evaluate both the benefits and potential harms of contact precautions to support evidence-informed MRSA prevention strategies.

3.2.2. Study design

This is a SR based on a pre-published Cochrane protocol²⁴³ and following Cochrane methods¹⁴². Deviations from the protocol are detailed in the review publication, specifically in its section titled “Differences between protocol and review”²⁴⁴.

3.2.3. Criteria for considering studies for this review

3.2.3.1. Types of studies

This review included RCTs and certain non-randomised studies of interventions (NRSIs) as eligible, irrespective of their language, publication status or statistical analysis. We considered the following study designs as eligible:

- RCTs
- Cluster-RCTs (CI-RCTs)
- Quasi-randomised controlled trials (Q-RCTs)
- Cluster-quasi-randomised controlled trials (CIQ-RCTs)
- Non-randomised controlled trials (NRCTs)
- Cluster non-randomised controlled trials (CI-NRCTs)
- Controlled before-and-after (CBA) studies
- Controlled cohort before-and-after studies (CChBA)
- Interrupted time series studies (ITS)
- Controlled interrupted time series studies (CITS)
- Repeated measures studies (RMSs)

Table 9 below details the features used to assess eligibility. We included experimental designs exclusively, as they can minimise some biases commonly present in infection

control studies¹¹³. A study was considered experimental if the intervention had been deliberately allocated by the researcher to observe its effects²⁴⁵. In particular, we considered the following minimum requirements for a study to be defined as experimental:

- 1) a prospective baseline assessment
- 2) a prospective allocation of the intervention; and
- 3) a prospective outcome assessment.

We excluded observational studies (studies in which the investigators do not seek to intervene, and simply observe the course of events²⁴⁵), and outbreak reports (the description of outbreaks and the subsequent interventions adopted for their control)¹¹³.

We also excluded in vitro laboratory-based studies that assessed the efficacy of gloves, gowns or masks impregnated with antiseptic or anti-infective agents to prevent the contamination of the outer surface of the barrier with pathogens.

Table 9. Study designs labels and features

Features	Study design labels										
	RCT ^a	CI-RCT ^a	Q-RCT	CIQ-RCT	NRCT	CI-NRCT	CBA	CChBA	ITS	CITS	RMS ^b
Allocation unit	Ind	Group	Ind	Group	Ind	Group	Ind	Group	Group	NA	
Nr. allocated units/arm	NA	>1 site ^c	NA	>1 site ^c	NA	≥ 2 sites ^c	NA	>1 site ^c	NA	NA	
Allocation method	Random	Random	Quasi-random	Quasi-random	Non-random	Non-random	Non-random		Non random: time differences	Non random: time differences	
BA & AI	Prospective						Prospective				
Outcomes assessment	Prospective						Prospective (for both pre- and post-intervention phases)				
Data collection	NA						Contemporaneous in both arms during pre-/post- intervention periods with same measurement methods ^{e, 246}		RMS is an ITS study where measurements are made in the same individuals at each time point		
Control group choice	NA						Study and control sites should be comparable concerning the setting ²⁴⁶		NA		
Data points	NA						At least 3 before and 3 after the intervention ¹⁵⁵				
Analysis	NA						Must not ignore secular (trend) changes. For example, a simple t-test of the pre versus post intervention periods must be avoided ^f				
Other	NA						Clearly time point when the intervention occurred				

Abbreviations

BA & IA: baseline assessment & allocation to the intervention. **CBA:** controlled before-and-after study. **CChBA:** controlled cohort before-after study. **CIQ-RCT:** cluster-QRCT. **CI-NRCT:** cluster-NRCT. **CI-RCT:** cluster-RCT. **CITS:** controlled ITS. **Ind:** individual. **ITS:** interrupted time series study. **NA:** not assessed. **NRCT:** non-randomised controlled trial. **Q-RCT:** quasi-RCT. **RCT:** randomised controlled trial. **RMS:** repeated measures study.

Footnotes:

^a The stepped wedge design applied in RCTs and CI-RCTs was also eligible. In this design, an intervention is rolled-out sequentially to all the trial participants (either as individuals or clusters of individuals) over a number of time periods. The order in which the different individuals or clusters receive the intervention is determined at random, and by the end of the allocation, all individuals or groups will have received the intervention. Stepped wedge designs incorporate data collection at each point where a new group (step) receives the intervention¹³³. This is a design increasingly used for patient safety interventions¹³², as it is particularly relevant where it is predicted that the intervention will do more good than harm and/or where, for logistical, practical or financial reasons, it is impossible to deliver the intervention simultaneously to all participants¹³³.

^b RMS is an ITS study where measurements are made in the same individuals at each time point. This study design label was not detailed in the Cochrane Handbook¹⁶⁹, but it was suggested as eligible by the EPOC group ¹⁵⁵.

^c In cluster studies with 1 intervention or control site the intervention (or comparison) is confounded by study site, which makes it difficult to attribute any differences to the intervention rather than to other site-specific variable ¹⁵⁵.

^d In order a study to be defined as 'experimental', the assessment of baseline, the allocation to intervention, and the assessment of outcomes should be done prospectively.

^e Seasonality can confound infection control studies, e.g., assessing the intervention group from Jan to June and the control group from July to Dec, may introduce spurious effects due to seasonal variations in infection rates ¹¹³.

^f For ITS and RMS we planned to assess if the statistical approach has ignored secular (trend) changes. Analysis of aggregated data of the pre- and post-intervention phases should be avoided because it does not provide information about trends over time ¹¹³. We excluded ITS studies or RMS without a parallel control group that had ignored secular changes by performing, for example, a simple t test of the pre- versus post-intervention periods. We considered these studies as uncontrolled before-and-after studies.

3.2.3.2. Types of participants

We included studies involving hospitalised patients, that is, patients admitted to healthcare facilities that provide board and room for the purpose of observation, care, diagnosis or treatment¹⁵⁶. Therefore, we excluded the following participants (see definitions in 7. Abbreviations, acronyms and glossary):

- Hospital outpatients: patients admitted to the hospital setting for the purpose of observation, care, diagnosis or treatment without receiving board and room, such as patients attending haemodialysis session.
- Patients attending any other healthcare facilities:
 - Ambulatory care facilities or other hospital outpatient clinics
 - Rehabilitation centres
 - Residential facilities (including assisted living facilities, group homes, halfway houses, homes for the aged, nursing homes, or orphanages)

3.2.3.3. Types of interventions

Experimental interventions: gloving, gowning and masking

The use of gloves, gowns, aprons or masks by any hospital staff (healthcare or non-healthcare professionals) or by any patient's caregiver or visitor for interactions with a patient colonised or infected with MRSA or with potentially contaminated areas in the patient's environment, for example in the patient's room, cubicle or operating room.

We considered the use of medical gloves. To be eligible, gloves needed to be disposable and intended for single patient use and then discarded. We considered using gowns, either isolation or surgical gowns. For masks, we considered procedure masks, surgical masks and particulate respirators.

We defined as eligible any care bundle that considered the use of gloves, gowns or masks, or any combination thereof. Therefore, gloves, gowns and masks could be used in the following ways:

- on their own as a single intervention, for example, the use of gowns alone;
- as a combination, for example, the use of gowns and gloves;
- combined with other barrier precaution, such as the placement of MRSA patients in isolation units to be attended by staff using gowns, gloves and masks; or
- combined with other infection control intervention, such as the decolonisation of patients with MRSA.

Only studies in which gloves, gowns or masks were used with patients who had MRSA were eligible. As a consequence we excluded studies that investigated the effects of the following interventions.

- Gloves, gowns or masks as 'routine practice' or 'standard precautions', that is, when there is anticipated exposure to a patient's blood, body, fluids, secretions, and excretions (except for sweat), non-intact skin, draining wounds and mucous membranes⁵. Therefore, we excluded studies assessing gloving, gowning or masking during routine vascular catheter insertion, surgical procedures, and patient care after organ transplantation.
- Universal gloving, gowning or masking, that is, their use for contact with all patients.
- The pre-emptive use of gloves, gowns or masks, that is, their use for all new admissions or for all patients admitted to a specific unit, until a negative screening culture for the target organism is reported⁵.

Control interventions

We considered any comparator that allowed the effects of gloving, gowning, or masking (used alone or in combination) to be assessed. In practical terms, we included those studies in which co-interventions were similar in the study groups, as this would allow us to assess the specific impact of the use of gloves, gowns or masks.

We excluded studies that evaluated the effects of MRSA screening programs, isolation of MRSA patients (such as placement in an isolation unit or ward, nurse cohorting or cohorting without designated staff), or campaigns to increase the use of contact precautions, as these do not allow the specific effects of the use of gloves, gowns or masks to be assessed. For example, in studies evaluating MRSA screening programmes, the observed effects could be attributed to early detection of MRSA carriers (which implies they do not become a continuous source of MRSA), rather than solely to the use of gloves, gowns, or masks.

3.2.3.4. Types of outcome measures

The eligible review outcomes are detailed in Table 10. We did not exclude studies solely on the basis of the reporting of the outcome data, since this might have introduced bias due to selective outcome reporting¹⁵⁷.

Table 10. Gloves, gowns and masks systematic review: outcomes definition

Review outcomes	Comments
Primary outcomes	
a. Outcomes measured in patients	
Healthcare-associated MRSA colonisations	- Colonisation is the presence of microorganisms (on skin, mucous membranes, in open wounds, or in excretions or secretions) that are not causing adverse clinical signs or symptoms. Hospital-acquired colonisation is a colonisation that was not present at the time of admission to the hospital¹. - We included colonisations only in studies reporting an existing screening policy at admission for the microorganism of interest. Without such a policy, colonisation data would likely be incomplete due to missed detection of asymptomatic carriers⁷⁴.
Healthcare-associated MRSA infections	- Infection acquired in the hospital as a result of the delivery of healthcare. Therefore, it was not present or incubating at the time of admission to the healthcare facility¹. - We excluded composite outcomes combining infections from different target organisms (e.g., MRSA, VRE, or both) or mixed endpoints (e.g., 'colonisation, infection, or both'), as these combine biologically distinct outcomes and are not informative¹⁵⁹.
Healthcare-associated MRSA bacteraemias	
Healthcare-associated MRSA pneumonias	
Mortality attributable to MRSA	
b. Outcomes measured in hospital staff, patients' caregivers or visitors	
Healthcare-associated MRSA colonisations	Only in studies reporting an existing screening policy during the study.
Prevalence of carriers of MRSA	
Secondary outcomes	
MRSA to MSSA ratios	
Length of stay, measured in days	
Antibiotic use	
All cause mortality	
Abbreviations:	
MRSA: methicillin-resistant <i>Staphylococcus aureus</i> . MSSA: methicillin-susceptible <i>S aureus</i> . VRE: vancomycin-resistant <i>Enterococci</i> .	

We would have accepted the study authors' report regarding the methods used to diagnose healthcare-associated MRSA colonisations, infections, bacteraemias or pneumonias and considered any measure of frequency. We would have admitted any definition used for healthcare-associated infections and colonisations, as they are not standardised⁴, and any metric for quantifying healthcare-acquired pathogens, such as incidence rate or incidence density rate.

3.2.4. Search methods for identification of studies

Full search strategies for electronic searches and other sources are detailed in the review publication (section Search methods for identification of studies)²⁴⁴.

3.2.4.1. Electronic searches

Information specialists searched the following electronic databases with no language, date, or setting restrictions applied.

- The Cochrane Wounds Group Specialised Register (searched 5 June 2015)
- The Cochrane EPOC Group Specialised Register (searched 9 July 2013)
- The Cochrane Infectious Diseases Group Specialised Register (searched 5 January 2009)
- The Cochrane Central Register of Controlled Trials (CENTRAL; The Cochrane Library 2015, Issue 6)
- The Database of Abstracts of Reviews of Effects (DARE; The Cochrane Library 2015, Issue 6)
- The Health Technology Assessment Database (HTA; The Cochrane Library 2015, Issue 6)
- The NHS Economic Evaluation Database (NHS EED; The Cochrane Library 2015, Issue 6)
- The Methodology Register (The Cochrane Library 2015, Issue 6)
- Ovid MEDLINE (1946 to June Week 1 2015)
- Ovid MEDLINE (In-Process & Other Non-Indexed Citations; 1946 to June Week 1 2015)
- Ovid EMBASE (1974 to 4 June 2015)
- Web of Science (WOS) Core Collection: Science Citation Index Expanded (SCI-EXPANDED; 1900 to 7 June 2015); Social Sciences Citation Index (SSCI); 1956 to 7 June 2015; Conference Proceedings Citation Index Science (CPCI-S; 1990 to 7 June 2015)
- EBSCO CINAHL (1982 to 5 June 2015)

- Ovid British Nursing Index (BNI; 1985 to 6 July 2010)
- ProQuest Dissertations & Theses A&I (1639 to 11 June 2015)

We combined EMBASE and CINAHL search strategies with validated methodological filters for the study designs eligible for our review (MEDLINE had no filters applied). EMBASE had the RCT UK Cochrane Centre filter¹⁵⁷, and the EPOC filter. CINAHL had the RCT filter²⁴⁷, and the EPOC filter.

We also searched ClinicalTrials.gov, WHO ICTRP, and the International Standard Randomised Controlled Trial Number Register for ongoing or unpublished studies (6th June 2015).

3.2.4.2. Searching other resources

We screened reference lists of the included studies, relevant reviews, and conference proceedings (2009–2011). We contacted the authors of key papers for additional studies. No separate searches for adverse effects were performed.

3.2.5. Selection of studies

We removed duplicates and implemented the study selection process in EndNote¹⁶¹. Two reviewers (JL-A and MM-M, MG, LOC, or SCN) independently screened titles/abstracts and full texts, resolving disagreements by consensus or a third reviewer (IS). Study authors were contacted to clarify eligibility. For the excluded full texts, we recorded the main exclusion reason. We planned to collate multiple reports of the same included study; the most complete and recent report was the primary reference and the main source for data extraction. We completed a PRISMA flow chart and a table with the description of the characteristics of the excluded studies. We were not blinded to the authors' names of the publications, or their institutions, journals or results during the selection process.

3.2.6. Remainder systematic review phases

We were unable to proceed with the remaining phases of the SR—including data extraction, risk of bias assessment, meta-analysis, heterogeneity assessment, subgroup and sensitivity analyses, and assessment of publication bias—because no studies met the eligibility criteria. The full review methods plan that would have been applied in case of finding studies is detailed in the published review²⁴⁴.

3.3. Methods for study III: Sex/Gender consideration in Cochrane reviews

3.3.1. Justification of the study

Sex and gender can help in understanding the transmission of infectious diseases. Integrating a sex/gender perspective into SRs of interventions for preventing HAIs is a relatively new but essential approach to improving infection control programmes³⁰. Although further research is needed to elucidate how sex and gender interact with HAIs, current evidence already supports their consideration in research on infection control interventions. However, infection control strategies often overlook these factors, resulting in uniform approaches for men and women^{30, 248}.

Incorporating sex and gender considerations into Cochrane reviews of HAIs prevention is important for four reasons. First, it enables the identification of the most effective and safest interventions for women and men. Second, it contributes to reducing health inequities between men and women and promotes human rights³⁰. Third, our study findings can contribute to promoting a sex/gender perspective across Cochrane reviews of any topic.

We focused on Cochrane reviews for several reasons. There is a high number of Cochrane reviews that have evaluated infection control interventions³⁰, and they were produced by diverse Review Groups (reflecting Cochrane's overall approach to sex and gender). Cochrane reviews are globally recognised as high-quality evidence and usually inform clinical guidelines²⁴⁹⁻²⁵¹ and policies of health insurers²⁵². For instance, they were included in 90% of WHO guidelines published in 2016²⁵³. However, if sex and gender are not considered, Cochrane reviews may fail to produce generalisable evidence, limiting their relevance for policy-makers²⁵⁴⁻²⁵⁶ and contributing to health inequities^{257, 258}.

3.3.2. Study design

This was a methodology study, that is, a study that assesses the methods used in randomised trials, other healthcare evaluations or systematic reviews²⁵⁹. The publication did not follow a specific reporting guideline, as— to the best of our knowledge—no formal guidance for reporting methodology studies was available at the time of submission. See publication in Lopez-Alcalde *et al.*²⁶⁰.

3.3.3. Types of reviews that were eligible

We defined the eligibility criteria as detailed in Table 11.

Table 11. Eligibility criteria of Cochrane reviews

Criteria	Inclusion criteria	Exclusion criteria
a. Publication characteristics		
Journal	▪ CDSR	
Publication date	▪ 1995 (journal launch) till 31st December 2016	
Stage	▪ 'Published review' ▪ 'Active review'	▪ Protocols ▪ Titles ▪ Withdrawn reviews
Review type	▪ Intervention review, that is, a review assessing the effects (benefits, harms or both) of health care or health policy interventions	▪ Methodology reviews ▪ Diagnostic reviews ▪ Overviews of reviews ▪ Prognosis reviews ▪ Any healthcare setting Qualitative reviews.
b. Participants		
	▪ Any healthcare consumer at risk of healthcare-associated colonisation or HAI	▪ Focus on neonates, pre-terms, low birth weight or immunocompromised patients
	▪ Any healthcare setting	▪ Focusing on the prevention of infections in healthcare professionals
c. Interventions		
Interventions	Any strategy, pharmacological or not, to prevent healthcare-associated colonisations or infections: • Regulatory interventions • Organisational measures • Education & training • Antimicrobial stewardship • HAIs surveillance • Monitoring, audit and feedback • Decontamination of surfaces, medical equipment, environmental infection control • Hand hygiene • Patient and healthcare personnel hygiene (not hand hygiene) • Physical barriers to reduce the transmission of microorganisms • Decolonisation • Prevention of infections associated with vascular accesses • Interventions to prevent infections associated with surgery • Interventions to prevent HAIs associated to non-surgical procedures • Interventions to prevent HAIs associated to dental procedures • Interventions to prevent respiratory HAIs (due to mechanical ventilation or not) • Interventions to prevent urinary catheter-associated infection • Interventions to prevent infection in non-surgical wounds • Interventions to prevent HAIs in the context of a medical condition • Interventions to prevent HAIs by physiotherapy and rehabilitation techniques	
Comparator	Any comparator: • Inactive comparator (such as doing nothing, use of a placebo, or use of a sham intervention) • Active comparator: ○ Pharmacological intervention ○ Non-pharmacological intervention, e.g., an educational or organisational intervention	
d. Outcomes		
Outcomes	The review must have planned to assess at least one of the following outcomes: • Occurrence of HAIs • Occurrence of Colonisations • Mortality due to HAI • Total mortality • Resistance to antimicrobials • Any surrogate measure of HAI, such as fever, positive culture, or antibiotic use. The review had to consider at least one of the previous outcomes in the “Types of outcome measures” section (as a primary or secondary outcome) or had to present results about any of these outcomes (“Results” section).	
Abbreviations: CDSR: Cochrane Database of Systematic Reviews. HAI: hospital-acquired infection		

3.3.4. Search methods for identification of reviews

We searched the *Cochrane Database of Systematic Reviews* (CDSR) looking for all the Cochrane interventions reviews active and published from 1995 (launch of the journal) until 31st December 2016. See the full search strategy in “Additional file 3” of the publication²⁶⁰. We used *EPPI-Reviewer 4* software²⁶¹ to create the database of reviews.

3.3.5. Selection of reviews

Two authors (JL-A and SCN or ES) screened each title and abstract independently to select potentially eligible reviews. If there was any uncertainty based on this information, we obtained the full-text review for further assessment. Two authors (JL-A and SCN or ES or AFC) independently assessed the eligibility of the retrieved full texts and resolved disagreements through discussion. If there was no consensus, we consulted a third author (JZ). We used *EPPI-Reviewer 4* software²⁶¹ to implement the selection process. We piloted the selection process with 100 records. We created a PRISMA flowchart²⁶² describing the results of the selection process.

3.3.6. Data extraction

We designed a data extraction template and piloted the form on ten reviews. Two of the piloted reviews were not eligible for this study, but we used them because they had been defined by the *Canadian Institutes of Health Research*²⁶³ as exemplar Cochrane reviews regarding the consideration of sex and gender.

We extracted data with the *EPPI-Reviewer 4* software²⁶¹. At least two authors (JL-A, ES, AF or SCN) extracted the data for each item of the form. For critical items, two authors extracted data independently. For other items, one author extracted the data, and another author cross-checked the information extracted. We resolved discrepancies by consensus. In the case of no consensus, a third author intervened. We did not contact the review authors to obtain missing information or clarification. Next, we detail the methods used to complete each specific objective of this study.

3.3.7. Analysis methods

3.3.7.1. Objective 1. To describe and assess the terminology and definitions used for sex and gender

We described the terms used for sex and gender and the sections in which these terms appeared. Moreover, we assessed the appropriateness of the terms and definitions used by comparing them with the proposals of the *SAGER (Reporting of Sex and Gender Equity in Research) guidelines*¹⁰¹. We followed the classifications detailed in Table 12 and Table 13.

Table 12. Classification of sex and gender terms

Classification	
Correct	Any of the following. 1. Male or female for sex and an adequate definition of sex (biological). 2. Men or women for gender and an adequate definition of gender (cultural and socially determined roles).
Incorrect	Any of the following. 1. Male or female for gender. 2. Men or women for sex.
Unclear	Any of the following. 1. Terms for sex or gender used without defining sex or gender. For example, a review stating that participants' sex were male (56%) and female (64%), but there was no definition for sex. We found the terminology unclear, as it was not evident whether it referred to sex or gender. 2. Terms inconsistently used in the review, e.g., using 'male' and 'men' for the same concept. 3. Abbreviations used without the full term provided.
Not applicable	No mention to sex or gender

Table 13. Classification of the sex and gender definitions

Classification	
Correct	Definitions according to the SAGER guidelines
Incorrect	Definitions different to the SAGER guidelines
Unclear	Terms for sex or gender used without a definition for sex or gender
Not applicable	There was no mention of sex or gender in the review

3.3.7.2. Objective 2. To determine the content of the reviews about sex and gender

We determined the sex and gender content of each review according to the domains proposed by the *Sex and Gender Appraisal Tool for Systematic Reviews (SGAT-SR)*¹³⁶. This 21-item tool assesses how a Cochrane review has considered sex and gender. It appraises seven review sections: (a) Background, (b) Objectives, (c) Criteria for inclusion/exclusion, (d) Methods, (e) Results and analysis, (f) Discussion and conclusions, and (g) Table of included studies. Each question of the tool has four answers: (a) “Yes, review met criteria”; (b) “No, the review did not meet criteria”; (c) “Item was not applicable to review”; or (d) “Unable to determine”. The tool allows adding free-text comments to each response, if needed. We made minor wording changes to the SGAT-SR. “Additional file 4” of the publication details the tool domains and the guidance on which we based our judgements²⁶⁰.

We tabulated the responses to the tool by simple counts, and summarised the results numerically to provide an indication of overall responses. We calculated the percentage of reviews meeting each item only when this was applicable (Number of reviews meeting item x 100 / Total number of included reviews in which the item was applicable); thus, when an item was not applicable for a review, that review was considered neither in the numerator nor in the denominator for that item. This omission applied to reviews focusing on females only, that is, those reviews addressing pregnancy and delivery. Breast cancer was not the case, as it can also affect males.

Two authors (SCN, JLA, ES, or AFC) independently answered each item of the tool, without being masked to the review details. We resolved disagreements through discussion and, if no consensus was reached, by consulting a third author. We tabulated the judgements of the SGAT-SR and used *PowerPoint 2016*²⁶⁴ and *Review Manager 5.3*²⁶⁵ to summarise our judgements graphically.

3.3.7.3. Objective 3. To describe the SGBA of the reviews

Objective 3a. To describe the reporting of the sex and the gender characteristics of the study participants

We described whether the review attempted to report the sex and gender characteristics of participants recruited for each included study. For a review to describe the study samples accurately, we agreed that it should have attempted to report at least the following information for each included study (based on Clayton *et al.*²⁶⁶):

- Sex measurement (ascertained by genotyping of the blood sample)
- Number of female and male participants

- Gender measurement (ascertained by self-report)
- Number of women and men participants

We focused on the information reported in the table of included studies. If a review reported that sex or gender information was missing, we considered it to have attempted to report this information. Thus, the review description was considered correct.

Objective 3b. To describe the SGBA in the reviews

First, we identified the SRs that had planned or used any SGBA. Second, we described the SGBA methods planned and finally used. We considered Welch *et al.*²⁶⁷ to describe the SGBA methods used.

- Subgroup analysis-pooled results: SRs that assessed impacts of health interventions on the outcome using subgroup analysis with pooling.
- Subgroup analysis-descriptive: SRs that described within-study differences without pooling.
- Targeted analyses of sex or gender populations.
- Other methods used for SGBA.

3.3.7.4. Objective 4. To assess whether the review conclusions considered the sex- and gender-related findings

We calculated the percentage of reviews considering the sex- and gender-related findings in the conclusions, in particular:

- % of reviews considering sex or gender findings in the “Implications for clinical practice” section
- % of reviews considering sex or gender findings in the “Implications for research” section
- % of reviews performing SGBA that considered sex or gender findings in the “Implications for clinical practice” section
- % of reviews performing SGBA that considered sex or gender findings in the “Implications for research” section

3.4. Methods for study IV: NRSIs consideration in Cochrane reviews

3.4.1. Justification of the study

RCTs are considered the gold standard for evaluating intervention efficacy due to their high internal validity and ability to minimise selection bias¹⁷⁶. However, non-randomised studies of interventions (NRSIs) of infection control interventions are widespread²⁶⁸. Although NRSIs are more susceptible to bias²⁶⁹, certain types may still offer valuable evidence to inform decision-making. Several factors often limit the feasibility of conducting RCTs of infection control interventions.

- **Ethical concerns:** Interventions such as environmental surface cleaning are typically perceived by healthcare workers and patients as beneficial. As a result, withholding such measures from a control group in an RCT may be considered unethical²⁷⁰.
- **Logistical challenges:** Infection control strategies are often implemented as part of complex, multi-component interventions, making RCTs difficult. Moreover, these interventions are commonly applied at the cluster level (e.g. hospital wards), yet the number of available clusters is often limited, reducing statistical power.
- **Urgency of implementation:** In certain situations, such as outbreak containment, immediate intervention is required, precluding the use of RCTs.

Given these constraints, a SR of existing NRSIs on infection control interventions can provide valuable insights and complement evidence derived from RCTs. NRSIs encompass a range of study designs that are often inconsistently labelled and defined²⁷¹. Examples are ITS, controlled before-and-after studies, and cohort studies. Furthermore, there is currently no universally accepted framework for determining which types of NRSIs are appropriate for addressing each specific PICO question²⁷¹.

This lack of standardisation presents a challenge for review authors of infection control interventions, particularly in defining eligibility criteria for NRSIs and implementing the study selection. Reviewers are frequently required to make complex judgments based on ambiguous or inconsistently applied study design labels.

Given the need to expand the scope of study designs of infection control interventions, which may increase demand for SRs incorporating NRSIs evidence, understanding current practices and identifying areas for methodological improvement is timely and important.

3.4.2. Study design

Cross-sectional descriptive observational study. See poster presentation in Annex 1.4²⁷².

3.4.3. Types of eligible reviews, search methods, review selection and data extraction

Active Cochrane reviews of interventions to prevent HAIs published before 1 January 2017. See 3.3. Methods for study III: Sex/Gender consideration in Cochrane reviews.

3.4.4. Analysis methods

Objective 1: To determine the number of Cochrane reviews of interventions to prevent HAIs admitting NRSIs

We reported the proportion (%) of reviews admitting NRSIs.

Objective 2: To describe and assess the justification provided in these reviews for admitting NRSIs

We examined the justifications given for including NRSIs and evaluated whether they aligned with the *Cochrane Handbook* ¹⁶⁹ (see Table 14).

Table 14. Cochrane Handbook's accepted reasons for including NRSIs

Reasons	Explanation
Reason 1: To provide an explicit evaluation of the weaknesses of available NRS in order to examine the case for undertaking a RCT	Findings from a review of NRSIs may also help inform the design of future RCTs, for instance, by identifying relevant subgroups
Reason 2: To provide evidence on the effects—either beneficial or harmful—of interventions that cannot be randomised or are highly unlikely to be studied through RCTs	An unbiased, SR of available NRSIs, including their findings and limitations, can offer valuable insights
Reason 3: To generate evidence on effects—both beneficial and harmful—that cannot be adequately studied in RCTs	Examples: rare outcomes, long-term outcomes, or outcomes not recognised as important at the time major RCTs were conducted
Abbreviations: NRS: non-randomised studies. RCTs: randomised controlled trials. SR: systematic reviews.	

Objective 3: To describe the study design labels used for NRSIs

We extracted the study design labels reported in the reviews and quantified the number of reviews that used each label.

Objective 4: To assess how the NRSIs were defined

We assessed the descriptions of NRSIs used in the reviews by comparing these descriptions against the study design features proposed in the *Cochrane Handbook* (Table 15 and Table 16)¹⁶⁹.

Table 15. Study design features for studies allocated at the individual level

	RCT	Q-RCT	NRCT	CBA	PCS	RCS	HCT	NCC	CC	XS	BA	CR/CS
Was there a comparison:												
Between two or more groups of participants receiving different interventions?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N
Within the same group of participants over time?	P	P	N	Y	N	N	N	N	N	N	Y	N
Were participants allocated to groups by:												
Concealed randomisation?	Y	N	N	N	N	N	N	N	N	N	na	na
Quasi-randomisation?	N	Y	N	N	N	N	N	N	N	N	na	na
By other action of researchers?	N	N	Y	P	N	N	N	N	N	N	na	na
Time differences?	N	N	N	N	N	N	Y	N	N	N	na	na
Location differences?	N	N	P	P	P	P	P	na	na	na	na	na
Treatment decisions?	N	N	N	P	P	P	N	N	N	P	na	na
Participants' preferences?	N	N	N	P	P	P	N	N	N	P	na	na
On the basis of outcome?	N	N	N	N	N	N	N	Y	Y	P	na	na
Some other process? (specify)												
Which parts of the study were prospective:												
Identification of participants?	Y	Y	Y	P	Y	N	P*	Y	N	N	P	P
Assessment of baseline and allocation to intervention?	Y	Y	Y	P	Y	N	P*	Y	N	N	na	na
Assessment of outcomes?	Y	Y	Y	P	Y	P	P	Y	N	N	P	P
Generation of hypotheses?	Y	Y	Y	Y	Y	Y	Y	Y	P	P	P	na
On what variables was comparability between groups assessed:												
Potential confounders?	P	P	P	P	P	P	P	P	P	P	N	na
Baseline assessment of outcome variables?	P	P	P	Y	P	P	P	N	N	N	N	na

Abbreviations:

Y=Yes; P=Possibly; P*=Possible for one group only; N=No; na=not applicable. **RCT**=Randomised controlled trial; **Q-RCT**=Quasi-randomised controlled trial; **NRCT**=Non-randomised controlled trial; **CBA**=Controlled before-and-after study; **PCS**=Prospective cohort study; **RCS**=Retrospective cohort study; **HCT**=Historically controlled trial; **NCC**=Nested case-control study; **CC**=Case-control study; **XS**=Cross-sectional study; **BA**=Before-and-after comparison; **CR/CS**=Case report/Case series.

Table 16. Study design features for studies allocated at the group level

	CIRCT	CIQ-RCT	CINRT	CITS	CChBA	ITS	ChBA	EcoXS
Was there a comparison:								
Between two or more groups of clusters receiving different interventions?	Y	Y	Y	Y	Y	N	N	Y
Within the same group of clusters over time?	P	P	N	Y	N	Y	Y	N
Were clusters allocated to groups by:								
Concealed randomisation?	Y	N	N	N	N	N	N	N
Quasi-randomisation?	N	Y	N	N	N	N	N	N
By other action of researchers?	N	N	Y	P	P	N	N	N
Time differences?	N	N	N	Y	Y	Y	Y	N
Location differences?	N	N	P	P	P	N	N	P
Policy/public health decisions?	Na	na	P	P	P	P	na	na
Cluster preferences?	Na	na	P	P	P	P	na	na
Some other process? (specify)								
Which parts of the study were prospective:								
Identification of participating clusters?	Y	Y	Y	P	P	P	P	N
Assessment of baseline and allocation to intervention?	Y	Y	Y	P	P	P	P	N
Assessment of outcomes?	Y	Y	Y	P	P	P	P	N
Generation of hypotheses?	Y	Y	Y	Y	Y	Y	Y	P
On what variables was comparability between groups assessed:								
Potential confounders?	P	P	P	P	P	P	P	P
Baseline assessment of outcome variables?	P	P	P	Y	Y	Y	Y	N
Abbreviations:								
Y=Yes; P=Possibly; P*=Possible for one group only; N=No; NR=Not required. CIRCT=Cluster randomised controlled trial; CIQ-RCT=Cluster quasi-randomised controlled trial; CINRT=Cluster non-randomised controlled trial; CITS=Controlled interrupted time series; CChBA=Controlled cohort before-and-after study; ITS=Interrupted time series; ChBA=Cohort before and after study; EcoXS=Ecological cross-sectional study.								

3.5. Methods for studies V & VI: SR methodological challenges & RCTs recommendations

3.5.1. Justification of the studies

This PhD offered the opportunity to identify the methodological challenges in SRs and RCTs of interventions to prevent HAIs. These interventions are often complex, context-dependent, and implemented in clusters. As a result, even minor design or analytical flaws can lead to relevant errors in effect estimates, potentially resulting in misinformed policies, inefficient resource allocation, and patient harm. The outputs of studies V and VI will inform the development of future SRs and RCTs of infection control interventions.

3.5.2. Study design

An integrative descriptive synthesis of the methodological observations and insights identified across the four preceding dissertation aims.

3.5.3. Data Sources

The **primary data sources** consisted of methodological observations documented during the execution of Aims 1–4. **Secondary data sources** included targeted literature searches conducted in PubMed throughout the PhD project, focusing on methodological papers, guidance documents, and meta-epidemiological studies. These sources addressed key challenges in RCTs and SRs of infection control interventions, the consideration of sex and gender in clinical research, and the inclusion of non-randomised studies in evidence synthesis.

3.5.4. Analytical framework: thematic categorisation

Observations were organised into thematic categories aligned with established methodological domains in RCTs and SRs. These categories emerged inductively through the identification of recurring themes across the four dissertation aims.

Methodological challenges were identified and compared against established guidance, including the Cochrane Handbook, GRADE, reporting guidelines, and risk of bias tools, to assess whether existing guidance adequately addressed each issue. A narrative synthesis resulted in a description of the methodological landscape and the identification of themes warranting further methodological investigation.

The design recommendations for RCTs of hospital infection control interventions are presented according to an adapted version of the 'Evidence, Population(s), Intervention, Comparison, Outcomes, Timestamp' (EPICOT) format²⁷³.

3.6. Role of funding sources

Study I and study II were funded by the *Agencia de Calidad del Sistema Nacional de Salud* (Ministerio de Sanidad y Política Social, Spain), the *Cochrane Wounds Group* (York, UK), which provided financial support to Jesús López-Alcalde in the form of accommodation and working space, and the *Instituto de Ciencias de la Salud* (Castilla-La Mancha, Spain; Grant No. EC08012).

Study III and study IV were conducted as part of the SEXCOMPLEX project (“Influence of sex and sex hormones on human chronic disorders of complex etiology”), a two-year initiative (2017–2019) coordinated by Hospital Universitario Ramón y Cajal (Madrid, Spain). The project was supported by the *Instituto de Salud Carlos III* under Plan Estatal de I+D+i 2013–2016 and co-financed by the European Regional Development Fund (ERDF) through Grant No. PIE16/00050 (“A way to achieve Europe”).

These funding sources had no role in the study design, data collection, analysis, interpretation, or decision to submit the results for publication.

3.7. Ethical considerations

Ethics approval was not required for any of the studies as the research did not include human subjects, human data or tissue, or animals.

4. Results

The results for each of the studies that make up the thesis are presented below.

4.1. Results of study I: SR on decontamination

4.1.1. Results of the search

As of March 3, 2025, the searches identified 10,528 records. After removing 2,064 duplicates, 8,464 records were screened by title and abstract, of which 8,153 were excluded. We assessed 311 full-text reports for eligibility and excluded 256 (82%). Ultimately, 11 studies were included in the review^{187, 196-198, 274-280}, reported across 51 publications. In addition, we identified four ongoing trials²⁸¹⁻²⁸⁴. The PRISMA flow diagram is presented in Figure 1.

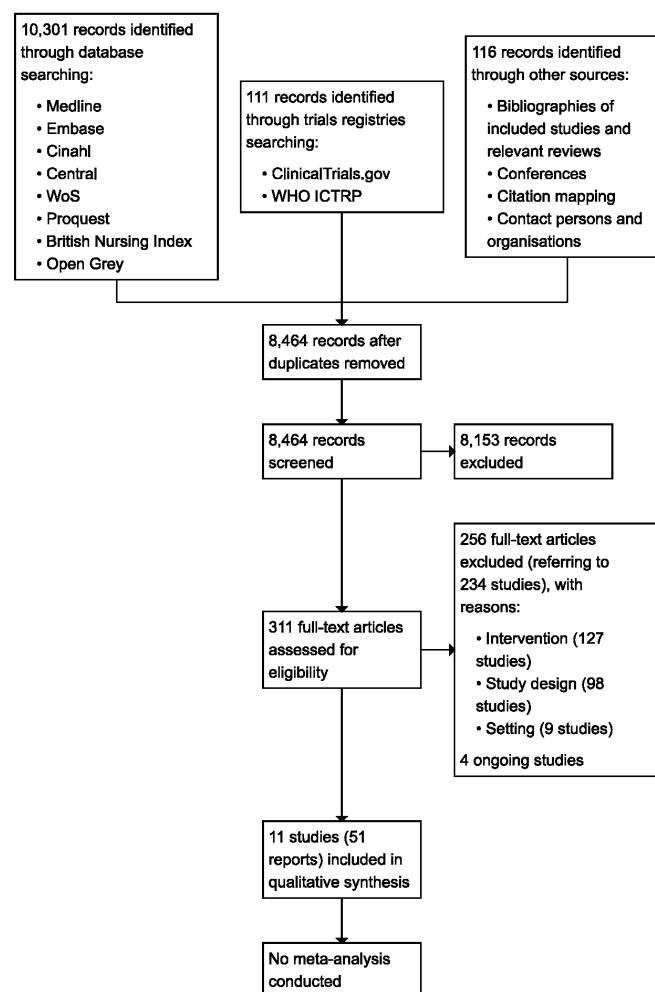


Figure 1. Flow chart decontamination systematic review

4.1.2. Description of included studies

See the characteristics of the eleven included studies^{187, 196-198, 274-280} in Table 17 and Table 18.

4.1.2.1. Study methods

Eight studies were cluster cross-over randomised controlled trials (CRXO-RCTs), and three were individually randomised parallel RCTs (i-RCTs). Of the CRXO-RCTs, only six incorporated a washout period. Reported sample sizes varied widely, ranging from 70 to 21,395 patients, although two trials did not report sample size data. Six studies were prospectively registered and seven studies had financial conflicts of interest.

4.1.2.2. Setting and epidemiological context

The studies were published between 1976 and 2024, with seven published after 2012. Recruitment began between 2007 and 2017 in nine trials, while two concluded before 1987. Study durations ranged from 6 to 33 months. Nine studies were conducted in North America and two in Europe; all were set in urban academic hospitals located in high-income countries. Most trials were single-centre studies ($n = 7$) conducted at hospitals with more than 500 beds ($n = 7$).

Study settings included general wards ($n = 5$), ICUs ($n = 3$), both wards and ICUs ($n = 2$), or operating rooms ($n = 1$). Three studies specifically targeted rooms occupied by patients known to be colonised or infected. Two trials were initiated in response to high infection rates or outbreaks. Colonisation pressure was reported in only one study, in which it was described as high¹⁹⁸.

4.1.2.3. Participants' baseline characteristics

When reported, the mean patient age ranged from 53 to 68 years. All trials included both sexes, with male participants comprising 52–63% of study populations. Race was reported in three studies, with white participants being the predominant group in two. None of the studies reported gender identity or socioeconomic status.

Patient populations varied: five studies included mixed medical and surgical patients, one focused exclusively on medical patients, and one on surgical patients. One trial specifically examined solid organ transplant recipients. Six studies were conducted in non-ICU settings, three in ICUs, and two in mixed settings. Reporting of comorbidities was generally limited across studies.

4.1.2.4. Interventions and comparators

Table 18 summarises the primary interventions and co-interventions evaluated across the studies. Most trials focused on the type of product used ($n = 7$), followed by interventions aimed at increasing the frequency of high-touch surface decontamination ($n = 3$), or reducing floor decontamination frequency based on expected contamination levels ($n = 1$). Interventions were implemented during routine decontamination ($n = 6$), terminal decontamination ($n = 2$), or both ($n = 3$). Intervention periods ranged from 7 days to 24 months, with nine studies lasting at least nine months, allowing for evaluation beyond seasonal variation.

Manual decontamination was the most commonly studied approach ($n = 8$), followed by no-touch disinfection methods ($n = 3$) and antimicrobial surfaces ($n = 1$). Manual disinfectants included quaternary ammonium compounds (QACs; $n = 4$), bleach ($n = 1$), bleach specifically for *C. difficile* rooms ($n = 2$), phenolic agents ($n = 3$), probiotics ($n = 1$), improved hydrogen peroxide (IHP; $n = 1$), and ultramicrofiber cloths with copper-based formulations ($n = 1$). No-touch disinfection techniques included UV-C light ($n = 2$) and pulsed xenon UV ($n = 1$). One study evaluated copper-coated surfaces.

Comparators varied and included another active intervention ($n = 4$), standard practice ($n = 1$), detergents ($n = 2$), sham procedures ($n = 2$), or no intervention ($n = 3$).

4.1.2.5. Review outcomes

Four studies did not report any outcomes relevant to this review^{196, 274, 275, 279}, while the remaining seven reported at least one outcome of interest^{187, 197, 198, 276-278, 280}. None of the included studies reported HAIs among staff, caregivers, or visitors; HAI-related mortality; or resistance to antibiotics or disinfectants (see Table 18).

We identified four types of unit-of-analysis errors (see details in Annex 2.3).

First, we assessed the statistical approaches applied in the included studies but could not re-analyse the data due to the lack of individual-level information. Among eight reported effect estimates on communicable outcomes, we identified UAEs in five (63%). Rock et al and the LAMP trial used Poisson regression for healthcare-associated colonisations¹⁸⁷ and HAIs¹⁹⁸, respectively. Danforth *et al.* and Salgado *et al.* applied a Chi² and Fisher tests for HAIs^{197, 278} and BSIs²⁷⁸. Both methods do not account for dependency in infection or colonisation data, potentially underestimating variability and producing overly narrow CIs.

Second, the review included five CRXO studies informing the review outcomes^{187, 197, 198, 276, 280}, of which two presented UAE in the analysis of HAI due to the inadequate account for within-cluster correlation^{197, 198}. However, we could correct this unit of analysis error by inflating standard errors accordingly. See Table 6. Correlation coefficients.

Third, across the eleven effect estimates reported in the included studies, we did not find UAEs for the inadequate analysis of events that re-occurred in the same participant. Danforth *et al.*¹⁹⁷ reported HAIs and BSIs as dichotomous data but did not specify whether outcomes recurred or how recurrent events were analysed. As the study did not report participants' follow-up duration, we could not estimate whether recurrences were likely common. Therefore, it remained unclear whether the analysis was inappropriate or what impact it might have had.

Fourth, the review did not present UAEs derived from inadequate consideration of multi-arm trials. Two multi-arm studies were included. The BETR trial²⁷⁴, a four-arm study with all arms eligible, reported no data for our outcomes, and the Karmin trial²⁷⁶, a three-arm study, included each arm only once per analysis.

Fifth, in the trial by Salgado *et al.*, the registered protocol specified HAIs as the primary outcome²⁸⁵, but the publication reported outcomes as "HAI and/or colonisation" and "HAI only," thus omitting patients with both²⁷⁸. Following Harbarth *et al.*¹⁵⁹, we re-analysed the outcome as patients with at least one HAI.

Table 17. Characteristics of included studies

Nr. of included studies	BETR	Boyce	Danforth	LAMP	Hess	KARMIN	Kundrapu	Rock	Salgado	Weber	Wilson
Publication date ^{Reference}	2017 ²⁷⁴	2017 ²⁷⁵	1987 ¹⁹⁷	2024 ¹⁹⁸	2013 ¹⁹⁶	2023 ²⁷⁶	2012 ²⁷⁷	2022 ¹⁸⁷	2013 ²⁷⁸	1976 ²⁷⁹	2011 ²⁸⁰
Study registration	Prospective	Not done	—	Prospective	Prospective	Prospective	—	Prospective	Retrospective	—	Prospective
Review outcome ^a	X	X	✓	✓	X	✓	✓	✓	✓	X	✓
Study methods											
Design type	CRXO-RCT	CRXO-RCT	CRXO-RCT	CRXO-RCT	CRXO-RCT	CRXO-RCT	i-RCT	CRXO-RCT	i-RCT	i-RCT	CRXO-RCT
Wash-out period, weeks	4	Absent	Absent	24	4	4	NA	5	NA	NA	1
Nr. arms (allocation ratio)	4 (1:1:1:1)	2 (1:1)	2 (1:1)	2 (1:1)	2 (1:1)	3 (1:1:1)	2 (1:1)	2 (1:1)	2 (1:1)	2 (1:1)	2 (1:1)
Nr. of patients ^b	21,395	—	5,883	19,413	190	13,896	70	7,172	614	—	2,583
Conflict of interest ^c	Present	Present	—	Present	Present	Not present	Present	Present	Present	—	Not present
Setting											
Country	USA	USA	Canada	USA	USA	Germany	USA	USA	USA	Canada	UK
Nr. hospitals/study	9	1	1	2	1	1	1	1	3	1	2
Nr. beds/hospital	148;950	—	930	273;334	757	≈ 3,100	215	1,059	98;460;660	—	665;839
Hospital area	Ward	ICU/Ward	Ward	ICU/Ward	ICU	Ward	Ward	Ward	ICU	OR	ICU
Target rooms	C/I	Any	Any	Any	C/I	Any	C/I	Any	Any	Any	Any
Epidemiological context											
High infection levels ^d	—	—	—	✓	—	X	—	—	—	—	✓
Colonisation pressure ^e	—	—	—	High	—	—	—	—	—	—	—
Baseline characteristics											
Age, mean (median), years	58 (—)	—	—	58 (—)	53 (—)	— (61)	54 to 68 (—)	—	60 (—)	—	59 (—)
Sex, % male	52	—	—	52	63	53	—	—	63	—	57
Gender identity, % men	—	—	—	—	—	—	—	—	—	—	—
Race, % of white patients	64	—	—	9	—	—	—	—	64	—	—
Socioeconomic status, % high	—	—	—	—	—	—	—	—	—	—	—
Patients' case mix ^f	—	Medical	—	—	Mixed	Mixed	—	Mixed	Mixed	Surgical	Mixed
Intensive care	X	Mixed	X	Mixed	✓	X	X	X	✓	X	✓

Footnotes: ^a Studies with ≥ 1 review outcome data. ^b Observed samples for the review outcomes. ^c Authors disclosed ties to organisations with a financial interest in the evaluated products. ^d Study prompted by high infection levels/recent outbreak. ^e Colonisation pressure: % patients colonised or infected. ^f Medical, surgical, or mixed patients. **Abbreviations:** — : Not reported. **C/I:** Rooms with colonised/infected patients. **CRXO-RCT:** cluster cross-over cross-sectional RCT. **i-RCT:** individually allocated parallel RCT. **NA:** Not applicable. **Nr:** Number. **RCT:** randomised clinical trial.

Table 18. Interventions and review outcomes informed in the included studies

Study ^{Ref}	Aspect evaluated Area; Surface; Timing	Intervention period	Technique: Intervention (compliance %)	Technique: comparator (compliance%)*	Co-interventions reported in both arms	Review outcomes								
						A	B	C	D	E	F	G	H	I
BETR ²⁷⁴	▪ Substance ▪ Ward; All; T	24 months	QAC (or bleach for rooms with CD) (100%)	Bleach (96%)	a ^{k,l} c d e									
			QAC (or bleach for rooms with CD) (93%) & UV-C (92%)	Bleach (96%)										
			QAC (or bleach for rooms with CD) ² (93%) & UV-C (92%)	QAC (or bleach for rooms with CD) (100%)										
			Bleach (99%) & UV-C (91%)	Bleach (96%)										
			Bleach (99%) & UV-C (91%)	QAC (or bleach for rooms with CD) (100%)										
			QAC (or bleach for rooms with CD) (93%) & UV-C (92%)	Bleach (99%) & UV-C (91%)										
Boyce ²⁷⁵	▪ Substance ▪ Ward/ICU; All; R/T	12 months	QAC (or bleach for rooms with CD) (95%)	IHP (including CD rooms, bleach not used) (94%)	d e									
Danforth ¹⁹⁷	▪ Substance ▪ Ward; Floors; R	6 months	Phenolic disinfectant	Detergent	a [?] j		✓		✓					
KARMIN ²⁷⁶	▪ Substance ▪ Ward; All; R	12 months	QAC / Alcohol /Amine disinfectant (97%)	Detergent (96%)	a b c d j									
			Probiotic disinfectant (97%)	Detergent (96%)			✓							
			QAC / Alcohol /Amine disinfectant (97%)	Probiotic disinfectant (97%)										
Kundrapu ²⁷⁷	▪ Target HTS ▪ Ward; HTS; R	≤ 7 days or until patient's discharge	Adding phenolic disinfectant (daily)	No intervention	a [?] b ⁿ g i								✓	
Wilson ²⁸⁰	▪ Target HTS ▪ ICU; HTS; R	12 months	Adding ultramicrofiber copper biocidal twice/day	No intervention	a ^{o,p} c d e f g h i j	✓ ^s								
Hess ¹⁹⁶	▪ Target HTS ▪ ICU; HTS; R	≈ 9 months	1 extra QAC disinfection/day (100%)	Sham intervention (26%)	a ^k									
Weber ²⁷⁹	▪ Reducing frequency ▪ OR; Floors; R	9 months	Phenolic between dirty surgery	Phenolic between all surgeries	a ^q									
LAMP ¹⁹⁸	▪ Substance ▪ Ward/ICU; All; T	24 months	Adding Pulsed xenon UV (90%)	Sham intervention (90%)	a b c d e i j		✓							
Rock ¹⁸⁷	▪ Substance ▪ Ward; All; R/T	24 months	Adding UV-C light (compliance varied by hospital unit)	No intervention	a b d i j	✓ ^{t,u}								
Salgado ²⁷⁸	▪ Substance ▪ ICU; HTS; R/T	11 months	Copper surfaces (47%)	Standard surfaces (87%)	a ^{k,l,r} b [?] d g j		✓		✓	✓		✓		

Footnotes:

a: routine touch decontamination of all rooms. **b:** terminal touch decontamination. **c:** gloves. **d:** hand hygiene. **e:** monitoring and feedback to the provider on decontamination compliance. **f:** monitoring and feedback on hand hygiene compliance. **g:** MRSA or VRE screening. **h:** MRSA eradication. **i:** patient's isolation. **j:** infection surveillance. **K:** QAC disinfectant. **I:** bleach in rooms with *Clostridioides difficile*. **m:** for all rooms, including those with patients with *Clostridioides difficile*. **n:** bleach. **o:** detergent. **p:** Isopropyl alcohol spray. **q:** phenolic disinfectant. **r:** Cavicide (Metrex) for spot cleaning of rooms and equipment (alcohol plus a QAC). **?:** Product not reported. **s:** hospital-acquired colonisations by MRSA. **t:** hospital-acquired colonisations by vancomycin-resistant *Enterococci*. **u:** hospital-acquired colonisations by *Clostridioides difficile*.

Review outcomes:

A: Hospital-acquired colonisations. **B:** Healthcare-associated infections. **C:** Healthcare-associated infections among staff, caregivers, or visitors. **D:** Bloodstream infections. **E:** All-cause mortality. **F:** Healthcare-associated infections-related mortality. **G:** Length of hospital stay. **H:** Adverse effects. **I:** Resistance to antibiotics or to disinfectants.

Abbreviations:

CD: *Clostridioides difficile*. **HTS:** high-touch surfaces. **ICU:** intensive care unit. **IHP:** improved hydrogen peroxide disinfectant. **MRSA:** methicillin-resistant *Staphylococcus aureus*. **NR:** not reported. **OR:** operating rooms. **QAC:** quaternary ammonium compound disinfectant. **R:** routine decontamination, that is, daily decontamination without terminal decontamination that is applied in the routine care of all patients at all times. **Ref:** reference. **T:** terminal decontamination, that is, decontamination of a room between occupying patients, also called deep decontamination. **UV-C:** no-touch disinfection with ultraviolet-C radiation. **VRE:** vancomycin-resistant enterococci.

4.1.3. Description of excluded studies

Full-text articles were excluded for the following reasons: ineligible interventions (n = 127), ineligible study designs (n = 98), or settings outside of hospitals (n = 9). Notably, 28 studies were excluded because they evaluated multi-component interventions, making it impossible to isolate the specific effects of decontamination from the broader infection control bundle. This criterion led to the exclusion of several recently published RCTs, including the CLEEN trial²⁸⁶, CLEAN FRONTLINE trial²⁸⁷, Loftus *et al.*²⁸⁸, the REACH study²⁸⁹, and the ASCOT trial²⁹⁰. Additionally, some RCTs were excluded because they assessed decontamination effectiveness based solely on environmental surface outcomes rather than patient-level outcomes^{143, 291-295}. The complete list of the primary exclusion reasons for studies that may otherwise appear eligible is provided in Annex 2.4.

4.1.4. Description of ongoing studies

Four RCTs were classified as ongoing due to the absence of published results at the time of review²⁸¹⁻²⁸⁴. These trials aimed to evaluate various interventions for the prevention of HAIs, including HPV²⁸¹, copper surfaces²⁸², engineered hospital rooms²⁸³, and surface disinfection with organosilane²⁸⁴. The expected completion dates range from 2017 to 2024, with the exception of HPVICU study²⁸¹, which did not report an anticipated end date. Further details are provided in Table 19. Characteristics of ongoing trials.

4.1.5. Risk of bias of the included studies

The risk of bias is presented in Table 20. Risk of bias judgements for each effect estimate and Table 21. Effects of decontamination of hospital environmental surfaces. Full risk of bias judgements will be presented as supplemental material in the corresponding publication of the systematic review.

Risk of bias was evaluated for 15 effect estimates derived from seven included studies informing review outcomes^{187, 197, 198, 276-278, 280}. The overall risk of bias was judged to be high for 11 of the 15 effect estimates (73%) and as having some concerns for four (27%). No effect estimate was at a low risk of bias.

Table 19. Characteristics of ongoing trials

Trial ID Reference	• Submission date	• Design	• Intervention	Primary outcome
	• Completion date	• Country • Setting	• Comparator	
ACTRN12614000034639 ²⁸¹ HPVICU	• November 2011 • Unknown	• Cluster RCT • Australia • ICU	I: HPV disinfection on discharge of patients from the ICU C: Traditional wet cleaning involving detergents and disinfectants	<i>Clostridium difficile</i> and/or MDRO acquisition rate (composite of all MDROs)
AHRQ HS021188-01 ²⁸²	• July 2012 • April 2017	• Parallel RCT • USA • ICU	I: Copper surfaces C1: Standard conventional surfaces (such as plastic or other types of coatings) C2: Sham copper-surfaces	• Incidence of HAIs • Cost- effectiveness analysis
NCT02463214 ²⁸³	• June 2015 • March 2018	• Parallel RCT • Canada • Hospital	I: Engineered room (single occupancy bone marrow transplant recovery room, engineered surfaces with manual-less devices, and surfaces coated with either copper or titanium dioxide) C: Standard room (standard bone marrow transplant recovery, single occupancy, room)	Change in bioburden on
NCT05673226 ²⁸⁴ ORG-CLEAN	• December 2022 • December 2024	• CRXO-RCT • Brazil • ICU	I: Surface disinfection with organosilane C: Usual surface disinfection	Incidence of HAIs
Abbreviations: C: Comparator. CRXO-RCT: cluster cross-over cross-sectional RCT. HAI: healthcare-associated infection. I: Intervention. ICU: intensive care unit. MDRO: multi-drug resistant organism. RCT: randomised controlled clinical trial.				

Table 20. Risk of bias judgements for each effect estimate

Outcome Study Reference	D1/D1a	D1b	D2	D3	D4	D5	Overall risk of bias	GRADE judgment
	Randomisation process	Participants' identification or recruitment timing	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result		
Comparison 1. QAC disinfectants versus with detergents for routine decontamination in the hospital ward								
1. Hospital acquired infections Karmin 276								Not serious
Comparison 2. Probiotic disinfectants versus detergent for routine decontamination in the hospital ward								
2. Hospital-acquired infections Karmin 276								Not serious
Comparison 3. Phenolic disinfectants versus detergent for routine decontamination in the hospital ward								
3. Hospital-acquired infections Danforth 197								Very serious
4. Bloodstream infections Danforth 197								Very serious
Comparison 4. QAC disinfectants versus probiotic disinfectants for routine decontamination in the hospital ward								
5. Hospital-acquired infections Karmin 276								Not serious
Comparison 5. Increased versus standard frequency of routine disinfection of high-touch surfaces								
6. MRSA colonisations Wilson 280								Serious ^a
7. Adverse effects in patients Kundrapu 277		Not applicable						Very serious
8. Adverse effects in staff Kundrapu 277		Not applicable						Very serious
Comparison 6. Adding UV light to standard practice versus standard practice alone								
9. VRE colonisations Rock 187								Serious
10. <i>Cl. difficile</i> colonisations Rock 187								Serious
11. Hospital-acquired infections LAMP 198								Serious
Comparison 7. Copper-surfaces versus standard surfaces in the intensive care unit								
12. Hospital-acquired infections Salgado 278		Not applicable						Very serious
13. Bloodstream infections Salgado 278		Not applicable						Very serious ^b
14. All-cause mortality Salgado 278		Not applicable						Very serious
15. Length of hospital stay Salgado 278		Not applicable						Very serious
Abbreviations: Low risk, Some concerns, High risk. MDRA: multidrug-resistant <i>A. baumannii</i> . MRSA: methicillin-resistant <i>Staphylococcus aureus</i> . VRE: Vancomycin-resistant <i>enterococci</i> .								
Footnotes: ^a MDRA outbreak before and during the study only the standard cleaning phase. This may have distorted the effect estimate. ^b High risk in the randomisation process and missing outcome data (suggested by sensitivity analysis in pessimistic and optimistic scenarios). Some concerns with outcome measurement and selective reporting.								

Table 21. Effects of decontamination of hospital environmental surfaces

Outcome (study) ^{Reference}	Nr. studies (Nr. participants) Mean arm follow-up	Relative effect (95% CI) UAE	Control risk for moderate risk scenario	Absolute effect (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Certainty of the evidence
Comparison 1. QAC disinfectants versus with detergents for routine decontamination in the hospital ward										
HAIs (Karmin) ²⁷⁶	1 CRXO-RCT (9,243) 33,168 patient-days	IRR 0.95 (0.69 to 1.31)	17 per 1,000 patient-days	– 1 per 1,000 patient-days (– 5 to 5)	Not serious	Not serious	Not serious	Extremely serious ^a	Not serious	⊕○○○ Very low
Comparison 2. Probiotic disinfectants versus detergent for routine decontamination in the hospital ward										
HAIs (Karmin) ²⁷⁶	1 CRXO-RCT (9,361) 33,150 patient-days	IRR 0.96 (0.69 to 1.32)	17 per 1,000 patient-days	– 1 per 1,000 patient-days (– 5 to 5)	Not serious	Not serious	Not serious	Extremely serious ^a	Not serious	⊕○○○ Very low
Comparison 3. Phenolic disinfectants versus detergent for routine decontamination in the hospital ward										
HAIs (Danforth) ¹⁹⁷	1 CRXO-RCT (5,883) —	RR 1.13 (0.57 to 2.24) UAE ^b	40 per 1,000 patients	5 per 1,000 patients (– 17 to 50)	Very serious ^c	Not serious	Serious ^d	Extremely serious ^a	Not serious	⊕○○○ Very low
BSIs (Danforth) ¹⁹⁷	1 CRXO-RCT (—) —	Range BSI incidence in phenolics wards: 0% to 1.3%. In detergents wards: 0% to 1.2%. Reporting incomplete: we could not analyse the data			Very serious ^e	Not serious	Serious ^d	Extremely serious ^f	Not serious	⊕○○○ Very low
Comparison 4. QAC disinfectants versus probiotic disinfectants for routine decontamination in the hospital ward										
HAIs (Karmin) ²⁷⁶	1 CRXO-RCT (9,188) 32,614 patient-days	IRR 1.00 (0.72 to 1.39) ^g	17 per 1,000 patient-days	0 per 1,000 patient-days (– 5 to 7)	Not serious	Not serious	Not serious	Extremely serious ^a	Not serious	⊕○○○ Very low
Comparison 5. Increased versus standard frequency of routine disinfection of high-touch surfaces										
HA MRSA colonisations (Wilson) ²⁸⁰	1 CRXO-RCT (2,504) —	OR 0.98 (0.58 to 1.66)	150 per 1,000 patients	–3 per 1,000 patients (– 57 to 77)	Serious ^h	Not serious	Serious ⁱ	Extremely serious ^j	Not serious	⊕○○○ Very low
AEs in patients (Kundrapu) ²⁷⁷	1 i-RCT (70) Mean 4.9 to 6.8 days	Patients reported no adverse effects during the use of the peracetic acid-based disinfectant.			Very serious ^k	Not serious	Not serious	Extremely serious ^l	Not serious	⊕○○○ Very low
AEs in staff (Kundrapu) ²⁷⁷	1 i-RCT (—) —	Nursing staff reported no complaints about the peracetic acid-based disinfectant			Very serious ^k	Not serious	Not serious	Extremely serious ^m	Not serious	⊕○○○ Very low

Outcome (study) ^{Reference}	Nr. studies (Nr. participants) Mean arm follow-up	Relative effect (95% CI) UAE	Control risk for moderate risk scenario	Absolute effect (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Certainty of the evidence
Comparison 6. Adding UV light to standard practice versus standard practice alone										
HA VRE colonisations (Rock)¹⁸⁷	1 CRXO-RCT (7,172) 22,937	IRR 1.00 (0.79 to 1.25)	18 per 1,000 patient-days	0 per 1,000 patient-days (– 4 to 5)	Serious ⁿ	Not serious	Not serious	Not serious ^o	Not serious	⊕⊕⊕○ Moderate
HA CD colonisations (Rock)¹⁸⁷	1 CRXO-RCT (7,172) 13,116 ^p	IRR 1.58 (0.97 to 2.58)	10 per 1,000 patient-days	6 per 1,000 patient-days (0 to 16)	Serious ⁿ	Not serious	Not serious	Very serious ^q	Not serious	⊕○○○ Very low
HAIs (LAMP)¹⁹⁸	1 CRXO-RCT (19,413) 90,477	IRR 1.10 (0.48 to 2.51) UAE ^r	17 per 1,000 patient-days	2 per 1,000 patient-days (– 9 to 26)	Serious ^s	Not serious	Not serious	Extremely serious ^a	Not serious	⊕○○○ Very low
Comparison 7. Copper-surfaces versus standard surfaces in the ICU										
HAIs (Salgado)²⁷⁸	1 i-RCT (614) Median 4 days	RR 0.64 (0.36 to 1.14) UAE ^t	240 per 1,000 patients	– 86 per 1,000 patients (– 154 to 34)	Very serious ^u	Not serious	Not serious	Extremely serious ^a	Not serious	⊕○○○ Very low
BSIs (Salgado)²⁷⁸	1 i-RCT (614) Median 4 days	RR 0.30 (0.08 to 1.05)	80 per 1,000 patients	– 56 per 1,000 patients (– 74 to 4)	Very serious ^v	Not serious	Not serious	Extremely serious ^w	Not serious	⊕○○○ Very low
All-cause mortality (Salgado)²⁷⁸	1 i-RCT (614) Median 4 days	RR 0.91 (0.63 to 1.33)	150 per 1,000 patients	– 13 per 1,000 patients (– 56 to 50) ^x	Very serious ^y	Not serious	Not serious	Extremely serious ^a	Not serious	⊕○○○ Very low
LOS (Salgado)²⁷⁸	1 i-RCT (614) Median 4 days	No difference detected in ICU LOS between groups (median 4 days in both; P = 0.74)			Very serious ^z	Not serious	Not serious	Extremely serious ^{aa}	Not serious	⊕○○○ Very low

Abbreviations

AEs: adverse effects. **BSI:** bloodstream infection. **CD:** *Clostridium difficile*. **CI:** confidence interval. **CRXO-RCT:** cluster cross-over cross-sectional randomised controlled trial. **HA:** hospital-acquired. **HAIs:** hospital acquired infections. **ICU:** intensive care unit. **I-RCT:** randomised controlled trial allocated at the individual level. **IRR:** incidence rate ratio. **LOS:** length of hospital stay. **MRSA:** methicillin-resistant *Staphylococcus aureus*. **—:** not reported. **OR:** odds ratio. **RR:** relative risk. **UAE:** unit-of-analysis error. **VRE:** vancomycin-resistant *enterococci*.

Footnotes

^a Downgraded 3 levels for extremely serious imprecision: 95% CI of the absolute effect includes both large benefit and large harm (crosses > three thresholds).

^b Corrected for UAE. First, the original Chi-square test assumed independence of events. Second, the original test did not account for cluster or cross-over correlations of CRXO designs. We applied an approximate analysis by inflating the standard error with the design effect. The corrected estimate (RR 1.13, 0.57 to 2.24), was similar to the original (RR 1.12, 0.94 to 1.35).

^c Downgraded 2 levels for very serious risk of bias. High risk due to deviations from intended interventions, missing outcome data, and outcome measurement. Some concerns about randomisation and selective outcome reporting.

^d Downgraded 1 level for serious indirectness: study conducted before 1987 (epidemiological context and CDC surveillance definitions for HAIs do not apply).

^e Downgraded 2 levels for very serious risk of bias. High risk due to deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting. Some concerns about randomisation.

^f Downgraded 3 levels for extremely serious imprecision. No CI 95% was presented.

^g Calculated by the reviewers.

^h Downgraded 1 level for serious risk of bias. An outbreak of multidrug-resistant *A. baumannii* occurred before and during the study in the standard cleaning phase only. This likely introduced differences between groups and may have distorted the effect estimate.

ⁱ Downgraded 1 level for serious indirectness: composite outcome (MRSA acquisitions, colonisations, or infections after 48 h) not exclusively assessing MRSA colonisation.

^j Downgraded 3 levels for extremely serious imprecision. 95% CI of the absolute effect includes from moderate benefit to moderate harm (crosses more than three thresholds).

^k Downgraded 2 levels for very serious risk of bias. High risk due to the randomisation process, deviations from intended interventions, missing outcome data, and outcome measurement. Some concerns about selective reporting.

^l Downgraded 3 levels for extremely serious imprecision. Neither the effect estimate nor its 95% CI was reported. The sample was small (70 patients analysed).

^m Downgraded 3 levels for extremely serious imprecision. Neither the effect estimate nor its 95% CI was reported. The staff sample size was not reported, but it was probably small.

ⁿ Downgraded 1 level for serious risk of bias. High risk due to deviations from intended interventions.

^o Not downgraded for imprecision. 95% CI of the absolute effect was limited to values consistent with a trivial or no effect.

^p The study did not plan to assess *C. difficile* colonisation. This outcome was added later with supplemental funding. As a result, *C. difficile* surveillance covered only a shorter period, whereas vancomycin-resistant *Enterococci* surveillance spanned the full study duration.

^q Downgraded 2 levels for very serious imprecision. The 95% CI of the absolute effect includes from trivial effect to moderate harm. It crosses two thresholds.

^r Corrected for unit-of-analysis error because the analysis did not account for the cluster design. We applied an approximate analysis by inflating the standard error with the design effect. The revised estimate (IRR 1.10, 0.48 to 2.51) was similar to the original (IRR 1.10, 0.94 to 1.29). The paper states that Poisson regression was used but does not clarify whether clustering was addressed. Given that the intervention and randomisation occurred at the unit level (15 units across two hospitals), failure to adjust for within-cluster correlation is likely. This is important because: nearly half of HAI cases involved patient transfers between units; environmental interventions act at the cluster level; and not accounting for clustering can lead to overly narrow confidence intervals and misleading statistical precision.

^s Downgraded 1 level for serious risk of bias. Some concerns with the randomisation process.

^t We re-defined the outcome. The registry specified the objective as reducing HAIs, but the article did not report the frequency of HAIs directly. Table 2 reported “HAI and/or colonisation” and “HAI only,” which excluded patients with both outcomes. Following the approach described in Harbarth *et al.*¹⁵⁹, we recalculated the outcome as “patients with at least one HAI” to obtain a patient-level measure consistent with the trial objective.

^u Downgraded 2 levels for very serious risk of bias. High risk in randomisation process and selective reporting. Some concerns with the outcome measurement.

^v Downgraded 2 levels for very serious risk of bias. High risk in the randomisation process and missing outcome data (suggested by sensitivity analysis in pessimistic and optimistic scenarios). Some concerns with outcome measurement and selective reporting.

^w Downgraded 3 levels for extremely serious imprecision. 95% CI of the absolute effect scenario includes from large benefit to trivial effect (crosses three thresholds).

^x Thresholds all-cause mortality ICU (absolute risk differences per 1,000 patients): small (2‰), moderate (5‰), and large (10‰).

^y Downgraded 2 levels for very serious risk of bias. High risk in randomisation process and some concerns with selective reporting.

^z Downgraded 2 levels for very serious risk of bias. High risk in the randomisation process and missing outcome data. Some concerns with outcome measurement and selective reporting.

^{aa} Downgraded 3 levels for extremely serious imprecision. It was only stated that the length of ICU stay did not differ between groups, with a median of 4 days in both ($P = 0.74$). A 95% CI for the difference of medians cannot be calculated from the available information.

4.1.6. Effects of interventions

We present the results only for outcomes with data from at least one study (see Table 21). We report unit-of-analysis errors when present and sensitivity analyses when they altered effect direction or statistical significance.

4.1.6.1 Manual touch decontamination

Four RCTs^{197, 274-276} evaluated manual touch decontamination products; however, only two^{197, 276} reported at least one review outcome, particularly HAIs and BSIs. Three of the studies were conducted in ward settings^{197, 274, 276}, while one took place in a mixed ward/ICU environment²⁷⁵. Although both the BETR multicentre, four-arm trial²⁷⁴ and the Boyce trial comparing QACs with IHP²⁷⁵ met inclusion criteria, neither reported any of the specified review outcomes.

Comparison 1. QAC disinfectants versus detergents for routine decontamination in the hospital ward

One RCT²⁷⁶ addressed this comparison and presented data for one review outcome.

Hospital-acquired infections

The evidence is very uncertain regarding the effect on HAIs (IRR 0.95, 95% CI 0.69 to 1.31; 1 RCT²⁷⁶; Absolute rate difference (ARaD) –1 infection per 1,000 patient-days, 95% CI –5 to 5; very low certainty evidence).

Comparison 2. Probiotic disinfectants versus detergent for routine decontamination in the hospital ward

One RCT²⁷⁶ addressed this comparison and presented data for one review outcome.

Hospital-acquired infections

The evidence is very uncertain regarding the effect on HAIs (IRR 0.96, 95% CI 0.69 to 1.32; 1 RCT²⁷⁶; ARaD –1 infection per 1,000 patient-days, 95% CI –5 to 5; very low-certainty evidence).

Comparison 3. Phenolic disinfectants versus detergent for routine decontamination in the hospital ward

One RCT¹⁹⁷ published in 1987 addressed this comparison and presented data for one review outcome.

Hospital-acquired infections

The evidence is very uncertain regarding the effects on HAIs (RR 1.13, 95% CI 0.57 to 2.24; re-analysed due to unit-of-analysis error; 1 RCT¹⁹⁷; ARD 5 ‰, 95% CI – 17 ‰ to 50‰; very low-certainty evidence).

Bloodstream infections

Evidence about the effects on BSIs is very uncertain. Danforth¹⁹⁷ reported BSI rates ranging from 0% to 1.3% in eight wards using a phenolic disinfectant, and from 0% to 1.2% in eight wards using detergents. However, due to incomplete reporting, the data could not be included in the analysis.

Comparison 4. QAC disinfectants versus probiotic disinfectants for routine decontamination in the hospital ward

One RCT²⁷⁶ addressed this comparison and presented data for one review outcome.

Hospital-acquired infections

The evidence is very uncertain regarding the effects on HAIs (IRR 1.00, 95% CI 0.72 to 1.39; 1 RCT²⁷⁶; ARaD 0 infection per 1,000 patient-days, 95% CI –5 to 7; very low-certainty evidence).

4.1.6.2. Increasing the frequency of manual touch decontamination of high-touch surfaces

Three RCTs^{196, 277, 280} evaluated increased frequency of routine disinfection of high-touch surfaces. However, only two studies (Wilson²⁸⁰ and Kundrapu²⁷⁷) reported eligible review outcomes. Hess¹⁹⁶ investigated the impact of additional daily disinfection of high-touch ICU surfaces using QACs, but the reported outcome—healthcare workers' gown and glove contamination—was not eligible for inclusion. Wilson²⁸⁰ implemented twice-daily ICU disinfection using ultramicrofiber cloths impregnated with a copper-based biocide, while both study arms received routine decontamination with detergent and isopropyl alcohol spray. In Kundrapu²⁷⁷, daily morning disinfection with peracetic acid was applied to high-touch surfaces, whereas routine decontamination in both arms occurred only when surfaces were visibly soiled, using unspecified products.

Comparison 5. Increased versus standard frequency of routine disinfection of high-touch surfaces

Hospital-acquired colonisations (MRSA)

The evidence is very uncertain regarding the effects on MRSA hospital-acquired colonisations (OR 0.98, 95% CI 0.58 to 1.66; 1 RCT²⁸⁰; ARD – 3 ‰, 95% CI – 57 to 77‰; very low-certainty evidence). Wilson also reported colonisations by other microorganisms, such as *Clostridium difficile*²⁸⁰, but these outcomes were ineligible for our review because the hospital screened only for MRSA. We included colonisation outcomes only when a screening policy for the microorganism was in place.

Adverse effects in patients and in staff

It is very uncertain whether increasing the frequency of high-touch surface disinfection affects safety, as this was reported in only one study²⁷⁷. The authors stated that no patients reported adverse effects and no staff reported any complaints. Conclusions are limited by the small sample size (patients: 70; staff: not reported) and short follow-up period (patients: mean 4.9–6.8 days; staff: not reported).

4.1.6.3. No-touch disinfectants: UV light-emitting devices

Three RCTs—the BETR trial²⁷⁴, the LAMP trial¹⁹⁸, and a study by Rock *et al.*¹⁸⁷—evaluated UV light-emitting disinfection devices. However, only two of these studies (LAMP trial¹⁹⁸ and Rock *et al.*¹⁸⁷) reported outcomes relevant to our review. The BETR trial²⁷⁴ assessed four terminal room disinfection strategies: standard manual disinfection using QAC (or bleach for *Clostridioides difficile*), standard disinfection plus UV-C, bleach alone, and bleach combined with UV-C. This trial, however, did not report any outcomes eligible for inclusion. The LAMP trial¹⁹⁸ compared pulsed xenon UV to a sham intervention for terminal decontamination across 15 units, including 10 wards and 5 ICUs. Rock *et al.*¹⁸⁷ evaluated the addition of UV-C light to routine and terminal cleaning protocols in four oncology units and one solid organ transplant inpatient unit.

Comparison 6. Adding UV light to standard practice versus standard practice alone

Hospital-acquired colonisations (vancomycin-resistant enterococci (VRE))

Adding UV light to standard practice probably results in little to no difference in VRE colonisations (IRR 1.00, 95% CI 0.79 to 1.25; 1 RCT¹⁸⁷; ARaD 0 cases per 1,000 patient-days, 95% CI – 4 to 5; moderate-certainty evidence).

Hospital-acquired colonisations (C. difficile)

The evidence is very uncertain regarding the effects of adding UV light to standard practice on *C. difficile* colonisations (IRR 1.58, 95% CI 0.97 to 2.58; 1 RCT¹⁸⁷; ARaD 6 cases per 1,000 patient-days, 95% CI 0 to 16; very low-certainty evidence).

Hospital-acquired infections

The evidence is very uncertain regarding the effect of adding pulsed xenon UV light to standard practice versus a sham intervention on HAIs (IRR 1.10, 95% CI 0.48 to 2.51; re-analysed due to unit-of-analysis error; 1 RCT¹⁹⁸; ARaD 2 cases more per 1,000 patient-days, 95% CI – 9 to 26; very low-certainty evidence).

4.1.6.4. Antimicrobial surfaces

One RCT evaluated the replacement of high-touch surfaces in ICUs with copper-coated materials²⁷⁸. Both study arms also employed routine and terminal disinfection using QACs—or bleach in cases of suspected or confirmed *Clostridioides difficile*—as well as Cavicide™, a combination of alcohol and QAC, for spot cleaning. No RCTs were identified that assessed other types of antimicrobial surfaces, such as those incorporating zinc, silver, triclosan, bacteriophages, cationic nanoparticles, light-activated coatings, or surfaces engineered with modified topographies or anti-adhesive properties.

Comparison 7. Copper-surfaces versus standard surfaces in the ICU

Hospital-acquired infections

The evidence is very uncertain regarding the effect on HAIs (RR 0.64, 95% CI 0.36 to 1.14; 1 RCT²⁷⁸; re-analysed by the reviewers; ARD – 86 ‰, 95% CI – 154 ‰ to 34‰; very low-certainty evidence).

Bloodstream infections

The evidence is very uncertain regarding the effect on BSIs (RR 0.30, 95% CI 0.08 to 1.05; 1 RCT²⁷⁸; ARD – 56 ‰, 95% CI – 74 ‰ to 4‰; very low-certainty evidence).

All-cause mortality

The evidence is very uncertain regarding the effect on all-cause mortality (RR 0.91, 95% CI 0.63 to 1.33; 1 RCT²⁷⁸; ARD – 13 ‰, 95% CI – 56 ‰ to 50‰; very low-certainty evidence).

Length of hospital stay

One RCT²⁷⁸ reported this outcome incompletely. It was only stated that ICU length of stay did not differ between groups, with a median of 4 days in both ($P = 0.74$). Thus, the effect of ICU copper surfaces on the length of hospital stay remains very uncertain.

4.1.6.5. Other aspects evaluated

One RCT²⁷⁹, published in 1976, compared the use of a phenolic disinfectant on operating room floors applied only after contaminated or septic procedures versus after all surgical procedures. However, the study did not report any outcomes relevant to our review.

4.2. Results of study II: SR on gloves, gowns and masks

4.2.1. Results of the search

After removing duplicates, the electronic databases searches up to June 2015 yielded 4,456 unique records. We screened the titles and abstracts to assess their potential relevance and retrieved 282 full-text articles for further evaluation. Of these, 62 appeared potentially eligible, while 220 were retrieved to verify exclusion based on information that required confirmation. However, no studies met the eligibility criteria and all the full-text articles were excluded. An additional 1,061 records were identified through trial registry searches (duplicates not removed), but none were eligible. No further studies were found through conference abstract screening or personal communication with field experts. The study selection process is illustrated in Figure 2.

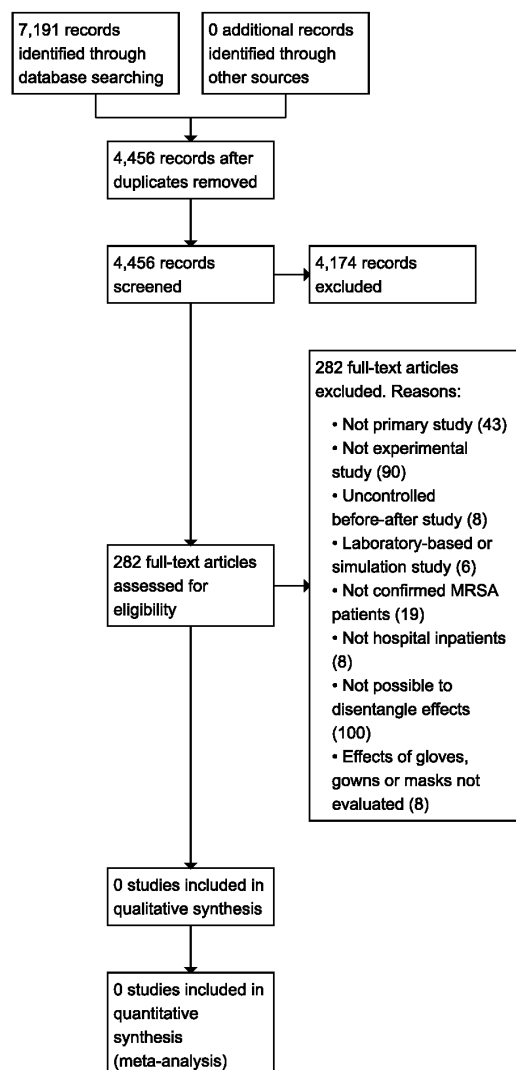


Figure 2. Flow chart gloves, gowns, masks systematic review

4.2.2. Description of included studies

No eligible studies were identified for inclusion in this review.

4.2.3. Description of excluded studies

All records were excluded following full-text eligibility assessment. The most common reason for exclusion was the inability to isolate the effects of masks, gloves or gowns (n = 100). The exclusion reasons are provided in page 34 of the publication²⁴⁴ and in Figure 2.

4.2.4. Description of ongoing studies

No ongoing studies were found up to June 2015.

4.2.5. Risk of bias of the included studies

As no studies met the eligibility criteria, a risk of bias assessment could not be conducted.

4.2.6. Effects of interventions

The effects of using gloves, gowns, or masks could not be determined, as no eligible studies—either completed or ongoing—were available at the time of this review.

4.3. Results of study III: Sex/Gender consideration in Cochrane reviews

4.3.1. Results of the search

The search strategy in the CDSR yielded 7,156 records. After screening titles and abstracts, 6,836 were excluded for not meeting the eligibility criteria. The full texts of the remaining 320 records were assessed, resulting in the exclusion of 207 full texts (reasons detailed in Figure 3). Ultimately, 113 Cochrane reviews were included (see references in “Additional file 5” of the publication)²⁶⁰.

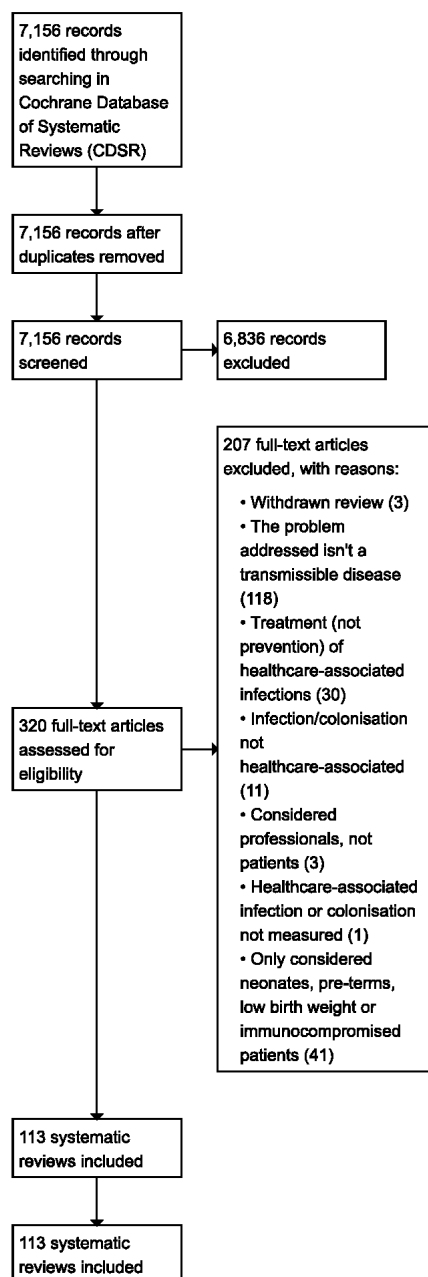


Figure 3. Flow chart of methodology study

4.3.2. Description of the included reviews

This study included 113 reviews. The reviews were published between 2003 and 2016 within 23 different Cochrane Review Groups. The Cochrane Wounds Group was the review group with the most reviews included in this study (35/113 reviews; 31%), followed by the Anaesthesia, Critical, and Emergency Care Group (13/113 reviews; 12%), and the Incontinence Group (10/113 reviews; 9%). Each of the remaining Cochrane Review Groups published less than ten of the included reviews.

All included reviews assessed the effects of interventions aimed at preventing HAIs. The most frequently interventions targeted surgical site infections (50/113 reviews; 44%), followed by those addressing infections related to vascular access devices (21/113; 19%) and hygiene practices involving patients and healthcare personnel (14/113; 12%). Other interventions included strategies to prevent urinary catheter-associated infections, educational and training initiatives to prevent HAIs, and interventions to prevent HAIs related to dental procedures.

All reviews planned to assess at least one of the predefined study outcomes. HAI occurrence was the most commonly assessed outcome, reported as eligible in 105/113 reviews (93%), followed by total mortality (66/113; 58%), surrogate measures of HAI (31/113; 27%), colonisation (19/113; 17%), HAI-related mortality (15/113; 13%), and antimicrobial resistance (14/113; 12%).

RCTs were eligible in all reviews (100%). In 57 reviews (50%), RCTs were the only eligible design, whereas 55 reviews (49%) also admitted at least one type of NRSI. In one review (1%), the NRSIs eligibility was not clearly reported.

4.3.3. Description and assessment of the terminology and definitions used for sex and gender

Out of 113 reviews, 100 (88%) used at least one sex- or gender-related term. However, terminology varied across reviews, and none explicitly distinguished between the concepts of sex and gender. Sex was the term used in the most reviews (58/113, 51%), followed by *male* (54/113, 48%), *woman* or *women* (53/113, 47%), *female* (50/113, 44%), *gender* (42/113, 37%), *men* or *man* (28/113, 25%), and other terms, particularly *boys* or *girls* (3/113, 3%). Thirteen reviews (12%) did not use any sex- or gender-related terminology. These terms appeared most frequently in the 'Characteristics of studies' section (84/113, 74%), while only 10 reviews (9%) used such terms in the conclusions. Table 22 presents a breakdown of the sections in which sex/gender terms were used.

Table 22: Reviews (%) using sex and gender terms in each review section

Review section	Sex	Gender	Male ^a	Female ^b	Men ^c	Women ^d	Other
Abstract	2%	-	-	1%	2%	8%	-
Background	3%	1%	4%	5%	3%	15%	-
Plain language summary	-	2%	1%	2%	-	8%	-
Eligibility criteria	4%	8%	1%	1%	4%	13%	-
Search methods	-	-	-	-	-	1%	-
Data collection and analysis	12%	12%	4%	4%	5%	9%	-
Results	9%	10%	12%	12%	7%	18%	1%
Discussion	4%	2%	2%	1%	4%	15%	-
Authors' conclusions	1%	-	-	1%	1%	7%	-
Characteristics of studies	31%	22%	42%	35%	13%	35%	2%
Other sections	5%	3%	-	-	-	3%	-
Not reported	49%	63%	52%	56%	75%	53%	97%

Footnotes:

^a 'Male', 'males' or 'm'. ^b 'Female', 'females' or 'f'. ^c 'Men' or 'man' or 'm'. ^d 'Women' or woman

None of the reviews provided definitions for sex or gender, which prevented an assessment of whether terms were used appropriately. In 13 reviews, such an assessment was not applicable due to the absence of relevant terminology. Among the remaining 100 reviews, 11 (11%) used incorrect terms—eight used *male* or *female* to refer to gender, and three used *men* or *women* to refer to sex.

Furthermore, 89 reviews (89%) employed unclear terminology. This was due to the lack of definitions for sex or gender (80 reviews), inconsistent use of both sex and gender terms to describe the same concept (8 reviews), or the use of the abbreviation “M” without clarification (1 review). The criteria used to classify terminology as unclear or incorrect are shown in Figure 4.

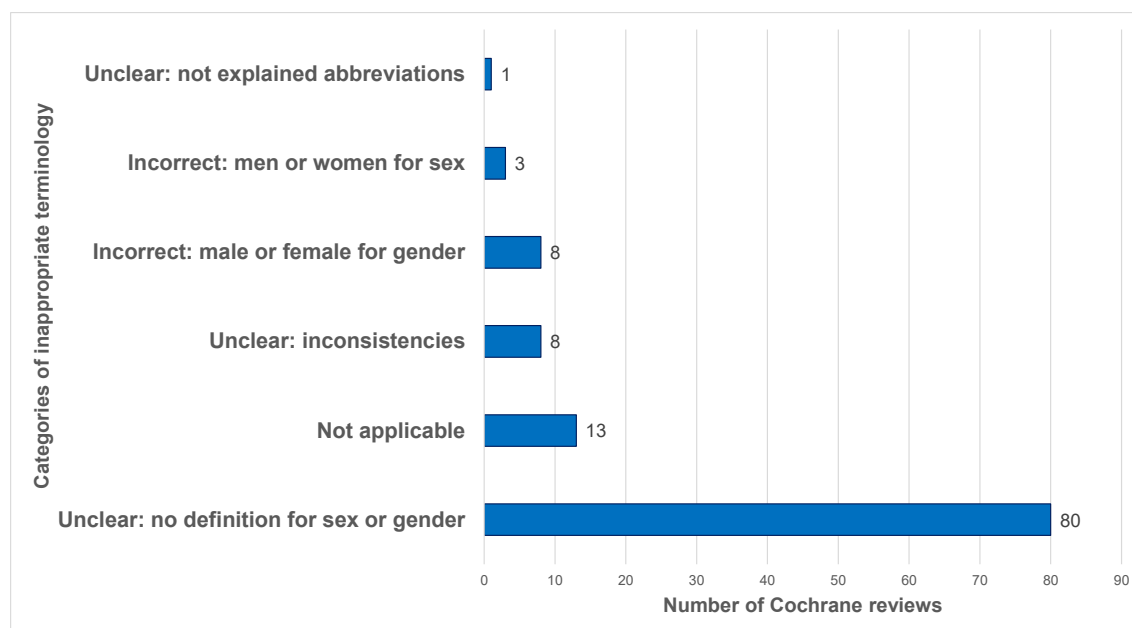


Figure 4. Appropriateness of the sex and gender terminology

4.3.4. Content of the reviews about sex and gender

The sex- and gender-related content addressed in each review section is described below. Sex and gender considerations were not reported for 11 reviews²⁹⁶⁻³⁰⁶ because, due to the nature of their topics, these reviews included only female participants. Examples of such topics include interventions to prevent healthcare-associated infections in caesarean section, operative vaginal delivery, abortion, amniotomy, and prelabour rupture of membranes. Figure 5 provides a graphical summary of the assessments, while Table 23. Responses to the SGAT-SR presents the overall responses to the SGAT-SR tool. Detailed assessments are available in “Additional file 6” and “Additional file 7” of the publication²⁶⁰.

None of the reviews met all applicable items of the SGAT-SR. Notably, 51 of 102 reviews (50%) fulfilled none of the applicable items. Among the remainder, 38 reviews out of 102 (37%) met one item, 9 (9%) met two items, 3 (3%) met three items, and 1 review (1%) met four applicable items.

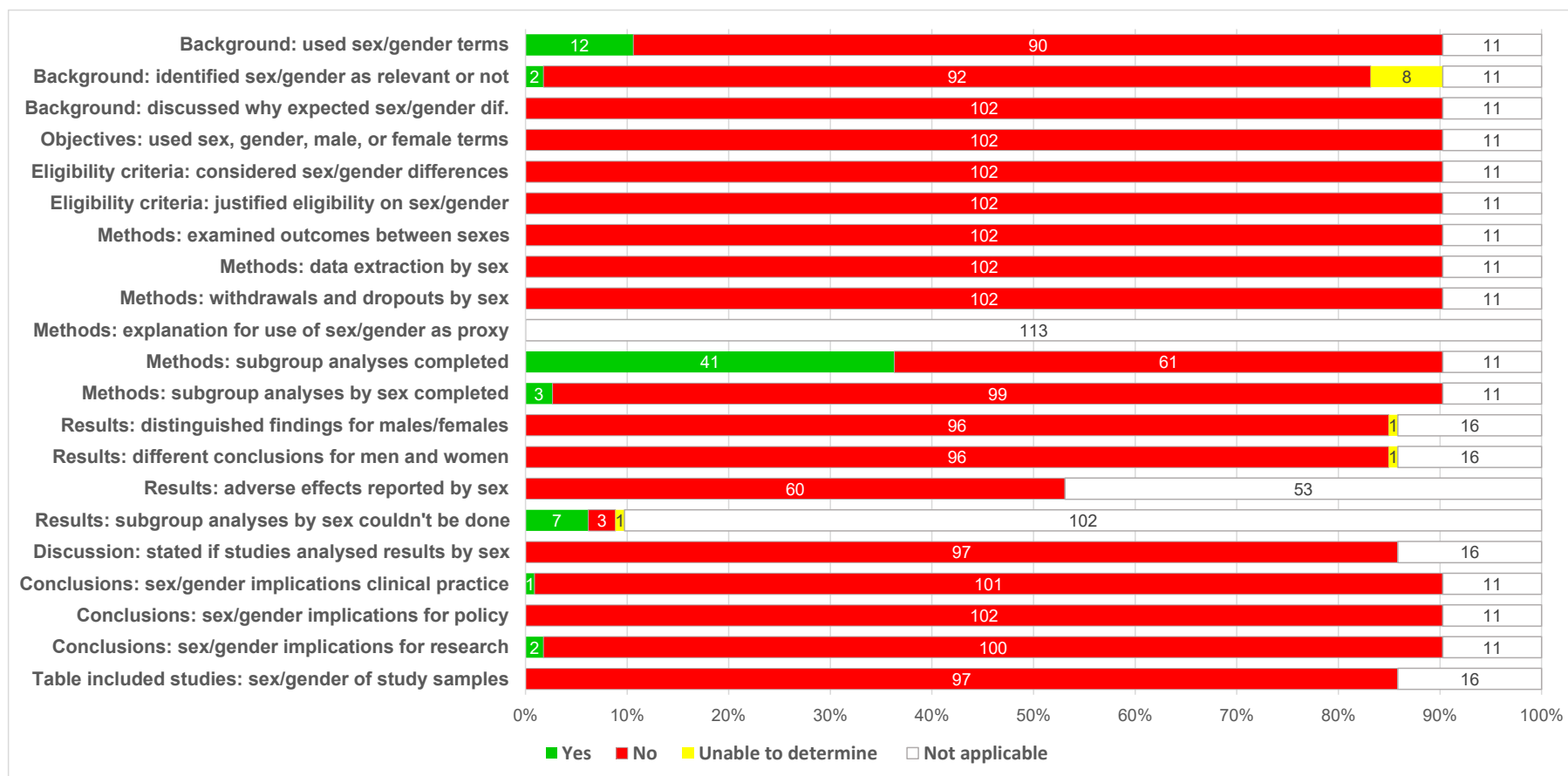


Figure 5. Sex and gender appraisal graph across reviews for each item of the tool

Table 23. Responses to the SGAT-SR

Review section	Tool question	Reviews meeting the criteria (n)			
		Yes	No	Unable to determine	Not applicable ^a
1. Background	1.1. Are the terms sex and gender used in the background?	12	90	0	11 ^b
	1.2. Are sex/gender identified as relevant or not to review question?	2	92	8	11 ^b
	1.3. Does background discuss why sex/gender differences may be expected?	0	102	0	11 ^b
2. Objectives	2.1. Are the terms sex, gender, male, or female used in objectives?	0	102	0	11 ^b
3. Inclusion-exclusion criteria	3.1. Do the review's inclusion-exclusion criteria consider sex-gender differences?	0	102	0	11 ^b
	3.2. Was there justification or explanation for the exclusion of some groups?	0	102	0	11 ^b
4. Methods	4.1. Does the review examine whether outcome measures are different for males and females?	0	102	0	11 ^b
	4.2. Did the review extract data by sex?	0	102	0	11 ^b
	4.3. Did the review extract data on sex of withdrawals and dropouts?	0	102	0	11 ^b
	4.4. In cases where sex/gender is used as a proxy, is there an explanation?	0	0	0	113
	4.5. Were any subgroup analyses completed?	41	61	0	11 ^b
	4.6. Were subgroup analyses by sex completed?	3	99	0	11 ^b
5. Results and analysis	5.1. Do results distinguish between findings for males/females?	0	96	1	16: 11 ^b , 6 ^c
	5.2. Does the review report conclusions that are different for men and women?	0	96	1	16: 11 ^b , 6 ^c
	5.3. If adverse effects are reported, is information sex-disaggregated?	0	60	0	53: 11 ^b , 6 ^c , 9 ^d , 33 ^e
	5.4. Does review note that subgroup analyses by sex could not be done?	7	3	1	102
6. Discussion & conclusion	6.1. Does the review report that primary studies analysed or failed to analyse results by sex?	0	97	0	16: 11 ^b , 6 ^c
	6.2. Does the review address sex/gender implications for clinical practice?	1	101	0	11 ^b
	6.3. Does the review address sex/gender implications for policy and regulation?	0	102	0	11 ^b
	6.4. Does the review address sex/gender implications for research?	2	100	0	11 ^b
7. Included studies table	7.1. Detailed information on sex/gender of the study samples?	0	97	0	16: 11 ^b , 6 ^c

Footnotes: ^a Some reviews were classified as "Not applicable" for more than one reason. ^b One sex topic. ^c No included studies. ^d Adverse effects planned in the review, but not reported as included studies reported no adverse effects. ^e Adverse effects not planned in the review.

4.3.4.1. Background

Only 12 of 102 reviews (12%) used sex- or gender-related terms in the background section. Of these, just two reviews (2%) explicitly stated the relevance of sex or gender to the review question, while in eight reviews (8%) this relevance was unclear. No review (0/102) discussed why sex or gender differences might be expected.

4.3.4.2. Objectives

No review (0/102) used the terms *sex*, *gender*, *male*, or *female* in its stated objectives.

4.3.4.3. Inclusion/exclusion criteria

No review used sex or gender as a criterion for study eligibility (0/102), nor did any review provide a rationale for considering sex or gender differences when determining eligibility (0/102).

4.3.4.4. Methods

No review (0/102) planned to examine, or ultimately examined, whether outcome measures differed between males and females. Similarly, no review planned to extract or extracted data disaggregated by sex (0/102), reported withdrawals or dropouts by sex (0/102), or used sex or gender as a proxy for other measures (0/102).

Although 86 of 102 reviews (84%) planned to conduct subgroup analyses, only 41 reviews (40%) were able to complete at least one such analysis. Sex was selected as the subgroup factor in 10 reviews (10%); however, only three reviews (3%) were able to complete this analysis.

4.3.4.5. Results and analysis

Among reviews for which assessment was applicable, none distinguished findings between males and females (0/97) or reported sex-specific conclusions regarding effectiveness, efficacy, or safety (0/97). For one review³⁰⁷, we judged that these two items of the tool were unclear because results and conclusions were reported separately only for some outcomes. No review reported adverse effects disaggregated by sex (0/60).

Of the 10 reviews that planned but were unable to perform subgroup analyses by sex, seven (70%)³⁰⁸⁻³¹⁴ explained why this analysis could not be completed.

4.3.4.6. Discussion and conclusions

No review for which assessment was applicable (0/97) discussed whether the included studies had analysed, or failed to analyse, results by sex. Overall, only 3 of 102 reviews (3%) considered sex- or gender-related implications in their conclusions. One review (1%) discussed implications for clinical practice, while two reviews (2%) addressed implications for future research. No review considered implications for policy or regulation.

4.3.4.7. Table of included studies

No review (0/97) provided complete information on both sex and gender for the samples of all included studies. Regarding the sex of the recruited participants, 78 of 97 reviews (80%) provided no information, while the remaining 19 reviews (20%) provided unclear information. With respect to gender of the recruited participants, 87 of 97 reviews (90%) provided no information, and 10 reviews (10%) provided unclear information.

Information about the sex or gender of the recruited samples was considered unclear for several reasons, including the absence of definitions for sex or gender, authors used sex or gender terms but they did not state if they referred to sex or gender, and the authors misused the terms (men or women for sex, or male or female for gender).

4.3.5. Sex- and gender-based analysis (SGBA) in the included reviews

4.3.5.1. Reporting of the sex and the gender characteristics of the study participants

None of the reviews accurately reported the sex or gender characteristics of the study participants, as none attempted to do so across all included studies. Moreover, the methods used to ascertain participants' sex or gender were never reported in any of the reviews.

4.3.5.2. SGBA in the included reviews

Ten reviews (10/102 [10%]) planned to conduct a SGBA, but only three (3/102 [3%]) could complete the analysis. In all cases, SGBA was conducted using subgroup analysis—based on sex in one review and gender in two. Two reviews performed subgroup analyses by pooling study results to evaluate the effect of sex or gender on the outcome, while the third conducted a descriptive subgroup analysis, reporting within-study differences by gender without pooling data.

4.3.6. Consideration of sex- and gender-related findings in the review conclusions

Only 3 of the 102 reviews (3%)^{307, 308, 315} considered sex- or gender-related findings in their conclusions. One review addressed clinical implications, noting that “siliconised catheters may be less likely to cause urethral side effects in men”³⁰⁷. The other two discussed research implications, stating that “sub-group analysis would give valuable data as to whether certain policies are more effective in sub-groups such as females”³⁰⁸, and recommending that “future trials comparing suprapubic and intermittent urethral catheterisation for short-term use in hospitalised men should be conducted [...]”³¹⁵. However, none of the reviews addressed the policy or regulatory implications of sex or gender findings.

4.4. Results of study IV: NRSIs consideration in Cochrane reviews

4.4.1. Results of the search

The number of Cochrane reviews evaluating the effects of interventions to prevent HAIs was 113 (see 4.3.1. Results of the search).

4.4.2. Number of Cochrane reviews of interventions to prevent HAIs admitting NRSIs

Of the 113 reviews, 57 (50%) explicitly excluded NRSIs, while 55 (49%) defined them as eligible. In one review (1%)³¹⁶, the eligibility of NRSIs was unclear.

4.4.3. Justifications provided for NRSIs admission

Of the 55 reviews that considered NRSIs eligible, only seven (13%)^{244, 317-322} provided at least one justification for their inclusion. In four of these reviews (57%)³¹⁹⁻³²², the justification was that NRSIs would be included only when no RCTs were available. The remaining three reviews (43%)^{244, 317, 318}, justified inclusion on the grounds of the expectation that the intervention was extremely unlikely to be studied in RCTs. Among these justifications, only the latter aligned with the guidance provided in the Cochrane Handbook¹⁶⁹.

4.4.4. Study design labels used for NRSIs

The most frequently used study design label for NRSIs was "quasi-randomised controlled trial," employed in 48 of the 55 reviews that included NRSIs (87%), followed by "controlled clinical trial," reported in 10 reviews (18%). Additional details are provided in Figure 6.

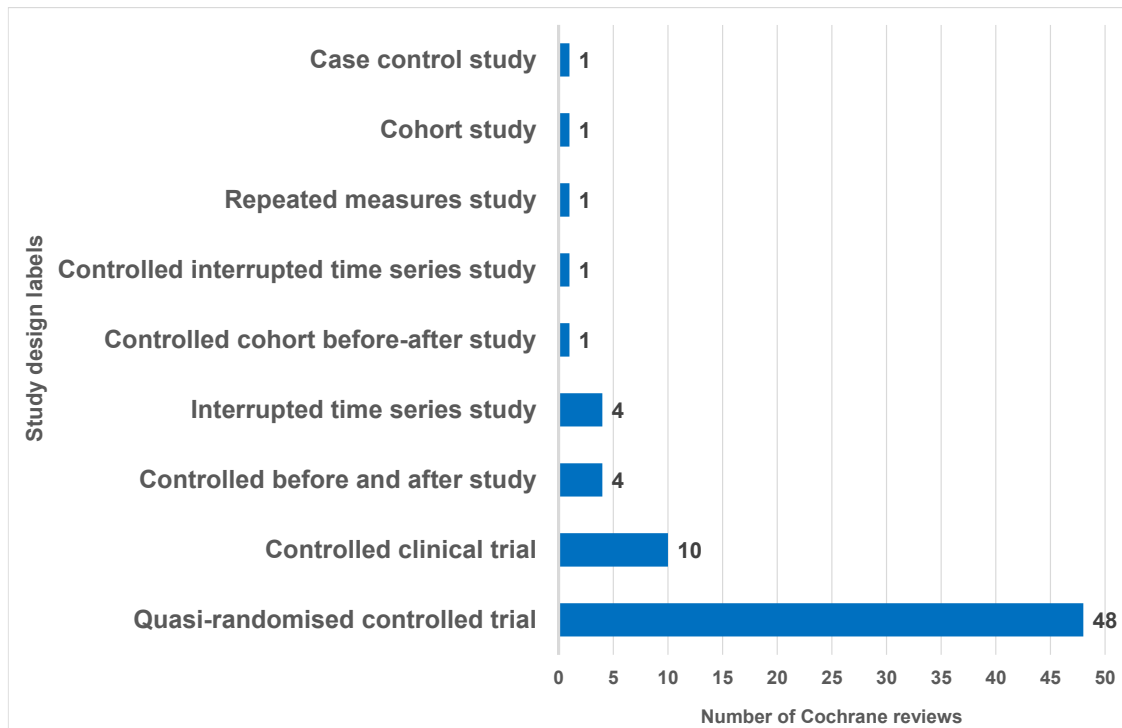


Figure 6. Study design labels used

4.4.5. Definitions used for NRSIs

Of the 55 systematic reviews that admitted NRSIs, 37 (67%) relied solely on study design labels without providing any explanation of the underlying design features. In contrast, 18 reviews (33%) described at least one key design feature for at least one eligible NRSI. However, no review fully described all key study design features as recommended by the *Cochrane Handbook*¹⁶⁹ for all eligible NRSIs. Figure 7 illustrates how study design features were characterised in the descriptions of eligible study designs across the reviews that included NRSIs.

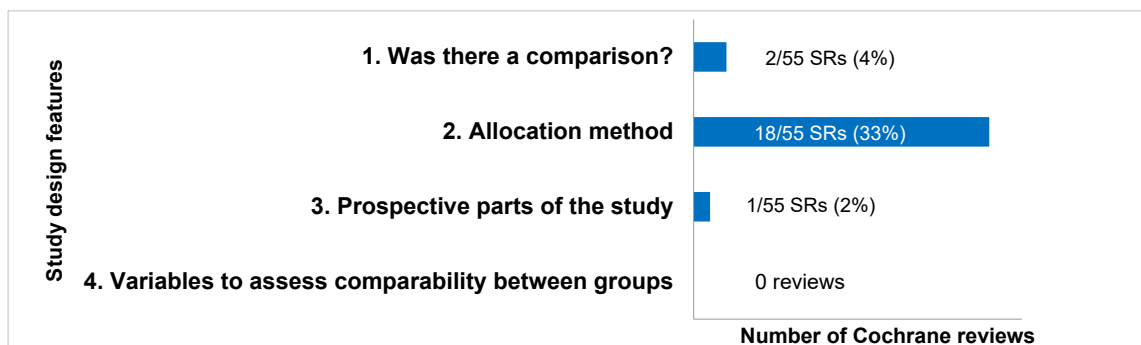


Figure 7. Nr. reviews describing each design feature for at least one NRSI

4.5. Results of study V: Methodological challenges in SRs

The methodological challenges in SRs of infection control interventions identified across the dissertation are listed below.

4.5.1. Definition of the review question

4.5.1.1. Evaluation of vertical or horizontal infection control interventions

SRs should ideally evaluate horizontal strategies. Nevertheless, if a vertical approach is selected, it must be explicitly stated and justified.

“Vertical” infection prevention strategies target specific organisms (e.g., MRSA surveillance and contact isolation), whereas “horizontal” strategies aim to reduce transmission of multiple pathogens (e.g., universal contact precautions in high-risk settings).

4.5.1.2. Core outcome set for RCTs of hospital infection control interventions

There is a need to develop a core outcome set for RCTs of hospital infection control interventions.

This core outcome set should prioritise clinically meaningful, patient-centred outcomes—such as HAIs and adverse effects—rather than surrogate measures like microbial surface burden^{113, 323}.

4.5.1.3. Evaluation of the unintended effects of infection control interventions

Assessing the risks associated with infection control interventions often requires methodologies beyond the scope of traditional RCTs³²⁴.

The evaluation of unintended effects frequently necessitates a separate SR focused specifically on harms, distinct from reviews assessing intended benefits.

4.5.1.4. Justification and definition of eligible study designs

Review authors should justify the inclusion of non-RCT designs and define eligibility criteria based on methodological features rather than design labels.

Review authors should be prepared to include alternative study designs beyond the conventional individually allocated RCTs. These may include group-level randomised studies, such as traditional cluster RCTs, as well as cluster designs with additional methodological advantages—particularly CRXO-RCTs and SW-CI-RCTs. Moreover, authors may consider including NRSIs.

4.5.1.5. Eligibility of outbreak reports

Clear guidance is needed to decide when outbreak reports are relevant for SRs of infection control interventions.

4.5.2. Study selection

4.5.2.1. Identification of the components of infection control interventions

There is a need for tools to help review authors assess whether studies of complex interventions allow isolation of specific intervention effects.

Infection control interventions are often implemented as bundles—combinations of strategies such as hand hygiene promotion, mupirocin decolonisation, and glove use. These bundles are frequently poorly described, making it difficult to determine whether a component is central or merely a co-intervention. This lack of clarity hampers the ability of review authors to assess whether a study comparison allows isolating the effect of a specific intervention.

4.5.2.2. Classification of the study designs during study selection

Infection control interventions are evaluated using a variety of study designs, many of which are non-randomised and inconsistently labelled or defined^{270, 271, 325, 326}. This poses challenges for authors of SRs of infection control interventions, particularly during the study selection process.

As the scope of study designs in infection control research expands—potentially increasing the demand for SRs that incorporate NRSI evidence—there is a growing need to evaluate study design classification frameworks proposed by Cochrane based on design features rather than study design labels alone²⁷¹. Such an approach may improve the identification and selection of eligible studies but it needs evaluation.

4.5.2.3. Distinguishing between experimental or observational studies

Distinguishing between observational and experimental designs is often difficult based solely on titles and abstracts.

A study should be classified as experimental when the intervention was deliberately allocated by the researcher with the intent to observe its effects. Specifically, the following minimum criteria must be met: 1) a prospective baseline assessment; 2) a prospective allocation of the intervention; and 3) a prospective outcome assessment²⁴⁵.

4.5.2.4. Workload implications of not excluding studies solely on the basis of the reporting of the outcome data

Review authors should consider the implications of considering outcome reporting during title and abstract screening, given its impact on the review team's workload and the exclusion of eligible studies.

The *Cochrane Handbook* advises against excluding studies solely due to missing outcome data, as this may introduce selective outcome reporting bias¹⁵⁷. Review authors should clearly state whether studies that do not mention HAIs in the title or abstract will be assumed not to report them and thus excluded. Given the high prevalence of studies evaluating decontamination efficacy based only on microbial surface load, this approach can substantially reduce screening burden. However, some studies may have reported HAIs only in the full text, and their exclusion may result in missed eligible studies—warranting cautious interpretation.

4.5.3. Data extraction

4.5.3.1. Adaptation of existing reporting guidelines for infection control intervention studies

Adapted reporting guidelines for primary studies of infection control interventions can also support review authors in guiding data extraction for their SRs.

The existing reporting guidelines for primary studies need to better accommodate the peculiarities of infection control intervention research. First, the ORION statement¹¹³—originally developed to improve transparency in reporting outbreak investigations and studies on nosocomial infection interventions—requires both updating and wider adoption. Second, although the TIDieR checklist¹⁶⁵ is a useful tool for reporting interventions, it does not adequately address elements specific to infection control.

4.5.3.2. Development of re-usable and standardised data extraction forms for studies of infection control interventions

There is a need for a standardised data extraction form that captures a minimum set of essential items to be efficiently collected from studies of infection control interventions.

Ideally, such a form should be informed by established reporting guidelines, electronic, easily shareable, and modifiable by other review authors, thereby saving time during implementation.

4.5.4. Risk of bias assessment of infection control interventions studies

4.5.4.1. Risk of bias assessment of cluster crossover RCTs and stepped-wedge cluster RCTs

There is a need of methodological guidance on how to assess the risk of bias of CRXO-RCTs and SW-CI-RCTs.

It remains unclear whether RoB 2 requires adaptation for CRXO-RCTs and SW-CI-RCTs.

4.5.4.2. Risk of bias factors specific to studies of infection control interventions

In addition to the standard RoB 2 domains, factors specific to infection control interventions should be assessed for infection control studies, but their formal integration into the RoB 2 tool should be piloted and evaluated.

The following factors are specific to infection control interventions.

Seasonality (also known as seasonal bias): The seasonal (period in the year) effects may provide alternative explanations for an observed effect of an infection control intervention. For instance, higher winter admissions of elderly patients can lead to increased MRSA cases unrelated to the intervention^{74, 113}.

Contamination: In a trial, application of one of the interventions in participants intended to receive the other¹⁷². Cluster allocation usually reduces the likelihood of contamination.

Carry-over effect: In a cross-over trial, carry-over is when the effect of an intervention given in one period persists into a subsequent period, interfering with the effect of the next intervention and biasing the overall effect estimate toward the null¹⁹⁴.

Further discussion is needed on key methodological issues, including the following.

- The minimum duration of wash out period to prevent carry-over effect in crossover designs of non-pharmacological infection control interventions. We consider that it should last at least one month, but we acknowledge that the minimal duration requires further study.
- Potential differences in carry-over risk between cross-sectional and longitudinal CRXO-RCTs
- Influence of temporal trends in SW-CI-RCTs, in which the intervention's effects might be confounded with any underlying temporal trend, as more clusters are exposed to the intervention towards the end of the study than in its early stages³²⁷.

4.5.4.3. Bias due to deviations from intended interventions

Assessing the risk of bias due to deviations from intended interventions can be especially challenging in studies of infection control interventions, as explained below.

Judgements about whether deviations from the intended interventions arise due to the experimental context

Review authors should pre-specify which deviations from the intended interventions will be interpreted as arising from the experimental context, but this can be difficult.

Review authors should pre-specify the review's analytical focus—either the effect of assignment at baseline (ITT effect) or the effect of adherence to the intervention protocol (PP effect)²⁰⁶.

The assessment of the risk of bias due to deviations from intended interventions should be aligned with this focus. However, guidance is still needed on how to judge whether deviations from intended infection control interventions can reasonably be attributed to the experimental context.

Studies of infection control interventions are susceptible to the Hawthorne effect

Operational guidance is needed to help review authors assess the risk of bias due to the Hawthorne effect.

The Hawthorne effect refers to behavioral changes resulting from awareness of being observed or participating in a study³²⁸. It can be relevant in studies of infection control interventions, as these practices are highly dependent on provider behavior. However, the specific conditions, mechanisms, and magnitude of the Hawthorne effect remain poorly understood³²⁸.

Cluster-RCTs—particularly those randomising hospitals—can reduce the risk of bias introduced by the Hawthorne effect. By randomising hospitals, cluster-RCTs can better reflect routine clinical practice, thereby potentially mitigating this bias^{329 127, 330}.

Poor reporting and the absence of standardised metrics to assess adherence to infection control interventions

Operational guidance is needed on how to summarise adherence to the allocated interventions by study arm and incorporate it into risk of bias assessments and interpretation of review findings.

Adherence to an intervention—also referred to as compliance, intervention integrity, or intervention fidelity—describes the extent to the study intervention was delivered as

intended, including the performance of planned procedures and the avoidance of proscribed ones³³¹. Accurate measurement and transparent reporting of adherence in RCTs are critical, as low adherence can compromise both the internal validity and generalisability of study findings³³².

Review authors should extract adherence data and use it to inform risk of bias assessments, as well as additional analyses such as subgroup analyses or meta-regression. Incorporating adherence information is essential for understanding the effectiveness of interventions.

However, authors of SRs of infection control interventions face challenges in assessing the risk of bias due to deviations from intended interventions, primarily because of: (1) limited monitoring and poor reporting of adherence in primary studies; (2) the lack of a standardised approach for assessing compliance with infection control interventions, such as environmental surface cleaning in hospitals; and (3) the absence of standardised metrics for summarising compliance at the study-arm level.

Blinding providers of infection control interventions

Regardless of whether blinding of providers is possible, review authors must assess the risk of bias due to deviations from the intended interventions.

The *Cochrane Handbook* identifies blinding of intervention providers as the primary method to prevent bias from deviations from intended interventions²⁰⁶. However, this is often difficult in infection control trials, where interventions are typically non-pharmacological and hard to mask^{333 175}. However, although designing credible sham interventions remains challenging, implementing them in control groups may be feasible.

Regardless of whether blinding is possible, review authors must assess the risk of bias due to deviations from the intended interventions in infection control intervention studies. When blinding is not feasible, performance bias can be minimised by a standardisation of the trial protocol to ensure that all groups receive identical ancillary care.

However, adherence to both the primary intervention and co-interventions is often poorly monitored and inadequately reported in the primary studies. This lack of transparency complicates the assessment of bias arising from deviations from the intended interventions.

4.5.4.4. Bias due to missing outcome data

Existing methods for assessing bias from missing outcome data focus mainly on longitudinal designs, but CRXO-RCTs with cross-sectional or mixed designs pose distinct challenges that require tailored guidance.

CRXO-RCTs can have cohort, cross-sectional, or mixed designs¹⁵³. In a **cohort design**, the same set of participants is followed over time. In a **cross-sectional design**, different participants are measured at each time point; thus, each cluster-period consists of a cross-section of different individuals. A *cluster-period* refers to a grouping of observations based on both the time of measurement and the cluster¹⁵⁴. In a **mixed design**, each cluster-period includes a repeated cross-section, which may involve the same or different individuals.

Current Cochrane guidance for assessing bias due to missing outcome data is tailored to longitudinal designs²⁰⁶. However, there is a lack of specific guidance for assessing this domain in trials with cross-sectional or mixed designs. Criteria from a recently developed tool for assessing the risk of bias in studies estimating prevalence may offer a useful framework in such cases³³⁴.

4.5.4.5. Bias in measurement of the outcome

Review authors should assess the risk of ascertainment and detection biases in measuring HAIs, even for seemingly objective outcomes such as bacteraemias.

The determination of infection outcomes—even in those outcomes that seem more objective, such as bacteraemia—involves clinical judgements prone to measurement biases.

Ascertainment bias may arise when clinicians aware of a patient's intervention group alter their behaviour to detect the outcome based on their expectations of the intervention's effectiveness.

Detection bias occurs when outcome assessors, unblinded to group assignment, influence the diagnosis through subjective interpretation. The diagnosis of HAIs is a complex process that requires clinical judgment, which may be affected by the lack of blinding of the outcome assessors. In the absence of blinding, they may unintentionally influence the diagnosis.

Besides, the adjudication of colonisations or infections as “healthcare-associated” depends on allocating the start of the infection to a particular timeframe, which is also a judgement subject to bias.

This context highlights the relevance of incorporating mechanisms to minimise measurement biases in infection control studies. Examples of mechanisms to minimise these risks are the following³³⁵: 1) Use of standard procedures to determine the presence of infections that do not rely on arbitrary decisions of clinicians; 2) Blind the outcome assessment, that is, blinded outcome adjudicators or involve external evaluators; 3) Use of objective measures, such as prioritising hard endpoints and structured observation, to reduce the impact of subjective interpretation.

Caution with colonisation as an outcome

Review authors should consider colonisation outcomes only in studies that implemented a screening policy at admission for the healthcare-associated pathogen(s) under investigation.

This approach ensures the validity of colonisation data by distinguishing between pre-existing and newly acquired colonisation during hospitalisation⁷⁴.

4.5.4.6. Bias in selection of the reported result

Prospective study registration not available

Guidance is needed on how to evaluate bias in the selection of reported results when no prospectively registered protocol is available.

Studies of hospital infection control interventions often lack pre-registered protocols in public registries. In some cases, protocols exist but were not registered in advance. This context limit the ability of review authors to assess the risk of selective outcome reporting.

To address this issue, formal guidance is needed on how to evaluate bias in the selection of reported results when no prospectively registered protocol is available. Clarification is also needed on whether review authors should consider information submitted to regulatory bodies (e.g., the FDA) during this assessment.

4.5.4.7. Assessment of the risk of bias in effect estimates from composite outcomes

Methodological guidance is needed to support the evaluation of risk of bias associated with composite outcomes

Studies of infection control interventions frequently report composite outcomes, which may combine infections caused by different target organisms (e.g., MRSA, VRE, or both) or include mixed endpoints (e.g., “colonisation, infection, or both”). Review authors

should plan how to address such outcomes. One option is to exclude composite outcomes and attempt to disaggregate the data into individual, non-composite outcomes.

If composite outcomes are admitted, reviewers should be aware that assessing their risk of bias is complex. For example, it is challenging to assess missing outcome data or the blinding of the outcome assessment.

4.5.5. Dealing with unit-of-analysis errors

4.5.5.1. Unit of analysis issues can be frequent in infection control studies

How review authors should address unit-of-analysis errors that cannot be corrected remains unclear.

Review authors should be able to identify and address UAEs that may present in studies of infection control interventions. These include the inappropriate use of statistical methods that assume independence of observations—such as Chi² tests or linear regression—to analyse infection or colonisation outcomes, UAEs in cluster and crossover trial designs, and the inadequate analysis of recurrent events within the same participant.

Although the *Cochrane Handbook* outlines methods for identifying and correcting UAEs¹⁹⁴, it remains unclear how to proceed when such errors cannot be corrected. For instance, while the Handbook states that UAEs should not be included in the risk of bias assessment—since they relate more to the precision of the estimate than to bias—it does not explicitly clarify whether their presence warrants downgrading the certainty of evidence (e.g., under the domain of imprecision), or how such decisions should be made.

4.5.5.2. Handling unit-of-analysis errors in non-conventional RCTs

Further guidance is needed on appropriate methods for addressing UAEs in CRXOs and SW-CI-RCTs.

Our SR applied an approximate correction for UAEs in CRXOs, as recommended by the Cochrane Methods Support Unit. However, methodological research on their integration into SRs remains limited^{153, 195}. The *Cochrane Handbook* currently offers no specific guidance on managing UAEs in these trial designs¹⁴¹.

To address these gaps, we recommend the development of dedicated guidance on the identification, correction, and interpretation of UAEs in CRXOs and SW-CI-RCTs, particularly in the context of meta-analyses of infection control interventions.

Additionally, the availability of a database containing within-period and between-period correlation coefficients (WPC and BPC) would support review authors in applying appropriate corrections for these errors.

4.5.6. Meta-analysis of infection control intervention studies

4.5.6.1. Meta-analyses with few studies

When only two to four studies are available, reviewers should consult current methodological guidance to perform and interpret meta-analysis³³⁶⁻³³⁸.

The *Cochrane Handbook* recommends random-effects meta-analysis when between-study heterogeneity is expected, assuming that studies estimate different but related effects³³⁸⁻³⁴⁰. Several methods exist to estimate between-study variance³³⁶. Until 2024, RevMan used only the DerSimonian and Laird moment-based method^{339, 340}; as of 2024, restricted maximum likelihood (REML) is the default³³⁸.

However, interpreting random-effects meta-analyses with few studies requires caution. Available methods for estimating between-study variance—such as Wald-type or the Hartung-Knapp-Sidik-Jonkman (HKSJ) adjustment—do not provide reliable CIs when study numbers are low^{336, 338, 341}. When very few studies are included, these methods may not reliably estimate heterogeneity, resulting in too wide 95% CIs^{336, 337, 342}.

4.5.6.2. Meta-analyses with studies with zero events

When few studies are available and many report zero events, reviewers should consult current guidance and select appropriate meta-analytical methods³³⁸.

Meta-analyses involving zero events pose significant methodological challenges in SRs of hospital infection control, especially for rare outcomes like HAIs or mortality. The *Cochrane Handbook* differentiates between single-zero (no events in one arm) and double-zero (no events in both arms) studies, each requiring distinct analytical approaches. Both scenarios are frequent in infection control studies, which complicates standard inverse-variance methods as they involve dividing by zero when calculating odds ratios or risk ratios and their standard errors.

4.5.6.3. Meta-analyses with heterogeneous infection outcomes

There is a need for methodological guidance to support review authors in performing clinically meaningful meta-analyses of HAIs outcomes.

Meta-analyses in infection control are often limited by inconsistent outcomes definitions, reporting and biological heterogeneity in these outcomes³⁴³. Studies report HAIs caused

by a wide range of pathogens (bacteria and viruses) and affecting various organ systems, such as the respiratory tract, bloodstream, or urinary tract³⁴⁴. In addition, composite outcomes are used and their components vary considerably, which introduces substantial methodological heterogeneity.

A problematic assumption is biological uniformity, that is, the idea that an intervention has a uniform effect across all pathogens and infection types. For instance, gloves use may reduce MRSA colonisation but have little impact on ventilator-associated pneumonia. Aggregating such diverse outcomes into a binary win/loss composite can lead to a misleading halo effect, where a benefit in one component inflates the perceived overall efficacy³⁴⁵.

There is a need for methodological guidance to support review authors in performing clinically meaningful meta-analyses of infection-related outcomes. Such guidance should ensure that HAI outcomes reflect true clinical impact rather than statistical artifacts.

Recommended approaches may be subgroup analyses based on infection severity—distinguishing high-severity outcomes (e.g., BSI, ventilator-associated pneumonia, mortality) from low-severity ones (e.g., asymptomatic bacteriuria, superficial surgical site infections)—to identify potential discordance. Additionally, transparent disaggregation of outcomes by infection type, such as through Summary of Findings tables that report results for individual infections, can enhance clinical relevance of the review findings.

4.5.7. Consideration of sex and gender in SRs of infection control interventions

Further piloting and evaluation are needed to determine whether the SGAT-SR-2 tool requires refinement.

The *Sex and Gender Appraisal Tool-Systematic Reviews-2* (SGAT-SR-2)¹¹⁰ is a valuable resource for incorporating sex and gender considerations in SRs, particularly in interventions for preventing HAIs, where such factors are often overlooked. However, further piloting and evaluation are needed to determine whether the tool requires refinement.

4.5.8. Evaluation of the certainty of the evidence of infection control interventions with GRADE

Throughout the course of this PhD project, we identified several challenges in applying the GRADE approach to the context of infection control interventions.

4.5.8.1. Hierarchy of evidence for infection control interventions research

There is a need to discuss the evidence hierarchy for studies of infection control interventions.

The GRADE framework has traditionally positioned RCTs as the gold standard for determine effectiveness of healthcare interventions. GRADE assigns RCTs a "high-certainty" starting point because randomisation effectively minimises bias and confounding. In contrast, non-randomised designs typically begin at "low certainty" due to their inherent methodological limitations¹⁷⁶.

However, the hierarchy of the evidence for infection control interventions remains under debate³⁴⁶. For instance, it is unclear whether cl-RCTs should be regarded as providing a higher certainty evidence than individually RCTs in this context. Similarly, the placement of ITS designs within the hierarchy warrants further clarification. Although ITS designs are non-randomised and thus potentially more susceptible to bias, they can account for dependencies in the outcome data^{113, 118, 119}, which is critical in infection control research—and may offer a viable alternative when RCTs are infeasible³⁴⁷.

Methodological work is needed to determine the extent to which estimates from NRSIs differ from those derived from RCTs and the impact of including NRSIs in infection control SRs, specifically their influence on effect estimates, certainty-of-evidence judgments and recommendations on the interventions.

In parallel, review authors would benefit from a standardised framework to guide the selection and appraisal of NRSIs most suited for infection control questions²⁷¹. Given the anticipated rise in SRs incorporating non-randomised evidence, strategies to support the rigorous implementation of NRSIs and to minimise bias should be prioritised.

4.5.8.2. Selection of outcomes for the summary of findings tables

There is currently no established consensus on which outcomes should be considered critical for inclusion in summary of findings tables.

HAIs may be reported using various formats, such as dichotomous data (e.g., cumulative incidence) or rate data (e.g., number of infections per person-time), and across different time points. Additionally, as previously discussed, infection control studies frequently

demonstrate inconsistencies in outcome definitions, reporting practices, and biological heterogeneity. Consequently, the number of potentially eligible outcomes for inclusion can be considerable.

To support consistency and relevance in evidence synthesis, review authors would benefit from formal guidance on how to select the most critical outcomes for inclusion in summary of findings tables.

4.5.8.3. Use of predefined thresholds to interpret effect sizes and assess imprecision

Applying thresholds in the context of infection control posed methodological and practical challenges.

Lack of standardised thresholds in infection prevention

No consensus-based thresholds exist for HAIs or colonisation outcomes, likely due to the field's epidemiological complexity.

HAIs involve diverse pathogens, anatomical sites, and patient populations across varied settings. For instance, the clinical importance of preventing BSIs in immunocompromised patients differs substantially from preventing asymptomatic colonisation in low-risk individuals. This heterogeneity complicates interpretation and makes threshold selection subject to debate.

Methodological challenges in calculation of thresholds for incidence rates

Calculation of thresholds for incidence rate outcomes requires additional assumptions

Thresholds for dichotomous outcomes (e.g., cumulative incidence) were based on clinical judgment and GRADEPro GDT calculator¹⁷⁹. For incidence rate outcomes (e.g., infections per 1,000 patient-days), GRADEPro GDT cannot be used and additional assumptions—such as near-constant infection risk over time and similar LOS across groups—were required, raising concerns about validity and generalisability.

Uncertain clinical acceptability of thresholds

Interest-holders acceptability of the proposed thresholds remains unclear.

While GRADE's recent initiative to incorporate thresholds supports a patient-centred approach, uptake in the infection control community is still emerging. Future research should involve stakeholders to refine thresholds across diverse settings.

4.6. Results of study VI: Design recommendations for RCTs

The following design recommendations were identified for RCTs evaluating hospital infection control interventions. While these recommendations are broadly applicable to infection control strategies, elements specific to decontamination* or contact precautions (e.g., gloves, gowns, masks)** are marked with the corresponding asterisk.

4.6.1. Evidence

Our SRs found that the effects on patient-centred outcomes of decontaminating hospital environmental surfaces or the use of gloves, gowns or masks are uncertain. Further RCTs are needed.

4.6.2. Population

- Select the patient population according to the available infrastructure and hospital-specific characteristics (size, staffing for laboratory and nursing, patient population, HAIs prevalence, and information technology support)³⁴⁸.
- Report adequately critical basal characteristics to allow adjusting for confounders and judging the study sample's applicability.
- Report the following characteristics:
 1. **Age:** Adults or children (homogeneous population)
 2. **Sex:** Similar proportion of male and female participants
 3. **Gender identity** should be approached inclusively, encompassing men, women, and non-binary individuals.
 4. **Race:** Representative sample of the local population
 5. **Condition:** Hospitalised patients
 - a. Patient type (medical or surgical patients)
 - b. Underlying comorbidity
 - c. Patients with urinary or vascular catheters
 - d. Patients under mechanical ventilation

4.6.3. Setting

Report adequately critical characteristics of the setting where the study took place.

1. **Geographical setting:**
 - a. Multinational study
 - b. Country income level
2. **Social context of the hospital area**
3. **Study centres characteristics:**

- a. Nr. of centres
- b. Academic status
- c. Centre size (nr. of beds)
- d. Type of care provided (inpatient/outpatient care)

4. Study area characteristics:

- a. Hospital area (ICU, hospital ward or operating room)
- b. Type of patient managed in the study area
- c. Proximity of the intervention and control areas
- d. Total Nr. of rooms
- e. Nr. of beds per unit
- f. Nr. of beds per room
- g. Presence of individual bathroom in each room

5. Infection control context:

- a. Staff characteristics in the study area:
 - i. Infection control team
 - ii. Nr. of infection control nurses per 100 beds
 - iii. Staffing workloads
- b. Staff-patient contact patterns
- c. Bed occupancy
- d. Total Nr. of admissions per unit during the study period.
- e. Antibiotic policy
- f. Antibiotic use

6. Epidemiological situation in the study area:

- a. Specify whether the study was conducted in endemic or outbreak setting.
 - i. If the study was prompted by unusually high infection rates (or by an outbreak), the effect size of interventions might be overestimated¹¹³.
 - ii. Generalising these results to endemic settings should be done with caution
- b. Colonisation pressure
- c. Proportion of colonised patients
- d. Proportion of infected patients
- e. Proportion of colonised or infected patients
- f. Proportion of patients with resistant strains
- g. Proportion of patients under isolation

4.6.4. Intervention and comparator

4.6.4.1. Intervention

- Describe the infection control intervention and its components.
- Define the study phases by major changes in infection control practices (with a start and stop dates)¹¹³.
- Provide a summary table with precise details of interventions, how and when were administered in each phase¹¹³.
- Detail compliance and acceptability^{113, 165, 349} (although there is an urgent need for an standardised reporting of compliance).
- Plan a study with a few interventions per study arm to allow the relative contribution of the infection control intervention being evaluated²³¹.
- The study report should avoid using terms that may not be universally understood, such as contact precautions or barrier nursing, without a description of the interventions¹¹³.
- **Describe critical aspects of the infection control intervention:**
 - Duration of the intervention period (months): the interventions should last at least one year to account for seasonality and demonstrate sustainability.
 - Seasons during which the interventions took place.
 - Report if the experimental intervention was introduced before the start of the study.
 - * Decontamination timing: routine or terminal decontamination.
 - * Decontamination technique: manual, no-touch, antimicrobial surfaces.
 - * Decontamination substance: detergents, manual disinfectants (such as bleach), no-touch disinfectants (such as UV light-emitting devices).
 - * Registered product.
 - * Concentration.
 - * UV light devices: number and duration of radiation cycles, shadowing management.
 - * Equipment for applying decontamination: standard mop or cloth (cotton) or new materials such as microfiber cloth.
 - * Frequency.
 - * Time dedicated.
 - * Area.

- * Hospital area. Examples: ICU, operating room or the hospital ward.
- * Target area: non-targeted decontamination or enhanced decontamination targeting high-touch surfaces.
- Patients' infection status in the decontaminated area.
- Training received.
- Presence of feedback.
- Compliance.
- Acceptability.

4.6.4.2. *Comparator*

- Allow determining the relative effect of the experimental intervention.
- Detail the type of comparator:
 - Inactive comparator (if possible, choose a credible sham procedure)
 - Active comparator:
 - Standard practice (describe in detail)
 - Another active infection control intervention
- Describe the comparator with the same level of detail as the experimental intervention.
- Detail compliance and acceptability^{113, 165, 349}.

4.6.4.3. *Co-interventions*

- Describe the co-interventions in both the intervention and comparator groups.
- Detail the compliance and acceptability of the co-interventions^{113, 165, 349}.
- Create a graphical depiction of the main components of the interventions in each study arm. For example, use of the Pat Plot tool³⁵⁰, a graph³⁵¹, or a summary table with precise details of the interventions¹¹³.
- To determine the effects of a particular infection control intervention, co-interventions should be comparable across study groups to ensure that any observed effects can be attributed to the intervention under evaluation.
- The graphical depictions stated above can help to decide if the comparison established allows determining the relative effects of a particular infection control intervention.

4.6.5. Outcomes

- Consensus-derived core outcome and core measurement sets for trials evaluating the effects of infection control interventions are urgently needed
- The outcomes should be patient-centred and consider benefits and harms
- * Avoid contamination as a surrogate outcome as there is currently no consensus on a safe threshold of contamination below which transmission is minimised, nor is there standardised guidance on how to sample surfaces or measure contamination
- Table 24 proposes a core outcome set of studies of infection control interventions. Aspects specific to decontamination interventions or the use of barrier precautions (gloves, gowns, masks) are marked with asterisks.

4.6.5.1. Core outcome set proposal

Table 24. Core outcome set proposal for RCTs of infection control intervention

Study outcomes	Comments/Examples
a. Health outcomes	
HAIs in patients	
HA-BSIs	
HAI-related morbidity	▪ Complications due to the HAI
All-cause mortality	
Health-related quality of life	
b. Intermediate outcomes	
HA-colonisations	▪ If colonisations are evaluated, there should be an existing screening policy at admission that is applied consistently throughout the study ⁷⁴ .
Mother-to-child transmission rate **	▪ For neonates only
c. Adverse effects	
Adverse effects in intervention provider	▪ Adverse effects in hygiene staff *
Adverse effects in healthcare providers	
Adverse effects in patients	▪ Impact on mental health, such as anxiety from isolation ** ▪ Increased risk of falls or pressure injuries due to delays or disruptions in routine patient care associated with the use of personal protective equipment **
Resistance to antibiotics	
Resistance to disinfectants *	
Ecotoxicity associated with disinfectant use *	
d. Resource use	
LOS	
Antimicrobial use	
e. Feasibility of the intervention	
Impact on clinical flow	▪ Frequency of healthcare worker visits ▪ Compliance with infection control procedures, such as hand hygiene ▪ Number of visits by healthcare staff
Time of decontamination *	
Staff training	
Surface damage *	
f. Acceptability of the intervention	
Acceptability by intervention providers	
Acceptability by healthcare providers	
Acceptability by patients	
g. Cost analysis	
*: Specific of studies of decontamination interventions. **: Specific of studies of gloves, gowns or masks.	
Abbreviations:	
BSI: Bloodstream infection. HA: hospital-acquired. HAI: hospital-acquired infection. LOS: Length of hospital stay.	

4.6.5.2. Recommendations for outcome data collection and assessment:

- Where possible, align data collection with the administrative capacities of the healthcare system to enhance feasibility³³⁰.
- Measure, collect and report outcome data in an objective, reliable, accurate, and actionable way. This particularly applies to healthcare-associated colonisation and infection, for which subjective elements in definitions and variations in the timing for hospital-associated should be avoided³³⁰.
- Follow recognised standard definitions and criteria for all specific types of infections, such as those developed by the CDC.
- Be cautious with the use of surrogate outcomes, such as colonisations, rather than clinical infection outcomes. While bacterial colonisation is more common and detectable, it does not reliably correspond to subsequent clinical infection¹⁸⁴. Moreover, trials using surrogate primary outcomes overestimate health benefits by greater than 40% compared to those using patient-relevant final outcomes³⁵².
- Avoid composite outcomes that combine infections from different target organisms (e.g., MRSA, VRE, or both) or that use mixed endpoints (e.g., "colonisation, infection, or both"). Such outcomes group biologically distinct events and therefore lack clinical specificity and interpretability^{159, 353-355}.

4.6.6. Study design

- Study protocols should adapt to clinical care, patient rest, visiting time, or routine healthcare activities.
- Register the study prospectively in a publicly accessible database.
- Define study hypothesis: Superiority, non-inferiority, or equivalence.
- Sequence generation method: Randomised. The most robust method to determine if infection control interventions prevent the transmission of microorganisms in hospitals is the randomised controlled design^{127, 215}.
- Unit of allocation: Randomise groups (clusters) rather than individuals (see characteristics below). The ideal unit of allocation to prevent contamination is the hospital.
- Advantages of cluster-RCTs over i-RCTs for infection control interventions^{127, 330}:
 - Enable assessment of interventions that cannot be easily assigned at the individual level

- May reduce costs and time by adapting to existing administrative systems, such as routine data collection^{329, 330}.
 - By allocating at the group level (e.g., ward or hospital), contamination is minimised—unintended exposure of control groups to the intervention or vice versa—which is common in infection control due to patient transfers^{347, 356}.
 - Well-suited to evaluating real-world effectiveness and group-level impacts, as they reflect typical implementation settings^{329, 330}.
 - When conducted across multiple centres, cluster-RCTs enhance generalisability by reducing the Hawthorne effect and requiring less care standardisation^{127, 329, 330}.
- Allocation concealment: The allocation procedure must be concealed.
 - Avoid identification and recruitment bias in cluster designs:
 - Identification and recruitment bias in cluster-RCTs is endemic³⁵⁷
 - Patient eligibility must be determined before cluster randomisation is revealed
 - Document strategies to blind recruiters to allocation status during patient identification
 - Blinding in studies of the effects of non-pharmacological interventions, such as gloves or decontamination, is challenging. However, some suggestions about how to overcome this situation are described elsewhere^{132, 175, 333, 335}.
 - Try to blind patients, intervention providers, care givers and outcome assessment wherever possible to minimise performance, attrition, and detection biases.
 - Recommendations to minimise the impact of these biases in decontamination intervention studies^{163, 335}:
 - Use standardised surveillance criteria for HAIs and colonisations (such as CDC)
 - Use objective outcomes that are less susceptible to bias, such as total mortality, LOS or antimicrobial use³³⁵
 - Assess study outcomes through structured observation by external evaluators
 - Use sham interventions as comparators
 - Use standardised protocols to implement the interventions

- Blinding reporting:
 - Describe the blinding clearly.
 - Avoid the use of expressions such as single- or double-blinding.
 - Detail who was (or was not) blinded.
- Consider non-conventional cluster-RCTs to evaluate infection control interventions:
 - The **SW-CI-RCT** is increasingly used to assess the effectiveness of organisational interventions to improve quality and safety¹³². It is particularly helpful where the intervention is predicted to do more good than harm. Also, where it is impossible to deliver the intervention simultaneously to all participants for logistical, practical or financial reasons¹³³
 - **CRXO designs** are gaining popularity in settings where a cluster allocation is required, but the parallel ci-RCT is not feasible because the required number of clusters is prohibitively large^{153, 195, 358}
- Report key methodological aspects of cluster and crossover studies (CI-RCTs, CRXO and SW-CI-RCTs):
 - Information used for a priori sample size estimation
 - Number of units and patients randomised per arm
 - Presence and duration of wash-out period
 - Correlation coefficients^{153, 359, 360}:
 - Within-cluster within-period correlation (WPC)
 - Within-cluster between-period correlation (BPC)
- Adverse effects associated with infection control intervention are unlikely to be adequately captured in RCTs. Certain outcomes—particularly adverse effects, antimicrobial resistance, resistance to disinfectants and ecotoxicity—may need to be evaluated through alternative study designs, such as cohort studies, case-control studies, or even case series and case reports.

4.6.7. Study sample size

- Plan studies with samples that are large enough to detect HAI differences that are clinically relevant.
- Define what constitutes a clinically relevant difference in HAIs (although there is no widely accepted definition).
- Large sample sizes are needed to appropriately power parallel ci-RCTs targeting infection prevention outcomes³⁵⁸.

▪ Designing adequately powered RCTs for infection control interventions is challenging for several reasons:

- Modest effect sizes: Infection control interventions are often added to existing preventive measures in both arms, reducing the expected effect and requiring larger sample sizes
- Low event rates: HAIs are relatively infrequent
- Correlation of hospital colonisation or infection rates³⁵⁸
- Cluster randomisation: Cluster-level allocation necessitates sample size inflation to account for intra-cluster correlation¹⁹³.
- Complex designs: In CRXO and SW-CI-RCTs, sample size estimation must consider both cluster allocation and outcome correlation. While cluster randomisation reduces precision, the crossover element in CRXO designs may mitigate this. However, sample size methodology for CRXO designs remains under-researched^{153, 195}.

▪ A database of correlation coefficients for CRXO designs is needed to support more robust planning and analysis. Few parallel cl-RCTs in hospital epidemiology report intra-cluster correlation coefficients³⁵⁸, and such data are even scarcer for CRXO designs¹⁹⁵. For CRXO studies, both within-period (WPC) and between-period correlations (BPC) are needed to calculate accurate standard errors.

▪ Estimate the sample size assuming the non-independence of outcome data. Consider the following guidance:

- Sample size estimation in parallel cl-RCTs³⁵⁸
- Sample size estimation in CRXOs¹⁹⁵
- Sample size estimation in SW-CI-RCTs^{154, 361}

4.6.8. Statistical analysis

▪ Avoid statistical approaches assuming independence of the colonisation or infection outcome data^{113, 118, 119, 153}.

▪ Take into account the peculiarities of Infection/colonisation outcomes for data analysis:

- The outcome occurrence in one patient depends on the status of other patients.
- Avoid statistical approaches assuming independence, such as two sample t-test or Chi²: Ignoring this correlation can lead to false inferences^{113, 118, 119}

- Define the analysis strategy:
 - Potential benefits: ITT population
 - Potential harms: per-protocol population

4.6.9. Funding

- Publicly funded studies in low-resource and non-Western settings should be supported to evaluate interventions applicable to diverse settings.
- Avoid real or perceived conflict of interests in comparative-effectiveness research of infection control interventions ⁴¹.
- * RCTs of early studies of decontamination agents or technologies are expected to be primarily funded by the manufacturers, which have relevant economic conflicts of interest⁴¹.

4.6.10. Study reporting

- Report the studies in a standardised, explicit, informative and transparent manner according to established reporting guidelines.
- Report transparently information that readers can use to make judgments about applicability (e.g., population and intervention characteristics as well as characteristics of context and setting).
- Describe the design based on design features and not just using a study design tag.
- Reporting guidelines for CRXO studies are needed.
- Updating the ORION statement is needed.
- Consider reporting guidelines useful for studies of infection control interventions:
 - ORION Statement checklist¹¹³
 - CONSORT statement (CONsolidated Standards of Reporting Trials) 2025³⁶²
 - CONSORT extension for non-pharmacological interventions¹⁶³
 - Template for intervention description and replication (TIDieR) checklist¹⁶⁵
 - CONSORT extension for cluster-randomised trials¹⁶⁴
 - CONSORT extension for harms³⁶³
 - CONSORT extension to randomised crossover trials^{364, 365}
 - CONSORT extension to stepped-wedge cluster randomised trials¹⁵⁴
 - SQUIRE 2.0: Standards for Quality Improvement Reporting Excellence³⁶⁶
 - Sex and Gender Equity in Research: SAGER guidelines¹⁰¹
 - Reporting of health equity considerations in cluster and individually RCTs³⁶⁷

5. Discussion

5.1. Main findings of the dissertation

5.1.1. Overall findings of the dissertation

Taken together, this thesis demonstrates the need to address persistent methodological challenges in both RCTs and SRs of non-pharmacological hospital infection control interventions.

HAIs are infections acquired during hospital care that were neither present nor incubating at the time of admission. They pose a global threat to patient safety and healthcare quality and challenge the long-term sustainability of healthcare systems. Traditionally, the prevention of microorganism transmission in hospitals has been guided by biological plausibility, clinical convention, and reactive measures implemented during outbreaks.

The prevention of HAIs relies on a combination of strategies that commonly incorporate non-pharmacological interventions. As infection control shifts toward a more evidence-based framework, non-pharmacological interventions to prevent HAIs—such as environmental surface decontamination and the use of personal protective equipment, including gloves, gowns, and masks—must undergo rigorous evaluation comparable to that applied to pharmacological therapies. This dissertation comprises six studies that examine how evidence for non-pharmacological infection control interventions is generated, synthesised, and interpreted, ultimately proposing a roadmap for advancing evidence-based practices in hospital infection control.

The dissertation begins by conducting two SRs aimed at generating empirical evidence on the effects of two core non-pharmacological interventions commonly used in hospitals to prevent HAIs: environmental surface decontamination and the use of contact precautions—specifically gloves, gowns, and masks—for preventing MRSA transmission. Both SRs concluded that RCT evidence on the impact of these non-pharmacological interventions on patient outcomes remains limited and inconclusive.

Regarding the effects of hospital environmental surface decontamination, the SR indicates that the evidence remains very uncertain for most outcomes. Meta-analysis was not feasible, as no more than one RCT contributed data per comparison and outcome. The certainty of evidence was frequently downgraded due to high risk of bias—particularly related to lack of blinding and deviations from intended interventions—as well as extremely serious imprecision. Many studies were underpowered to detect clinically meaningful differences in infection rates, which are relatively rare events. Notably, none

of the included trials evaluated standard detergents, despite their widespread use as a foundational practice in many healthcare settings, or were implemented in low-resource settings.

Regarding the effects of gloves, gowns, or masks on MRSA transmission, the SR—following a sensitive search of 4,456 records—identified no eligible studies, either completed or ongoing. All retrieved reports were excluded, primarily because they assessed bundled interventions, which precluded the isolation of the specific effects of gloves, gowns, or masks. The resulting "empty review" is a significant finding in itself; it highlights a critical gap in the evidence base. Although these barrier measures are cornerstone components of global infection control guidelines (e.g., CDC, WHO), their independent contribution to MRSA prevention has not been established through high-quality experimental research.

This absence of evidence, or the presence of evidence with very low certainty, should not be misinterpreted as evidence of no effect. Rather, it likely reflects the methodological and practical challenges of conducting RCTs in the context of hospital infection control. Nevertheless, this evidence gap places clinicians and policymakers in the position of relying on low-quality observational data or expert opinion, rather than robust empirical evidence, to inform practice and policy decisions.

The dissertation continues by arguing that the uncertainty identified in the initial two SRs reflects broader deficiencies in infection control evidence synthesis. This claim is supported by the findings of the subsequent two studies. Studies III and IV conducted methodological appraisals of 113 Cochrane reviews on interventions to prevent HAIs, aiming to identify gaps in how evidence is synthesised, assessed, and reported.

Study III examined the extent to which sex and gender were considered in Cochrane reviews of interventions aimed at preventing HAIs. These factors were largely overlooked in the reviews analysed, which may obscure important differences in intervention effectiveness or safety, thereby limiting the development of more targeted and equitable infection control strategies.

Study IV investigated how the same group of Cochrane reviews in the field of HAI prevention address NRSIs. Given the ethical and practical challenges of conducting RCTs in infection control, NRSIs can serve as an important source of evidence. The analysis revealed that although 49% of the 113 Cochrane reviews deemed NRSIs eligible for inclusion, their characterisation and the rationale for their use were often poorly described or entirely absent. 67% of the Cochrane reviews admitted NRSIs

without describing their specific methodological features. This finding underscores the need for review authors to clearly define and justify the inclusion of non-randomised evidence. The frequent reliance on study design *labels* rather than detailed methodological *features* is particularly problematic, as these labels are often applied inconsistently by both primary and review authors. Without a clear description of underlying design characteristics, there is a higher risk of misclassifying studies, which may lead to misleading conclusions.

The dissertation concludes by identifying specific challenges that must be addressed to advance evidence-based infection control. Study V categorises these challenges within the context of SRs, while Study VI offers actionable recommendations to guide future research based on RCTs. The two final PhD studies draw on three sources of input: (1) the findings from the first four studies; (2) established methodological frameworks and tools, including the Cochrane Handbook, GRADE, risk of bias instruments, and reporting guidelines; and (3) insights from experienced researchers in evidence synthesis who contributed to the first four studies. The main specific challenges in evaluating infection control interventions are outlined below.

One challenge identified is the evaluation of complex interventions implemented as bundles. The prevention of HAIs relies on a combination of strategies, often implemented as *care bundles*—a set of evidence-based interventions that, when applied collectively, yield better outcomes than when used in isolation. These bundles commonly incorporate non-pharmacological interventions. An example of bundle is education, monitoring, feedback, and physical barriers. Determining the effect of individual elements of the bundle (such as a specific disinfection technique) is inherently difficult and often insufficiently addressed by primary investigators.

Furthermore, researchers often encounter difficulties in monitoring and reporting intervention integrity (also known as adherence or intervention fidelity). Accurate assessment of adherence is essential for interpreting outcomes. However, Study I found that compliance was inconsistently or poorly reported, which makes it difficult to determine whether a lack of clinical effect is due to the intervention itself or suboptimal implementation.

Regarding the statistical analysis, many infection control studies overlook the transmissible nature of their outcomes. The risk of colonisation or infection in one patient is inherently influenced by the status of other patients within the same unit. Applying statistical tests that assume independence—such as the Chi² test—can result in unit-of-analysis errors, which artificially narrow confidence intervals and overstate the precision

of the findings. As a result, managing these data statistically poses significant challenges for both trialists and review authors.

Collectively, the findings of Studies V and VI underscore the need to adopt non-conventional RCT and SR methodologies for evaluating infection control interventions. Moreover, future review authors and trialists must be equipped to address the methodological complexities that characterise this research domain.

In relation to SRs, a key issue identified is the lack of an agreed framework to guide the selection and appraisal of non-randomised studies that are most appropriate for infection control research questions. Given the expected increase in SRs incorporating non-randomised evidence, developing strategies to ensure the rigorous integration of both non-randomised studies and RCTs should be a priority.

Regarding primary studies, this dissertation critiques the reliance on uncontrolled designs and patient-level RCTs to evaluate infection control interventions. In particular, Study VI advocates for non-conventional cluster-RCTs—particularly SW-CI-RCT and CRXO designs. These designs are suited for organisational interventions where simultaneous delivery to all participants is impractical and where the intervention is expected to do more good than harm. They better reflect real-world clinical settings, reduce contamination risks, and mitigate the Hawthorne effect.

Finally, this dissertation highlights the urgent need to develop a Core Outcome Set for infection control research. A standardised set of outcomes would enhance both primary studies and SRs. Currently, many trials rely on surrogate microbial indicators, such as surface colony counts, which do not necessarily correlate with patient-centred results. Study VI advocates for prioritising patient-centred outcomes—such as HAIs, BSIs, HAI-related mortality, and adverse effects on patients and staff—which would also strengthen outcome consistency in SRs.

Following, the main results of each PhD study are summarised.

5.1.2. Main results of study I: SR on decontamination

We included 11 RCTs (eight CRXO and three i-RCTs) conducted between 2007 and 2017 in high-income countries academic hospitals. These studies enrolled between 70 and 21,395 adult participants of both sexes. Participants were predominantly white; gender identity and socioeconomic status were not reported, and comorbidities were inadequately described. Seven trials disclosed financial conflicts of interest.

The studies evaluated different interventions, including manual disinfection agents (QACs, bleach, probiotics, IHP, and ultramicrofiber cloths with copper), no-touch technologies (UV-C light, pulsed xenon UV), and antimicrobial copper surfaces. Interventions were multi-component and implemented during routine or terminal decontamination, or both. The intervention periods ranged from 7 days to 24 months. Nine studies lasted nine months or longer, which enabled evaluation of effects beyond seasonality.

Despite the relevance of this topic and the variety of interventions evaluated, few RCTs have been conducted. No study assessed the use of detergents, steam, ozone, or non-copper antimicrobial surfaces. Safety data were limited: only one study reported adverse events, and none examined the development of resistance to antibiotics or disinfectants. Most evidence in this area is derived from non-randomised, uncontrolled studies, which primarily focus on surface contamination rather than HAIs.

The current RCT evidence on the impact of hospital surface decontamination on patient-centred outcomes remains inconclusive. This reflects both the limited number of RCTs and the very low certainty of their findings, primarily due to risk of bias and imprecision. However, these inconclusive findings should not be misinterpreted as evidence of no effect, nor should they discourage the implementation of decontamination practices in healthcare settings. Given that hospital infection prevention strategies—such as hand hygiene and antimicrobial stewardship—are routinely implemented, baseline HAI rates are often low, complicating efforts to isolate the specific contribution of environmental decontamination from other measures.

Although four ongoing RCTs were identified—three of which assess HAI outcomes—there remains a need for further high-quality RCTs to evaluate the effects of conventional cleaning methods and emerging technologies on patient-centred outcomes.

5.1.3. Main results of study II: SR on gloves, gowns and masks

No eligible studies, either completed or ongoing, were identified for inclusion in this review. Consequently, this SR was unable to assess the effect of wearing gloves, gowns, or masks, when contact with hospitalised patients with MRSA or their immediate environment is anticipated, on MRSA transmission.

5.1.4. Main results of study III: Sex/Gender consideration in Cochrane reviews

While 113 Cochrane reviews evaluated various interventions for preventing HAIs, sex and gender considerations were almost entirely overlooked. This omission likely stems from several underlying factors.

First, SRs often mirror the limitations of their primary studies, specifically regarding research questions, data analysis and interpretation of findings¹³⁶. Among primary studies in infection control research, sex and gender are frequently overlooked³⁶⁸. This neglect may stem from researchers' perceived difficulties in drawing conclusions from small sample sizes or a lack of granular data in electronic health records informing observational studies, such as genotypic sex or self-reported gender identity. Consequently, many studies may not report the sex and gender composition of their samples, or they may only indicate that study groups were balanced in terms of male and female participants, using this as a proxy for successful randomisation. In such cases, sex is merely "controlled for" rather than analysed to explore variations in outcomes across sex or gender groups³⁶⁹. While our study did not examine the data reported in the primary studies and thus cannot confirm this pattern directly, previous research has shown that RCTs rarely provide disaggregated data by sex or gender^{136, 370-375}. Moreover, existing sex/gender reporting policies have not significantly improved the frequency of sex-specific reporting in results³⁷⁰. Nonetheless, the absence of sex/gender considerations in the SRs included in our study cannot be attributed solely to limitations in the primary studies, as none of the SRs planned to conduct a SGBA.

Second, Cochrane launched the SGSR-AT in 2011¹⁰⁹, making formal guidance on integrating sex and gender considerations in Cochrane reviews relatively recent. As such, this guidance was not available when the protocols for many of the included reviews were developed. Specifically, 31 reviews (27%) were published in 2011 or earlier, and the 43 reviews published between 2012 and 2014 were likely based on protocols formulated before the SGSR-AT was widely adopted.

Third, it is possible that the authors of the included SRs did not perceive sex and gender as relevant factors in evaluating the effectiveness of interventions to prevent HAIs.

However, this assumption cannot be confirmed, as it was not explicitly stated in any of the reviews.

Fourth—and perhaps most plausibly—the review authors may have not considered the role of sex and gender at any stage of the review process. In our view, this is the most concerning explanation, as it reflects a broader knowledge gap regarding the potential influence of sex and gender in the context of HAI prevention.

5.1.5. Main results of study IV: NRSIs consideration in Cochrane reviews

Of the 113 Cochrane reviews on interventions for preventing HAIs, nearly half (55; 49%) considered at least one type of NRSI eligible for inclusion. However, justification for including NRSIs was infrequently provided: only 7 of the 55 reviews offered any rationale, of which just 3 aligned their justification with a criteria recommended in the Cochrane Handbook.

The most commonly used label for NRSIs was "quasi-randomised controlled trial," applied in 48 of the 55 reviews (87%), followed by "controlled clinical trial," which appeared in 10 reviews (18%). Notably, most of the reviews admitting NRSIs (67%) used study design labels without explaining the underlying features of the included studies.

5.1.6. Main results of study V: Methodological challenges in SRs

This doctoral research synthesised findings from the initial four dissertation objectives, and insights from relevant methodological literature to identify methodological challenges in conducting SRs of infection control interventions. These challenges were identified across several critical phases of the SR process.

In defining review questions, investigators are constrained by the absence of a core outcome set that prioritises patient-centred outcomes, such as HAIs, over surrogate measures like microbial surface burden. Furthermore, review authors must rigorously justify the inclusion of non-randomised designs and explicitly define eligibility criteria based on specific methodological features rather than ambiguous design labels.

Study design classification remains particularly problematic during the selection phase. Non-randomised studies in this field often lack consistent labelling, complicating the distinction between experimental and observational frameworks. This ambiguity necessitates labour-intensive screening and the assessment of full-text reports. Moreover, there is a critical need for analytical tools to assist reviewers in determining whether complex, bundled interventions permit the isolation of specific infection control effects.

The data extraction process is further challenged by suboptimal reporting of critical items in primary studies and the need to update existing reporting guidelines (e.g., ORION, TIDieR)^{113, 165} to current needs in infection control research.

Finally, a significant gap exists in methodological guidance for assessing risk of bias in cluster crossover RCTs and stepped-wedge cluster RCTs. Although these designs are increasingly utilised for patient safety interventions, they lack specific adaptations within the RoB 2 tool¹⁷². Additionally, infection control studies are susceptible to unique bias sources—such as seasonality, contamination, and carry-over effects—all of which warrant formal integration into established risk of bias frameworks. Importantly, clearer operational guidance is required to assess bias due to deviations from intended interventions.

5.1.7. Main results of study VI: Design recommendations for RCTs

This doctoral research synthesised findings from the initial four dissertation objectives and insights from relevant methodological literature to develop recommendations for addressing specific challenges within the context of RCTs of infection control interventions.

Regarding study design, researchers are encouraged to consider non-conventional cluster frameworks, such as stepped-wedge and cluster crossover RCTs, particularly when simultaneous intervention delivery is logistically infeasible.

Concerning study populations, baseline characteristics must be rigorously documented, including comprehensive reporting of comorbidities, demographic factors, and contextual epidemiological aspects like colonisation pressure.

Outcome selection should prioritise clinically relevant, patient-centred endpoints—ideally aligned with established core outcome sets—over surrogate measures. However, the development of a core outcome set is urgently needed. Furthermore, outcome definitions must adhere to recognised standards from agencies such as the CDC, avoiding composite outcomes that aggregate biologically and clinically distinct events. To capture adverse effects and long-term outcomes, trialists should acknowledge that the use of observational designs, such as cohort or case-control studies, may be more appropriate than RCTs.

The statistical analysis plan must explicitly define the analytical approach (e.g., intention-to-treat vs. per-protocol), as the effectiveness of infection control measures is often intrinsically linked to intervention provider adherence and behavior.

Statistical analyses must account for the data dependency inherent in communicable disease outcomes, employing models that accommodate clustering rather than assuming independence. Additionally, investigators should transparently report key methodological parameters for cluster and crossover trials, including *a priori* sample size estimations and correlation coefficients.

Finally, studies should align data collection processes with healthcare administrative capacities and use standardised surveillance criteria. From an ethical and global health perspective, it is crucial to support publicly funded research in low-resource and non-Western settings to ensure the generalisability of findings. Moreover, researchers should avoid conflicts of interest, particularly regarding manufacturer-funded studies of new decontamination agents.

5.2. Completeness and applicability of evidence

5.2.1. Overall completeness and applicability of the findings of this dissertation

This dissertation offers a comprehensive contribution to the field of infection control. As a whole, the six studies of this thesis represent an integrated critical analysis of the evidence ecosystem in infection control.

Studies I and II represent the **current state of knowledge of non-pharmacological interventions to prevent HAIs**, in particular environmental surfaces decontamination and the use of contact precautions. The evidence for the effects of these interventions is characterised by the clinical uncertainty due to low-certainty evidence or the absence of RCTs.

Studies III and IV provide the **critical analysis of Cochrane reviews of infection control interventions**—they identify key methodological limitations contributing to this uncertainty, including the lack of sex and gender considerations and the suboptimal characterisation of non-randomised studies in Cochrane reviews of infection control interventions.

Finally, Studies V and VI **propose potential solutions**. Study V outlines challenges specific to conducting and interpreting SRs in this field, including the evaluation of complex interventions and difficulties in assessing adherence—marking an initial step toward improving the current situation. Study VI proposes a set of actionable recommendations aimed at improving the design of RCTs.

This integrative framework makes explicit the interconnections among the components of the thesis. The low-certainty evidence regarding the effectiveness of non-

pharmacological interventions for preventing HAIs is due, in part, to the limitations of the available SRs. These reviews are limited both by the scarcity or suboptimal design of RCTs and by evidence synthesis methods that often neglect key dimensions such as sex and gender, contextual complexity, and the characterisation of non-randomised studies.

5.2.2. Completeness and applicability of study I: SR on decontamination

5.2.2.1. Completeness of the evidence

The evidence identified in this review is incomplete, primarily due to the small number of RCTs. This situation is unlikely to improve, given the limited number of ongoing RCTs.

Evidence from RCTs on hospital surface decontamination for reducing HAIs remains incomplete. This review identified eleven RCTs, a small number considering the global burden of HAIs, the broad scope of the review—which included any form of decontamination intervention—and the wide range of available decontamination methods. As a result, most review comparisons were supported by either one or no studies, making meta-analysis unfeasible.

Despite the review accepted any decontamination method, the identified trials assessed only eight interventions. These comprised manual disinfection agents (QACs, bleach, probiotics, IHP, and ultramicrofiber cloths with copper), no-touch technologies (UV-C light, pulsed xenon UV), and antimicrobial copper surfaces. Therefore, no RCTs evaluated conventional cleaning methods (plain detergents and water), other emerging technologies (HPV systems, steam cleaning, ozone-based systems, or alternative antimicrobial surfaces, such as silver or zinc surfaces) or other aspects of decontamination, including targeted cleaning strategies or cleaning duration.

In addition to their limited number, most of the included RCTs did not contribute relevant data to our review outcomes. Because our focus was on patient-centred outcomes, such as HAIs, we excluded studies that assessed decontamination efficacy solely through surface contamination measurements, that is, performance studies. As a result, seven RCTs were excluded for this reason during the full-text assessment stage^{143, 291-295, 376}.

Another reason for excluding data on hospital-associated colonisation or infection was the misalignment between outcome reporting in the included RCTs and our predefined criteria. Although the studies applied diagnostic criteria based on established definitions (e.g., CDC), they often reported composite outcomes, which were not eligible for inclusion in our review. Furthermore, following the ORION statement¹¹³, we excluded colonisation outcomes in studies lacking a screening policy in place. These limitations

were common across the included trials, reducing the usability of the data and highlighting the need for standardised outcome measures in this field³⁷⁷.

Adverse effects were either poorly reported or not reported at all in the included trials. Only one study addressed adverse effects²⁷⁷, but provided insufficient detail for meaningful analysis. Additionally, none of the studies reported on resistance to antibiotics or disinfectants—an important omission given growing concerns about biocide overuse³⁷⁸. Although ecotoxicological impact was beyond the scope of this review, it remains a critical consideration for sustainable and acceptable interventions³⁷⁹.

Finally, our review did not assess patient or environmental service staff satisfaction with the decontamination products—an important factor in informing implementation and decision-making.

5.2.2.2. Applicability of the evidence

The evidence identified in this review has limited applicability due to the small number of included RCTs. Nonetheless, the findings remain valuable.

The inconclusive findings of this review should not be interpreted as evidence that environmental surface decontamination in hospitals is ineffective—that is, the absence of evidence does not constitute evidence of no effect. Accordingly, the review results should not be interpreted as a recommendation against the decontamination of environmental surfaces in hospitals.

The review findings are still valuable as they highlight the need to design and conduct new RCTs to evaluate decontamination interventions of hospital environmental surfaces. We identified four ongoing RCTs. This low number suggests that environmental surface decontamination is not currently a priority in randomised clinical research, and that high-quality RCT evidence is unlikely to be available in the near future to adequately inform decision-making in this field.

Furthermore, the ongoing trials will evaluate hydrogen peroxide vapour, copper surfaces, engineered hospital rooms, and surface disinfection with organosilane. However, there appears to be little justification for prioritising RCTs on these approaches, given that the effects of simpler, cheaper and less toxic interventions, such as standard detergents, which are also more feasible to implement in low-resource settings, have not yet been thoroughly evaluated with RCTs.

This low number of RCTs underscores the need to incorporate evidence from NRSIs to inform decision-making in this field. As suggested by Cuello-García *et al.*³⁸⁰, applying a

framework that assesses the certainty of evidence from randomised and non-randomised studies—initially separately, and then in an integrated manner—can improve both the certainty and comprehensiveness of the overall evidence base. This approach is particularly valuable when addressing questions about interventions to prevent HAIs, as it allows for the inclusion of diverse study designs.

A key limitation in the applicability of the evidence lies in the narrow geographical scope of the included studies, all of which were conducted in high-income countries (the USA, Canada, and the UK). No studies were carried out in LMICs, despite the higher incidence of HAIs reported in these settings^{7, 12}. This geographical limitation fails to reflect the global burden of HAIs.

Furthermore, the participants in the included studies were predominantly drawn from ICUs and general hospital wards. Only one study²⁷⁹, conducted prior to 1980, was set in an operating room, limiting the relevance and applicability of its findings to current clinical practice in that setting.

Finally, none of the included studies focused exclusively on paediatric populations, and five were conducted within a single institution. As such, the generalisability of the findings to other healthcare settings with differing infection control practices and HAIs rates may be limited. These limitations should be carefully considered by decision-makers when interpreting the evidence in relation to their specific context.

5.2.3. Completeness and applicability of study II: SR on gloves, gowns and masks

5.2.3.1. Completeness of the evidence

We identified a large number of potentially relevant studies; however, none met the eligibility criteria for inclusion. As a result, the evidence base remains incomplete, and the effectiveness of using gloves, gowns, or masks for hospitalised patients colonised or infected with MRSA remains uncertain. The absence of eligible studies was unexpected, given that this is not an emerging field and the evaluated interventions are routinely employed in clinical practice. Several factors may account for this lack of studies.

First, our eligibility criteria defined a narrowly focused population: hospitalised patients colonised or infected with MRSA. Consequently, we excluded studies that assessed broader populations, including those evaluating universal use of gloves and gowns regardless of MRSA status (e.g., BUGG Study²⁴²), or those assessing MRSA screening strategies (e.g., MOSAR Study³⁸¹), as not all participants had MRSA at recruitment.

Second, we sought to isolate the effects of three specific infection control interventions—gloves, gowns, and masks. To achieve this, we excluded studies that examined multifaceted interventions without allowing for assessing the relative contribution of each intervention. This reduced pool of eligible studies was anticipated, as gloves, gowns, and masks are rarely implemented in isolation but rather as components of broader infection prevention bundles (e.g., screening, patient isolation, hand hygiene) often within quality improvement initiatives²³¹.

Third, the challenges associated with evaluating complex, non-pharmacological interventions may also contribute to the scarcity of evidence. These interventions involve multiple interacting components and pose unique methodological difficulties, such as challenges in blinding participants and healthcare providers, or the impracticality of using placebo controls^{163, 175, 333, 382}. The evaluation of such interventions requires careful design, which may limit the number of studies meeting rigorous inclusion criteria³⁸³.

Fourth, we restricted inclusion to the strongest feasible study designs for infection control research. Specifically, we required prospective data collection, allocation of interventions, and outcome assessment. Consequently, we excluded studies relying on retrospective data, which are common in this field. We also excluded uncontrolled before-and-after studies, which are prevalent but have limited internal validity due to their inability to adequately control for confounding factors^{74, 113, 245}. Such studies typically compare average MRSA rates before and after an intervention using conventional statistical methods assuming outcome data independence, such as the chi-squared test.

5.2.3.2. Applicability of the evidence

As no eligible studies were identified for inclusion in this review, it is not possible to assess the applicability of the evidence in this area.

5.2.4. Completeness and applicability of study III: Sex/gender consideration in Cochrane reviews

This study aimed to assess the extent to which Cochrane reviews of interventions for preventing HAIs consider sex and gender. We are confident that this objective was achieved. First, we comprehensively identified all relevant Cochrane reviews in this area, rather than relying on a sample. Second, our findings clearly demonstrate that SGBA was virtually absent in these reviews.

Our findings apply specifically to Cochrane reviews focused on HAI prevention interventions. Therefore, they cannot be directly extrapolated to Cochrane reviews in other health domains or to non-Cochrane systematic reviews. There are several reasons

for this limitation. First, other Cochrane reviews may have adopted the guidance developed by the Sex/Gender Methods Group¹⁰⁷. Second, many interventions aimed at preventing HAIs are non-pharmacological—such as hand hygiene or the use of PPE. The methodologies used to evaluate non-pharmacological interventions may differ from those used in drug evaluations, potentially leading to different approaches regarding the consideration of sex and gender. Third, in some health areas, awareness of the importance of sex and gender may be more established than in infection control research.

Nonetheless, our findings are relevant in showing that the examined reviews did not consider sex or gender in relation to the body of evidence synthesised. As a result, these reviews lack critical information needed to assess the applicability of their findings to specific populations³⁸⁴. Furthermore, sex and gender characteristics should have been considered when evaluating the “indirectness” domain of the GRADE framework, which informs judgments about the quality of evidence³⁸⁵. However, our analysis indicates that this was not the case.

The tables of characteristics of included studies are particularly important for describing the sex and gender distribution of participants in each study. In our view, the most relevant information is the sex and gender characteristics of the actual study samples from which results were derived—rather than the inclusion criteria alone. Despite this, specific guidance for collecting and reporting such information in Cochrane reviews remains lacking.

5.2.5. Completeness and applicability of study IV: NRSIs consideration in Cochrane reviews

This study examined how Cochrane reviews of interventions to prevent HAIs considered NRSIs. Specifically, we assessed whether NRSIs were considered eligible, how eligibility was justified, and how NRSIs were defined and labelled. We are confident that these objectives were met, as we analysed the entire set of relevant Cochrane reviews in this topic area (113 reviews published before 1 January 2017), rather than a sample, and applied explicit criteria from the *Cochrane Handbook* (Version 5.1.0, updated March 2011)¹⁶⁹ to evaluate justifications and the reporting of design features.

Our findings are primarily applicable to Cochrane reviews focused on HAI prevention within the specified timeframe. Therefore, the results should not be assumed to reflect current practice or be generalised to Cochrane reviews in other clinical domains, or to non-Cochrane SRs, where study design distributions, editorial policies, and methodological expectations for NRSIs may differ.

Nevertheless, our findings have important implications for any SR of interventions where RCTs may be infeasible or unlikely. Most reviews that include NRSIs will probably rely primarily on study design labels, without reporting the underlying design features necessary for transparent classification. This lack of detail hampers review authors' ability to assess which studies will be included or excluded in the review.

5.2.6. Completeness and applicability of study V: Methodological challenges in SRs

Study V offers a comprehensive overview of the methodological challenges encountered in SRs of hospital infection control interventions. It builds on an integrative synthesis of insights derived from the preceding four dissertation studies. Studies I and II conducted in-depth evaluations of standard infection control interventions using Cochrane methodology, while Studies III and IV systematically examined the consideration of sex and gender as well as the classification of study designs across Cochrane reviews. Together, these investigations revealed methodological issues across diverse stages of the SR process and highlighted gaps in current guidance.

The findings of Study V have broad applicability to SRs of infection control interventions and, more generally, to complex, cluster-based interventions in healthcare settings. Key challenges identified—such as inconsistent classification of study designs and the absence of tailored RoB 2 guidance for cluster crossover trials—are particularly pertinent to review authors working in infection prevention and patient safety.

5.2.7. Completeness and applicability of study VI: Design recommendations for RCTs

The completeness of the recommendations presented in Study V is underpinned by the broad methodological scope captured across Studies I to V, which enabled the identification of key challenges relevant to RCTs of infection control interventions. While the limited number of RCTs included in the two SRs may constrain the empirical basis for deriving certain recommendations, this limitation was mitigated by incorporating methodological insights from external guidance documents.

The applicability of the recommendations is wide, extending to healthcare settings globally—from high-income countries to low-resource environments where infection control trials are particularly needed. The recommendations emphasise the importance of adapting RCT designs to local healthcare infrastructure, administrative capacity, and resource constraints. Rather than prescribing standardised models that may not align

with diverse institutional contexts, the guidance prioritises feasibility and integration within existing health systems.

5.3. Quality of the evidence of decontamination of hospital environmental surfaces

The certainty of evidence was rated as very low across all comparisons and effect estimates, with one exception: the effect of adding UV light to standard practice versus standard practice alone on healthcare-associated VRE colonisation¹⁸⁷, for which the certainty was rated as moderate.

5.3.1 Risk of bias

The included studies exhibited limitations in study design, implementation, and reporting. The overall risk of bias was high for 11 of the 15 effect estimates (73%) and having some concerns for the remaining four (27%). Therefore, no effect estimate was at a low risk of bias. Taking the risk of bias into account, the certainty of the evidence was downgraded in most cases. In only three estimates (20%) was the risk of bias deemed insufficient to justify downgrading.

Critical information required to assess the risk of bias was frequently missing, which limited the ability to evaluate several risk of bias domains. For example, inadequate reporting of randomisation procedures and allocation concealment challenged the assessment of selection bias. In addition, a poor description of participants' baseline characteristics made it difficult to determine whether groups were comparable at the start of the study. Such information is essential for judging the risk of selection bias, particularly in studies with unclear randomisation or allocation methods. Also, we could not assess selective outcome reporting in studies without a prospective registration^{197, 277, 278}.

There are inherent challenges in blinding participants and intervention providers in studies evaluating decontamination interventions. However, we did not overlook the potential biases arising from the lack of blinding, particularly among those delivering the interventions. Anyhow, we chose not to penalise all studies for performance bias uniformly. Instead, we applied trial-specific judgments based on the characteristics of each intervention and the RoB 2 guidance²⁰⁶.

Manual decontamination procedures are highly dependent on the provider's behaviour, and thus, we considered these interventions susceptible to performance bias when providers were aware of group allocation. In contrast, we judged certain interventions—such as the placement of copper surfaces²⁷⁸ and the use of UV devices^{187, 198}—to be less

dependent on provider behaviour and, therefore, less prone to performance bias, despite the lack of blinding. Additionally, two studies employed sham interventions^{196, 198}, which may have mitigated some bias.

Key considerations in assessing performance bias included adherence to the allocated intervention, the implementation of co-interventions (e.g., hand hygiene), and deviations from the intended protocol (intervention integrity). Unfortunately, these factors were often poorly reported, making the assessment of performance bias particularly challenging.

5.3.2. Inconsistency

As this review included at most one trial per comparison and outcome, it was not possible to assess heterogeneity of the study results and, consequently, inconsistency.

5.3.3. Indirectness

In general, we did not downgrade the certainty of the evidence for indirectness. However, poor reporting of participants' baseline characteristics and the epidemiological context of the intervention settings limited our ability to fully assess this domain.

For most effect estimates, the intervention periods were sufficiently long to allow for evaluation beyond seasonal variation. Thus, we did not downgrade for indirectness on this basis. Although seven of the eleven included studies^{187, 196, 197, 275-277, 279} were single-centre trials, we did not downgrade for indirectness, as we considered the findings potentially generalisable to other hospital settings, despite possible differences in infection control practices and HAI rates. Similarly, while Salgado *et al.*²⁷⁸ excluded children and pregnant women, we found no strong rationale to downgrade for indirectness.

We downgraded for indirectness in three effect estimates. Specifically, we downgraded by one level the effect estimates reported by Danforth *et al.*¹⁹⁷ for HAIs and BSIs, as the study was conducted prior to 1987, and the epidemiological context and CDC surveillance definitions used at that time are not aligned with current practice. We also downgraded by one level hospital-acquired MRSA colonisations in Wilson *et al.*²⁸⁰, as this study reported a composite outcome (MRSA acquisition, colonisation, or infection after 48 hours) that did not exclusively assess MRSA colonisation.

5.3.4. Imprecision

The studies included in the review were underpowered resulting in wide CIs 95% and high imprecision—a common issue across the review. Consequently, we downgraded the certainty of the evidence due to imprecision in all but one of the effect estimates. In

particular, imprecision was judged to be extremely serious in 13 effect estimates and very serious in one. Only one effect estimate was not downgraded for this reason.

5.3.5. Publication bias

Our comprehensive search strategy, which included electronic databases as well as additional sources such as conference proceedings, reference lists, and trial registries, aimed to minimise the risk of publication bias. A formal assessment of publication bias was not feasible, as several key conditions were not met. Specifically, there were fewer than ten studies per effect estimate, insufficient variation in sample sizes among the included studies, and no statistically significant findings in any of the analyses. As a result, although we were unable to detect publication bias, this does not confirm its absence.

5.3.6. Financial conflict of interest

As recommended in the *Cochrane Handbook*²⁰⁶, we did not consider conflicts of interest in the formal assessment of risk of bias or certainty of evidence. However, it is noteworthy that only two of the eleven included studies declared the absence of financial conflicts of interest^{1276, 280}. Seven trials^{187, 196, 198, 274, 275, 277, 278} reported financial conflicts, with several authors having ties—such as consultancy roles—with for-profit organisations that had a financial interest in the products evaluated. On the other hand, two studies^{197, 279} did not report conflicts of interest disclosures, leaving their status unclear.

Among the seven studies with declared financial conflicts, four were prospectively registered^{187, 196, 198, 274}, which may be considered a step towards reducing the potential influence of bias. Nevertheless, these conflicts likely did not affect the outcomes relevant to this review, as none of the studies demonstrated a clear benefit of the interventions.

5.4. Strengths of this PhD project

5.4.1. Overall strengths of the dissertation

This dissertation offers a comprehensive and methodologically rigorous contribution to the field of infection control, with several overarching strengths that span its six constituent studies. A key strength lies in the integration of diverse methodologies—SRs, methodological appraisals, and conceptual frameworks—into a cohesive programme of research that addresses critical evidence and methodological gaps across the evidence lifecycle of non-pharmacological interventions. This multifaceted approach ensures that the dissertation not only identifies what is missing in the current evidence base, but also offers tools and strategies to build a more reliable, inclusive, and clinically meaningful infection control decision-making.

The dissertation maintains high methodological standards. SRs adhered to Cochrane and GRADE guidance, using predefined protocols, validated tools, and robust risk of bias assessments. Studies I and II addressed decontamination and barrier precautions with a broad yet focused scope, prioritising patient-centred outcomes to enhance clinical relevance. Studies III and IV applied structured tools (SGAT-SR and Cochrane-based criteria for describing non-randomised studies) to assess Cochrane reviews of infection control interventions, implementing independent data extraction to minimise bias. Studies V and VI synthesised previous findings to formulate actionable recommendations, drawing on empirical data, expert input, and established guidance. The resulting narrative synthesis identified key priorities for strengthening infection control research.

5.4.2. Strengths of study I: SR on decontamination

This review has several strengths.

First, we followed recent Cochrane and GRADE guidance to identify and synthesise the available RCT evidence and report findings ^{141, 152, 181, 210, 386}.

Second, the broad scope of the review encompassed any decontamination intervention, which provides a comprehensive overview of the available evidence. In addition to the many interventions available for decontamination, these interventions can be applied in different moments (routine or terminal decontamination) and several hospital settings, such as the ICU, operating room or the hospital ward. Furthermore, many aspects can be evaluated, such as the product, the frequency or the equipment. Our review was able to capture this complexity and synthesise the evidence base.

Third, although our review scope was broad, we attempted to establish clinically meaningful comparisons including studies with sufficiently similar features, that is,

homogeneous comparisons in terms of participants, interventions, outcomes and setting, as suggested in the *Cochrane Handbook*¹⁴¹. This process was informed by a non-systematic overview to identify critical factors for establishing meaningful comparisons, which was based on the 'WASTE' scheme¹²⁸: Workforce, Area, Substance, Technique, and Equipment. We acknowledge that we did not pre-define the list of comparisons that the review would address at the protocol stage. Still, we established the review comparisons without considering the included studies' results, which reduced the possibility of bias. Furthermore, we created specific comparisons, and avoided combining different types of decontamination interventions in one group. Although this precluded meta-analyses,, we ensured that the review findings are applicable in the clinical setting.

Third, we focused exclusively on RCTs, which represent the most robust design for estimating intervention effects. Although decontamination is often implemented as part of multi-component bundles¹²³, randomisation allows for the detection of the effects of infection control interventions that are difficult to predict with modelling or to disentangle from confounding in non-randomised studies, offering valuable insights for clinical practice^{127, 330}. Therefore, identifying and appraising RCTs represents a critical first step to map the existing evidence in this field.

Fourth, we extracted data using standardised forms informed by key methodological and reporting guidelines^{113, 163-167}. This process, although time-consuming, was essential. We drew on relevant checklists^{113, 165, 333} to describe core components of the interventions, co-interventions, and compliance in both intervention and comparison groups. This information supported our risk of bias assessments, particularly in the domain of deviations from intended interventions.

We also collected key data on participants and the epidemiological context¹¹³, which helped us to define the review comparisons, determine which studies could be meaningfully grouped, and assess the indirectness domain with GRADE. An additional strength of our data extraction approach was its foundation in Saldanha's guidance on well-reported outcomes¹⁷⁰, which informed the extraction of outcome data.

Our data extraction process also enabled the identification of reporting deficiencies that impeded interpretation of intervention effects¹⁶⁵. For instance, incomplete reporting of compliance limited our ability to determine whether the observed lack of effect from environmental decontamination resulted from true intervention failure or poor adherence.

Fifth, we prioritised patient-relevant outcomes—such as HAIs, colonisation, and adverse effects—while excluding surrogate measures like surface contamination, due to their uncertain clinical relevance and lack of standardised definitions⁴³. We also excluded composite outcomes, such as infections caused by multiple organisms (e.g., MRSA, VRE, or both) or combinations of “colonisation or infection or both”. We avoided composite measures as they assume equal importance across distinct events, mix different biological mechanisms, and complicate interpretation^{353, 354}. Instead, we focused on non-composite outcomes related to any HAI, which more accurately reflect biological and clinical relevance¹⁵⁹. This narrow focus accounts for the fact that some included trials did not contribute usable outcome data for our review.

Sixth, we used predefined decision thresholds to interpret the magnitude and meaningfulness of effects^{181, 183}. The use of thresholds is a recent approach proposed by GRADE, offering several advantages. It helps make implicit judgments explicit, enhances transparency and consistency across GRADE ratings, and extends beyond evidence appraisal. Thresholds can inform study design, guide sample size calculations, and support the interpretation of effect sizes, thereby contributing to more meaningful, efficient, and well-planned research and health decision-making³⁸⁷.

5.4.3. Strengths of study II: SR on gloves, gowns and masks

The strengths of this SR are similar to the previous one.

First, the methodological approach is rigorous and transparent, following Cochrane guidance with a pre-published protocol, clearly defined eligibility criteria, and pre-specified plans for study selection, risk of bias assessment, and data synthesis. The review also applied a very broad and sensitive search strategy across multiple bibliographic databases, Cochrane specialised registers, trial registries, conference proceedings and grey literature sources, without language or date restrictions, thereby minimising the risk of publication bias.

A second important strength is the conceptual clarity of the review question. We specifically aimed to isolate the effects of gloves, gowns and masks on MRSA transmission in hospitalised patients known to be colonised or infected, rather than considering broader, heterogeneous infection control bundles. This narrow focus highly relevant for understanding the independent contribution of individual barrier precautions and for informing context-appropriate control strategies.

Third, the review demonstrates careful consideration of study design issues typical of infection control research. Only experimental and quasi-experimental designs with

prospective allocation and outcome assessment (including RCTs, cluster-RCTs, and controlled before–after or ITS designs) were deemed eligible, while observational studies and outbreak reports were excluded because of their high susceptibility to bias. We justify the inclusion of stronger non-randomised designs in light of ethical and logistical challenges in randomising contact precautions, and outline how such designs should be analysed to reduce confounding.

Finally, the review handles its empty status robustly. We comprehensively document the volume of screened records, the reasons for exclusion, and emphasise the distinction between absence of evidence and evidence of no effect, explicitly warning against over-interpretation of non-experimental data and providing clear priorities for future research.

5.4.4. Strengths of study III: Sex/Gender consideration in Cochrane reviews

Our team conducted a comprehensive search for Cochrane reviews evaluating interventions to prevent HAIs. We retrieved all reviews published in the *CDSR* up to the end of 2016 and screened them for eligibility using clearly defined criteria. To maintain high methodological standards and reduce bias, two reviewers independently assessed each record; a third reviewer mediated any disagreements. We applied clearly defined exclusion criteria to ensure a rigorous and transparent selection process.

To assess the extent to which each review considered sex and gender, we applied the SGAT-R. Again, to reduce bias, the assessments were independently conducted by two reviewers, with discrepancies resolved by a third one. To enhance consistency in the application of the tool, we piloted it on a sample of reviews and developed a detailed user guide.

The SGAT-SR enabled us to systematically examine how sex and gender were addressed across the various sections of each Cochrane review. We selected this tool based on the recommendation of the Sex/Gender Cochrane/Campbell Working Group³⁸⁸. In addition, an extensive literature search conducted up to April 2017 by our team did not identify alternative tools specifically designed to appraise the integration of sex and gender in SRs. The SGAT-SR had previously been applied to SRs on cardiovascular disease, which allowed us to compare our assessments with published evaluations and better understand the tool¹³⁶. Moreover, the tool had been reviewed by independent subject experts to ensure alignment with accepted definitions of sex and gender, as well as compatibility with Cochrane review standards and structure¹³⁶.

5.4.5. Strengths of study IV: NRSIs consideration in Cochrane reviews

A key strength of this study lies in its comprehensive scope, as we included the full set of Cochrane reviews of interventions to prevent HAIs. This approach minimised selection bias in estimating how frequently NRSIs were considered eligible in this research field in Cochrane reviews.

Second, our assessment was guided by explicit, a priori criteria derived from the *Cochrane Handbook*¹⁶⁹. Furthermore, beyond merely recording whether NRSIs were admitted, we evaluated the justifications provided, assessing their alignment with Handbook-endorsed reasons for considering NRSIs. We also systematically analysed how review authors characterised these study designs. This theory-informed approach enhances interpretability and supports reproducibility.

Third, we went beyond design labels to examine whether reviews described the key methodological features recommended for transparent classification of non-randomised designs. Distinguishing between labels and underlying design features allowed for a more granular and actionable analysis.

Finally, the study benefited from structured procedures shared with Study III, including standardised data extraction, piloting, and independent assessments with consensus processes.

5.4.6. Strengths of studies V and VI: Methodological challenges in SRs & Design recommendations for RCTs

The main strength of Studies V and VI lies in the triangulation of three key inputs. First, the preceding four studies identified recurring methodological issues in infection control interventions that may not have emerged from a single SR or RCT. Second, authoritative sources—including the *Cochrane Handbook*¹⁴¹, GRADE⁹⁶, risk of bias tools^{171, 206}, and reporting guidelines^{01, 113, 154, 163-165, 332, 372-376}—were consulted to confirm that identified gaps were not fully addressed in current best practices. Third, experienced researchers in evidence synthesis contributed to all studies and their observations were collected as well.

A narrative synthesis approach enabled the integration of these diverse inputs, offering a comprehensive overview of the methodological landscape organised by SR and RCT phases. Notably, gaps such as the lack of a RoB 2 adaptation for cluster crossover RCTs identifies clear targets for future methodological development.

5.5. Limitations of this PhD project

5.5.1. Overall limitations of the dissertation

This dissertation is subject to overarching limitations arising from both the nature of the existing evidence base and the methodological challenges of the PhD studies.

A key limitation in Studies I and II was scarcity of RCTs. The evidence base in non-pharmacological infection control interventions is marked by heterogeneity, underpowered studies, and a predominance of uncontrolled designs with surrogate outcomes. These limitations prevented the conduct of meta-analyses and reduced the certainty of evidence for patient-centred outcomes. In addition, the focus on hospital settings and vertical, pathogen-specific approaches (e.g., MRSA) may restrict the generalisability of findings to broader horizontal strategies or other care environments, such as long-term care facilities.

Methodologically, Studies III and IV were based solely on published reports. The absence of direct author contact means that our judgements may not fully capture the actual practices of the reviews. Our assessments of sex and gender was further limited by the SGAT-SR tool, which sometimes lacked operational clarity and did not differentiate sex and gender dimensions, complicating interpretation. Moreover, the temporal scope of Study IV (pre-2017) may not reflect more recent developments in Cochrane's guidance on the inclusion of NRSIs.

Finally, the recommendations proposed in Studies V and VI were formulated based on the preceding studies. The absence of formal interest-holders engagement—such as input from trialists, review authors, or evidence synthesis organisations—and the reliance on narrative synthesis may affect the practical applicability and uptake of the proposed design recommendations. Additionally, several important outcomes—including ecotoxicity, intervention-related harms, and equity considerations—fell outside the primary scope of this dissertation, pointing to critical areas for future research.

5.5.2. Limitations of study I: SR on decontamination

This review has several limitations.

First, as the review protocol was published in 2010 in the CDSR¹⁵⁰, we made modifications to align methodology with current guidance. However, these changes are methodologically justified and unlikely to introduce bias. To ensure transparency, all deviations from the original protocol were documented. The review team judged that an updated protocol was unnecessary, as the modifications were primarily methodological and reflect developments in review guidance (e.g., updated *Cochrane Handbook*, RoB 2,

GRADE, *Methodological Expectations of Cochrane Intervention Reviews* (MECIR)), while the clinical question remained unchanged.

Second, the main limitation of our review was the inability to conduct a meta-analysis due to the limited number of included RCTs. However, we consider this reflects the limited and underdeveloped research in this field rather than shortcomings in the review methodology. Moreover, the complexity of synthesising multi-component interventions further contributed to the difficulty of performing a meta-analysis. We could not pool data because of scarce and heterogeneous evidence, including inconsistent outcome measurement³⁴³. For example, as indicated in similar reviews, studies reported HAIs caused by various organisms, mainly bacteria, but also viruses, and they affect different body systems, such as the respiratory tract, bloodstream, and urinary tract³⁴⁴.

Furthermore, the studies were underpowered for HAIs, which frequently resulted in wide CIs and extremely serious imprecision, downgrading the certainty of the evidence. Besides, RCTs are not well suited to detect rare adverse effects, which require larger observational designs³²⁴.

During title and abstract screening, we found that most studies were non-randomised and did not assess patient-centred outcomes. Several factors may explain the scarcity of RCTs in decontamination research. Randomisation is often difficult in infection control due to ethical, logistical, or urgent implementation constraints²⁶⁸. As a result, non-randomised designs—particularly uncontrolled before-and-after studies—are common despite their susceptibility to bias, especially in interventions targeting antibiotic-resistant pathogens²⁶⁸. Additionally, our focus on patient-centred outcomes, that is, HAIs, led to the exclusion of many studies assessing only surface contamination.

We applied predefined thresholds for absolute differences to interpret intervention effect sizes. While this approach had several advantages, the absence of standardised thresholds for HAIs or colonisations—likely due to variability in infection types, patient populations, and resource settings—made interpretation challenging and results open to debate.

Finally, another limitation of this review is that it did not evaluate several important outcomes, as doing so would have required methodologies beyond the scope of our project. First, we did not assess surface damage resulting from decontamination procedures. This outcome is relevant because damaged surfaces may increase the risk of recontamination. Moreover, understanding how different decontamination methods affect various surface types can inform the selection of the most appropriate techniques

and products. Second, we did not evaluate the ecotoxicity associated with disinfectant use, which is a critical factor in determining the overall benefit–risk balance of decontamination interventions. Third, the review did not explicitly assess patient and staff satisfaction with the decontamination processes. Fourth, we did not examine the feasibility of the interventions, including practical considerations such as organisational factors and staff training, which may influence the implementation of specific decontamination strategies. Despite these limitations, we believe the review addressed the most important patient-centred outcomes.

5.5.3. Limitations of study II: SR on gloves, gowns and masks

This SR is subject to a common limitation observed in reviews of infection control interventions: the scarcity of controlled experimental studies. This limitation reflects the evidence base and is not specific to our review methods, as infection control interventions are frequently evaluated using uncontrolled study designs¹¹⁴.

One review limitation is that it did not assess the potential harms associated with the use of gloves, gowns, or masks. This represents a limitation, as there are legitimate concerns regarding the unintended effects of these commonly used interventions. However, the decision not to evaluate harms was based on two considerations. First, a SR of harms necessitates different methodological approaches from those used to assess beneficial outcomes. This includes the consideration of a broader range of study designs (e.g., cohort studies, case-control studies, or case reports), the use of additional data sources, highly sensitive search strategies, and the application of specific tools for risk of bias assessment³²⁴. Second, assessing harms requires a broader definition of the study population, including individuals without confirmed MRSA colonisation or infection, and those in non-hospital settings.

Another limitation of the review question is its focus on the effects on a single pathogen, that is, MRSA, which may limit the direct applicability of the review findings. This reflects a vertical approach to infection prevention, which targets specific organisms (e.g., active MRSA surveillance and contact isolation), in contrast to horizontal strategies that aim to reduce transmission of a broad range of pathogens (e.g., universal contact precautions in high-risk settings). The choice between vertical and horizontal approaches has been a subject of debate in the prevention of HAIs^{158, 389}.

In clinical practice, gloves, gowns, and masks are rarely used solely to prevent the transmission of one microorganism, that is, MRSA. These precautions are also employed to prevent the spread of other MDROs, such as VRE and *Clostridium difficile*. Nevertheless, the focus on MRSA can be justified, given differences in transmission

dynamics across pathogens³⁷, and evidence suggesting that infection control interventions may have differing effects on specific antibiotic-resistant bacteria. For example, in the BUGG Study²⁴², the use of gloves and gowns for all patient contact in intensive care units significantly reduced MRSA acquisition, but no impact was found on VRE acquisition.

Another review limitation concerns its exclusive focus on hospital settings. It is plausible that the effectiveness of these interventions may differ in other healthcare environments, such as long-term care facilities and nursing homes³⁹⁰. These contextual differences should be taken into account when interpreting and applying the findings to non-hospital settings. Notably, a related Cochrane review assessing infection control strategies to prevent MRSA transmission in nursing homes for older adults also identified a lack of high-quality evidence in this area²²⁷, underscoring a broad research gap across settings.

We considered both RCTs and selected NRSIs for inclusion, acknowledging that NRSIs are more susceptible to bias. Nevertheless, the inclusion of NRSIs was appropriate, as we chose non-randomised experimental designs capable of reducing major threats to the internal validity of infection control studies, specifically biases related to secular trends, seasonal variation, and regression to the mean^{74, 113, 245, 391, 392}.

We excluded observational studies, outbreak reports, and other weaker designs. Outbreak reports, which are common in infection prevention literature, typically describe novel phenomena (e.g., emergence of a new MRSA strain) or the measures taken during outbreaks responses. While they can be valuable for hypothesis generation, they offer limited value in assessing the effectiveness of interventions^{113, 393}.

This review did not plan formally address sex, gender, or equity considerations, as relevant guidance had not yet been fully implemented within Cochrane methodology at the time of its preparation³⁹⁴.

5.5.4. Limitations of study III: Sex/Gender consideration in Cochrane reviews

This study aimed to assess how the Cochrane reviews were conducted, rather than how they were reported. However, we did not contact the review authors to clarify missing, incomplete, or ambiguous reported information. In such cases, we generally assumed that the absence of reporting indicated that the element in question had not been addressed—though we acknowledge that this may not reflect the actual practice of the review authors.

During the selection and data extraction processes, reviewers were not blinded to the identity of the review teams or their institutional affiliations. Additionally, two of the

authors of this methodological study were as well authors of three of the included Cochrane reviews^{395, 396}. Nevertheless, to minimise potential bias, all selection and extraction procedures were independently performed by at least two reviewers, with disagreements resolved through consultation with a third one.

We did not assess inter-rater reliability (e.g., using kappa statistics) for the SGAT-SR ratings. Therefore, we cannot formally confirm the consistency of our judgments across reviewers.

We encountered several challenges in applying the SGAT-SR. First, the tool would benefit from being more user-friendly and operational, ideally including detailed guidance and illustrative examples from existing reviews. Second, it was often unclear whether some items referred to the planning phase of the review or to what was ultimately carried out. Third, the tool does not specify when certain items may be not applicable. For example, in reviews with no included studies, it is unclear whether result-related items should be marked as not meeting the criteria or not applicable. Fourth, the SGAT-SR combines sex and gender within the same items, limiting the ability to appraise each dimension independently. We believe that separate, focused assessment of sex and gender is warranted. Fifth, the tool does not cover several important sections of Cochrane reviews, such as the abstract, plain language summary, discussion, or summary of findings tables.

Alba Antequera *et al.* revised the SGAT-SR tool following a literature review on sex, gender, and intersectionality, along with input from an expert advisory board. The updated version, SGAT-SR 2¹¹⁰, was subsequently developed and applied to the evaluation of systematic reviews on sepsis.

We did not use the SGAT-SR in reviews addressing topics inherently limited to one sex. This applied to eleven SRs that included only female participants addressing interventions to prevent HAIs in caesarean section, operative vaginal delivery, abortion, amniotomy, or prelabour rupture of membranes^{296, 297, 299-306, 397}. While these reviews were not appropriate for evaluating sex-related content, we acknowledge that examining how gender was considered remains relevant.

Although sex and gender are increasingly recognised as critical variables in clinical research¹⁰¹, further efforts are needed to standardise how they are measured, reported, and analysed. Currently, there is no consensus on best practices for disaggregating demographic or outcome data by sex, gender, or both, nor on how such information should be reported. This ongoing lack of standardisation contributes to persistent gaps in

both primary studies and SRs, ultimately hindering progress toward more personalised and equitable healthcare.

Finally, our study protocol was neither guided by a specific reporting guideline nor pre-registered in an open-access repository, such as the *Open Science Framework*. At the time of study inception, we were unable to identify relevant reporting guidelines applicable to our methodology. Regarding protocol registration, it was not common practice to register methodological study protocols during that period. For instance, we did not register this study in the PROSPERO database, as it did not meet the eligibility criteria—primarily because it was not a SR³⁹⁸.

5.5.5. Limitations of study IV: NRSIs consideration in Cochrane reviews

This study shares the limitations of Study III, that is, its reliance on information reported by review authors in published Cochrane reviews. Also, the applicability of our findings is limited by both scope and timing. We analysed Cochrane reviews of HAI-prevention interventions published prior to 1 January 2017; therefore, the results may not reflect current Cochrane practices following methodological developments introduced thereafter (such as the new guidance of the *Cochrane Handbook* to include NRSIs²⁷¹), nor are they necessarily generalisable to other clinical domains.

In addition, our analysis focused solely on the eligibility criteria, justifications, and descriptions of NRSIs. We did not examine how the inclusion of NRSIs, when present, influenced synthesis decisions, effect estimates, or certainty of evidence assessments.

5.5.6. Limitations of studies V and VI: Methodological challenges in SRs & Design recommendations for RCTs

Studies V and VI share several limitations that should be considered when interpreting their findings in the context of specific reviews or trials.

First, both studies drew on evidence from the preceding four dissertation aims, which were limited by the small number of RCTs included in the first SR and the lack of eligible studies in the second one. These constraints narrowed the empirical foundation for identifying methodological challenges.

Second, there was no formal engagement with key stakeholders—such as review authors, trialists or funders—through consultation or consensus-building processes. This omission may affect the relevance and applicability of the resulting recommendations.

Third, the narrative synthesis required subjective judgments, which may have affected the selection of topics.

5.6. Interpretation of the results in the context of current knowledge

5.6.1. Integrating the findings of this dissertation: a critical synthesis

The integration of the six PhD studies offers a comprehensive and critical analysis that extends beyond the individual findings of each study. Considered collectively, the dissertation reveals a persistent, circular challenge in hospital infection control research: the scarcity of high-quality RCT evidence leads to inconclusive primary data, which in turn results in SRs that are either empty or provide evidence of very low certainty. Notably, even Cochrane reviews of infection control interventions—regarded as the gold standard in healthcare evidence—exhibit significant limitations, particularly the absence of a sex and gender perspective and insufficient transparency in the characterisation of non-randomised studies.

The overarching argument of this dissertation is that advancing evidence-based infection control requires an epistemological shift toward a patient-centered model—one that evaluates clinical outcomes through the lens of an inclusive approach. This shift is exemplified across several PhD studies. For example, Study I excluded performance studies that focused exclusively on surface contamination. Study III assessed the integration of sex and gender considerations in Cochrane reviews. Study VI advocated for the development of core outcome sets that prioritise health-related quality of life and morbidity associated with HAIs.

The studies included in this dissertation help explain the low certainty and limited availability of RCT evidence in infection control from multiple and complementary angles. The very low certainty findings reported in Study I are contextualised by methodological challenges identified in Studies III, IV, V, and VI. For example, the high risk of bias reflects the inherent difficulties in blinding non-pharmacological interventions and measuring adherence (Study V). The issue of indirectness is linked to inadequate baseline reporting of sex and gender (Study III), while the observed imprecision is due to sample size calculations that fail to account for correlations in infection outcomes (Study VI). Similarly, the empty review (Study II) reflects the frequent reliance on non-randomised or uncontrolled studies in infection control research, as evidenced by the large number of excluded studies in the two SRs of this dissertation.

The integration of Studies V and VI offers a corrective roadmap for advancing infection control research. Progress requires not merely an increase in the number of RCTs, but a commitment to conducting methodologically robust and context-sensitive and inclusive research. This includes the adoption of innovative designs—such as the stepped-wedge cluster RCT—that accommodate the logistical and ethical complexities inherent to

infection control while preserving scientific rigor. Equally essential is a commitment to research equity, including the systematic disaggregation of data by sex and gender, to ensure that interventions are safe, effective, and inclusive for all patient populations.

The following subsections examine how each dissertation study aligns with—or diverges from—current knowledge in the field.

5.6.2. Agreements and disagreements of study I: SR on decontamination

5.6.2.1. Findings of other reviews

Previous SRs have consistently highlighted the need for further research on environmental surface decontamination, citing recurring methodological limitations and challenges in the existing evidence base^{41, 42, 115, 323, 344, 347, 399-403}. These include the use of bundled interventions, which make it difficult to determine the specific effects of surface decontamination, and the heterogeneity of intervention types, which precludes meta-analytical synthesis. Additionally, many studies focus on surface contamination rather than clinical outcomes such as HAIs, and much of the available evidence is derived from laboratory settings rather than real-world clinical environments^{323, 404-406}. The body of evidence is further limited by the scarcity of RCTs, with most studies employing observational or non-randomised uncontrolled designs¹¹⁴.

Our review identified all relevant RCTs included in prior reviews and reached similar conclusions^{41, 42, 115, 323, 344, 347, 399-403}. We excluded certain trials included in other SRs because the interventions were not eligible (e.g., infection control bundles or copper-treated textiles⁴⁰⁷), the study outcomes were limited to microbial surface burden, or the study designs were non-randomised. Notably, some prior reviews presented methodological limitations, often omitting assessments of risk of bias or certainty of evidence^{41, 42, 115, 400}. For instance, only one review employed the GRADE approach⁴⁰³.

Our findings align with those of Alsaggaf¹¹⁴, who reported that most decontamination studies are uncontrolled. We concur that while decontamination can reduce microbial surface burden, its effect on HAIs in complex healthcare settings—where multiple transmission pathways exist—remains uncertain^{125, 126}. Nonetheless, we disagree with Schmidt's assertion that GRADE is unsuitable for evaluating the evidence provided by infection control trials⁴⁰⁸. On the contrary, GRADE remains a valuable framework for guiding evidence-based decisions in infection prevention and control, including during public health emergencies such as the COVID-19 pandemic^{139, 140}.

Our review identified substantial variability in how HAIs and colonisation outcomes were measured and analysed across the included studies. Such heterogeneity, also observed

in other research fields³⁴³, limits the ability to synthesise findings across trials and formulate robust conclusions.

5.6.2.2. Infection outcomes that were not eligible in our review

Our review did not include certain outcomes commonly reported in published studies. While this decision may be perceived as a limitation—given that we did not synthesise potentially relevant data from the included studies—we consider it appropriate and justified based on the objectives and scope of our review.

Exclusion of surface contamination outcomes (bacterial counts on surfaces)

This review did not include surface contamination as an outcome. Although most studies reported this information, we consider its exclusion a strength. Our primary objective was to provide robust evidence on the effects of decontamination on patient-centred outcomes, particularly HAIs, which are critical for clinical decision-making. Surface contamination is a surrogate outcome for colonisation or infection, and its direct relevance to patients and decision-makers remains uncertain.

Multiple factors can confound the relationship between reduced environmental contamination and pathogen transmission in hospital settings. These include the number of colonised or infected patients, the use of antibiotic prophylaxis, and compliance with hand hygiene and decontamination protocols³⁴⁶. Moreover, there is currently no consensus on the contamination threshold below which transmission is effectively minimised⁴³. Standardised guidance for sampling environmental surfaces and defining cleanliness is also lacking. To our knowledge, no universally accepted criteria exist for determining when a surface can be considered “clean”⁴³. Finally, contamination levels may reflect either the efficacy of the decontamination process or the level of compliance with its implementation^{41, 146, 409}.

Exclusion of composite outcomes

We excluded composite outcomes, such as “presence of colonisation, infection, or both.” While this decision limited our ability to synthesise data from many included studies, we believe it allowed for a more focused and clinically meaningful analysis. By concentrating on the frequency of “any HAI,” we prioritised the most biologically and clinically relevant endpoints¹⁵⁹.

A composite endpoint combines multiple individual outcomes into a single measure⁴¹⁰. Thus, the occurrence of any one of the multiple outcomes is classified as an outcome⁴¹¹. For example, a composite endpoint might be healthcare acquisition, defined as

colonisation, infection, or both. While such outcome can increase the statistical power of a RCT compared to a RCT testing colonisation and infection separately, it poses interpretative challenges^{354, 355}. Composite endpoints typically register the first event a patient experiences (e.g., colonisation), which may be less clinically relevant than subsequent infection³⁵³. Furthermore, composite outcomes assume that all components have similar importance and impact on health³⁵³—a problematic assumption when comparing colonisation and infection. Infections are generally more meaningful to both patients and healthcare systems. Additionally, evaluating the risk of bias in effect estimates from composite outcomes is complex. Overall, we maintain that the exclusion of composite outcomes represent the most biologically and clinically relevant approach¹⁵⁹.

Exclusion of HAIs of specific microorganisms

We excluded HAIs targeting specific microorganisms as a review outcome. Decontamination is a horizontal intervention designed to reduce infections caused by a broad range of pathogens¹⁵⁸. Defining decontamination as a vertical intervention—i.e., one that targets only specific organisms—could misrepresent its broader preventive potential.

Exclusion of colonisation in studies without an existing screening policy at admission

We considered colonisation outcomes only in studies that implemented a screening policy at admission for the healthcare-associated pathogen(s) under investigation. This approach ensures the validity of colonisation data by distinguishing between pre-existing and newly acquired colonisation during hospitalisation⁷⁴.

5.6.3. Agreements and disagreements of study II: SR on gloves, gowns and masks

To our knowledge, the only SR explicitly evaluating the effects of gloves, gowns, or masks for preventing the transmission of MRSA in the hospital setting is our 2015 Cochrane review, which forms part of this PhD²⁴⁴.

Prior to the publication of our SR in 2015, several SRs had evaluated the effectiveness of various strategies for preventing the transmission of microorganisms in hospital settings^{129, 389, 412-414}, with some specifically addressing MRSA^{74, 226, 229, 415}. However, none of these reviews assessed the relative effectiveness of gloves, gowns, or masks as individual interventions for managing patients colonised or infected with MRSA. Moreover, all concluded that the existing evidence base had significant limitations and was mostly based on non-randomised/outbreak of bundled approaches.

Another Cochrane review evaluated infection control strategies to prevent MRSA transmission in nursing homes for older adults²²⁷. This SR concluded also that there is a lack of research assessing the impact of such interventions in this setting. Across three updates of the review, meta-analysis was not possible due to the inclusion of only a single RCT⁴¹⁶. These findings highlight a broad research gap in infection prevention and control strategies beyond hospital settings.

Since the publication of our 2015 Cochrane review, several SRs have examined the effectiveness of contact precautions in reducing microorganism transmission in healthcare settings, with findings consistent with our own.

The SR by Cohen *et al.*⁴¹⁷, published in 2015, aimed to assess the effectiveness of contact precautions alone in preventing the transmission of any MDRO among adult acute care patients. The authors concluded that the poor quality of available evidence continues to hinder meaningful interpretation of the findings. This review did not identify any studies eligible for inclusion in our review.

Chang *et al.*'s⁴¹⁸ attempted to determine whether implementation of universal gloving, that is, wearing gloves for all patient interactions regardless of colonisation status, was associated with decreased incidence of HAI in clinical settings. Its pooled analysis revealed a statistically significant association between universal gloving and reduced HAI incidence (IRR: 0.80, 95% CI: 0.67–0.96) but stratified analyses showed non-significant associations for MRSA (IRR: 0.94, 95% CI: 0.79–1.11). Studies evaluating universal gloving alone demonstrated a significant reduction in HAI incidence (IRR: 0.77, 95% CI: 0.67–0.89), whereas those incorporating it into intervention bundles showed no significant effect (IRR: 0.95, 95% CI: 0.86–1.05). This review included eight studies, seven of which our SR had identified but excluded due to ineligible designs (uncontrolled before-and-after studies^{84, 85}, retrospective cohort study⁴¹⁹), RCTs including patients with or without confirmed MRSA colonisation or infection^{242, 420, 421}, or studies conducted in nursing homes⁴²². The eighth study, published after our review in 2018⁴²³, was also ineligible as it was a retrospective, non-randomised observational study.

Kleyman *et al.*'s SR⁴²⁴ updated a prior review⁴²⁵ to assess whether discontinuing contact precautions for patients with MRSA and VRE affected HAI rates. It included 17 studies, none of which met our inclusion criteria: 15 were uncontrolled before-and-after studies^{239, 426-439} and two were observational studies^{440, 441}. The review found no evidence of changes in hospital-associated MRSA infection rates following the removal of contact precautions.

The *Making Healthcare Safer IV* (MHS IV) initiative⁴⁴², updated till 2024, builds upon a SR published in 2013 for the Agency for Healthcare Research and Quality (AHRQ)³⁸⁹. The review evaluated the certainty of evidence regarding several infection control practices aimed at reducing in-facility infections with MDROs in adult patients. The practices included universal gloving, contact precautions, cohorting, environmental decontamination, patient decolonisation, and the adverse effects of isolation. The certainty of evidence was evaluated using GRADE.

The MHS IV initiative identified the SR by Chang *et al.*⁴¹⁸ (see above), which evaluated the effectiveness of universal gloving in reducing HAIs. The review was assessed as being of good methodological quality and no new studies on universal gloving for MDRO control were identified. The MHS IV initiative concluded that there is low-certainty evidence suggesting that universal gloving may be beneficial in specific patient populations, particularly in paediatric ICUs⁴⁴².

Regarding the effects of contact precautions, defined as the use of gowns, gloves, and single-room isolation for infected or colonised patients, the MHS IV concluded that there is mixed evidence, and there is a very low certainty signal that isolation may be associated with some adverse health effects⁴⁴². The SR included six studies^{440, 443-447}, none of which met our eligibility criteria. Two studies^{440, 447}, published before 2015, were identified in our review but excluded because they evaluated bundled interventions, preventing isolation of the effects of gloves, gowns, or masks. The remaining four studies⁴⁴³⁻⁴⁴⁶, published after our review, were also ineligible, as their interventions were not aimed at reducing MRSA transmission. Of these, two were controlled before-and-after studies^{445, 446}, and two were cluster-RCTs^{443, 444}.

5.6.4. Agreements and disagreements of study III: Sex/gender consideration in Cochrane reviews

Our findings align with other studies examining SGBA in Cochrane reviews^{136, 448}, which similarly concluded that SGBA was virtually absent. In this context, our study reinforces the notion that current Cochrane reviews largely overlook sex and gender considerations, highlighting a substantial opportunity for improvement in this area. This gap extends to non-Cochrane SRs as they infrequently address or report on equity-related issues⁴⁴⁹⁻⁴⁵¹, including sex and gender specifically⁴⁵²⁻⁴⁵⁶. Finally, the integration of sex and gender considerations into health research reporting guidelines remains limited and sex and gender concepts are often incorrectly used⁴⁵⁷.

5.6.5. Agreements and disagreements of study IV: NRSIs consideration in Cochrane reviews

Integration of NRSIs into SRs of interventions has shifted substantially in recent years. Cochrane and GRADE have traditionally emphasised RCTs as the most reliable source for estimating interventions effects to inform guidelines¹⁷⁶. Both now acknowledge that NRSIs can contribute valuable evidence: as a replacement when RCTs are unavailable, as complementary evidence alongside RCTs, or sequentially^{380, 458}. However, although NRSIs may generate more generalisable or precise estimates in some contexts, confounding and other biases remain key limitations⁴⁵⁹.

Furthermore, as Axon *et al.*³²⁵ note, Cochrane's 2025–2030 Scientific Strategy⁴⁶⁰ prioritises multiple chronic conditions, climate change, and sustainability, where RCT evidence may be scarce or impractical. Therefore, rigorous and appropriate integration of NRSIs into evidence syntheses will become even more frequent. In this line, the new version of the *Cochrane Handbook* continues to recommend that eligibility criteria, data collection and assessment of included studies place an emphasis on specific features of study design rather than 'labels' for study designs^{271, 461}.

Our findings align with research showing suboptimal inclusion of NRSIs in Cochrane reviews as many reviews provide no justification, or justifications that do not follow Cochrane guidance. A 2025 scoping review of 87 Cochrane intervention reviews found fewer than half justified including NRSIs (41%)³²⁵. Similarly, Ijaz *et al.*²⁷⁰ assessed 202 Cochrane reviews and reported that 56% gave no reason for including NRSIs. These SRs used varied non-randomised designs, with controlled before and after studies being the most frequent. The COVID-NMA initiative—an international living SR and meta-analysis of COVID-19 interventions—has further highlighted challenges in identifying and incorporating non-randomised studies in living reviews in the infection prevention field³²⁶.

5.6.6. Agreements and disagreements of studies V and VI: Methodological challenges in SRs & Design recommendations for RCTs

Identifying methodological challenges in SRs of infection control interventions and proposing design recommendations for RCTs aligns with a growing meta-epidemiological literature highlighting the fragility of the evidence base for complex interventions in general³⁵¹ and infection control in particular^{43, 114, 118, 123, 462}.

Intervention integrity is key challenge across various non-pharmacological fields, including psychological³³² and digital interventions^{463, 464}, where reporting is often inadequate and standardised assessment tools are lacking. This supports Study VI's call

for rigorous fidelity monitoring and detailed reporting to distinguish between true intervention failure and non-adherence.

Study V's identification of challenges in managing a rapidly expanding evidence base reflects findings by Iannizzi *et al.*⁴⁶⁵, who considers that living SRs are well-suited to settings of clinical uncertainty and evolving evidence. Such reviews require regular updates, reinforcing this thesis's emphasis on adaptive syntheses that incorporate non-randomised evidence to inform timely policy decisions.

The 2024 WHO guideline on COVID-19 infection prevention cautions against isolating individual interventions of care bundles, noting that doing so may overlook synergistic effects¹²¹. Interventions such as gloves, gowns and masks, and environmental surface decontamination are intended to function as an integrated package; isolating elements may compromise effectiveness and raise ethical concerns by potentially endangering patients and staff. While this project acknowledges the limitations of evaluating single measures—particularly in complex settings with multiple transmission pathways^{125, 126}—it aligns with Ioannidis's view that assessing individual components can yield valuable insights for practice¹²⁷.

Debate persists regarding the adequacy of the GRADE framework for complex interventions. This dissertation supports scholars who advocate for GRADE's utility even in complex interventions and public health emergencies, such as the COVID-19 pandemic^{139, 140, 466}. Still, concerns persist that GRADE may not fully capture the complexity of such interventions⁴⁰⁸, often resulting in lower certainty ratings than simpler interventions⁴⁶⁷. Consequently, some researchers argue that over-emphasising randomisation may unfairly penalise complex interventions that may be better evaluated through implementation science and real-world data rather than traditional randomised trials⁴⁶⁷.

5.7. Implications for practice

5.7.1. Overall implications for practice derived from this dissertation

This dissertation highlights a research field marked by low-certainty evidence regarding patient outcomes, particularly in relation to essential non-pharmacological practices such as decontamination and the use of personal protective equipment, which are largely unsupported by RCTs. These limitations are exacerbated by a systemic neglect of sex and gender considerations in Cochrane reviews of infection control interventions, as well as a lack of transparency in the integration of non-randomised evidence into these SRs. The overall findings of this dissertation have important implications for hospital infection risk management and for the formulation of evidence-based recommendations by guideline developers.

The complete absence of RCT evidence for the use of gloves, gowns, and masks in preventing MRSA transmission (Study II), alongside the very low certainty of evidence for hospital surface decontamination (Study I), indicates that these practices are precautionary rather than evidence-based. This does not imply that such measures should be discontinued; rather, their implementation must be guided by transparency. Guideline developers should explicitly acknowledge the low certainty of the evidence, enabling hospital administrators to make informed decisions about resource allocation—particularly when considering high-cost interventions such as UV-C disinfection robots or antimicrobial copper surfaces.

The absence of sex and gender considerations in Cochrane reviews of infection control interventions, as identified in Study III, represents a clear call to action for policy makers. National health agencies, journal editors and international organisations, such as Cochrane, should mandate the inclusion of sex- and gender-based analysis in all evidence syntheses—or, at a minimum, require explicit justification when it is omitted. Clinical guidelines should systematically assess whether the effectiveness or safety of interventions varies across demographic groups. An actionable recommendation would be require that review authors assess whether their SRs meet the criteria of tools such as SGAT-SR-2, to ensure that sex and gender considerations are adequately addressed throughout the evidence synthesis process.

Advancing the evidence synthesis ecosystem for infection control requires a framework that integrates both randomised and non-randomised evidence to maximise the utility of all available data. A starting point could be to address the gaps identified in Study IV—specifically, by improving the characterisation of non-randomised studies. Improved

identification and classification of non-randomised studies would support the extraction of actionable evidence, particularly in contexts where RCTs are absent or unfeasible.

Finally, dedicated training programmes should be made available to equip future review authors and trialists with the skills necessary to address the methodological complexities inherent in infection control research.

5.7.2. Implications for practice from study I: SR on decontamination

Evidence from RCTs on the impact of hospital surface decontamination on patient-centred outcomes (e.g., colonisations, HAIs, BSIs, mortality, length of stay, adverse effects, and resistance to antibiotics or disinfectants) remains inconclusive due to the limited number of studies and their very low certainty.

This review identified 11 RCTs evaluating manual disinfectants (quaternary ammonium compounds, probiotics, phenolics), no-touch methods (UV-C light), and antimicrobial surfaces (copper), all yielding very low-certainty evidence. The effects of cleaning and disinfection interventions—and differences between them—remain uncertain.

The effects of other critical aspects related to the decontamination process are also uncertain, such as the impact of decontamination frequency, timing (routine or terminal decontamination), targeted areas (high-touch surfaces or areas with infected or colonised patient), equipment (microfiber mops) or decontamination duration.

These inconclusive findings should not be interpreted as evidence of no effect but rather as indicative of substantial knowledge gaps requiring further research.

In the absence of high-certainty evidence, hospitals should adhere to current infection prevention guidelines and consider local epidemiology, as well as factors such as safety, environmental impact, cost, and sustainability when selecting products.

Guideline developers should clearly report the certainty of evidence and rationale for recommendations, allowing transparent decision-making and iterative updates based on patient-centred outcomes.

Guideline developers should use existing methods that integrate evidence from randomised and non-randomised studies to enhance certainty and support stronger recommendations^{140, 380}. When RCTs are absent or provide only low or very low certainty evidence, well designed non-randomised studies, including observational designs, can complement the evidence base³⁸⁰. Including such studies can increase certainty, particularly when they address gaps in RCTs (e.g., rarely evaluated interventions or outcomes, short follow-ups, or non-diverse populations). Although not the focus of this

review, which included only RCTs, there are good examples of non-randomised studies that could complement the evidence base and support decision making^{71, 468-471}.

5.7.3. Implications for practice from study II: SR on gloves, gowns and masks

We found no studies evaluating the effects of wearing gloves, gowns, or masks during contact with hospitalised patients carrying MRSA, or with their immediate environment, on MRSA transmission. As a result, we cannot draw conclusions about the impact of these interventions on healthcare-associated MRSA outcomes in hospitalised patients or among hospital staff, caregivers, or visitors.

The lack of evidence regarding the effectiveness of these interventions should not be interpreted as evidence of ineffectiveness; rather, it reflects the absence of eligible studies addressing this question.

In the absence of high-certainty evidence, hospitals should adhere to current infection prevention guidelines and consider local epidemiology, as well as factors such as safety, environmental impact, cost, and sustainability when selecting infection control interventions.

Guideline developers should clearly report the certainty of evidence and rationale for recommendations, allowing transparent decision-making and iterative updates based on patient-centred outcomes, including potential benefits and harms. Guidelines should also clearly specify when the use of barriers—gloves, gowns, or masks—is required, whether for all room entries or only during activities identified as high-risk for contamination.

5.7.4. Implications for practice from study III: Sex/gender consideration in Cochrane reviews

Cochrane should develop an effective strategic plan to address current deficiencies in the consideration of sex and gender across its reviews. As part of this effort, the incorporation of explicit criteria for SGBA into the MECIR³⁸⁶ standards and PRISMA reporting guidelines¹⁵² could be a key action.

Although the SGAT-SR facilitates the assessment of sex and gender considerations in SRs¹³⁶, this tool still has room for improvement. Cochrane should offer review authors more practical and operational guidance on how to effectively incorporate sex and gender into their reviews. The SGAT-SR-2¹¹⁰ may serve as a valuable resource in this regard and warrants further testing.

5.7.5. Implications for practice from study IV: NRSIs consideration in Cochrane reviews

Given that RCTs of interventions to prevent HAIs may be unavailable, delayed, or infeasible, Cochrane reviewers conducting SRs in this area should be prepared to include NRSIs, provided that rigorous methods are applied to minimise bias.

Two critical requirements for Cochrane reviews that include NRSIs are: (1) providing a clear and well-justified rationale for the inclusion of these study designs, and (2) applying explicit eligibility criteria based on methodological characteristics, rather than relying solely on study design labels.

In light of the expected increase in demand for SRs that incorporate non-randomised evidence, Cochrane should adopt strategies to enhance the implementation of its NRSI guidance.

5.7.6. Implications for practice from study V: Methodological challenges in SRs

Review authors must clearly define eligible study designs through explicit design features and consistently apply selection criteria.

Data extraction tools should capture information on intervention fidelity and relevant contextual factors.

Adaptations of the Risk of Bias 2 tool for cluster crossover and stepped-wedge RCTs are urgently needed, including formal integration of specific bias sources such as seasonality, contamination, carry-over effects, and intervention protocol deviations.

Evidence synthesis organisations and funding bodies should support methodological innovation for the evaluation of infection control interventions. In light of the growing inclusion of non-randomised studies in SRs, strategies to ensure the rigorous integration of NRSIs with RCTs must be prioritised.

5.7.7. Implications for practice from study VI: Design recommendations for RCTs

Trialists should embrace non-conventional cluster designs (stepped-wedge and cluster crossover RCTs).

Baseline documentation must capture comorbidities, demographics, and epidemiological factors.

Infection control professionals and researchers should develop a core outcome set that prioritises patient-centred outcomes over surrogate measures. Outcome selection in trials should prioritise clinically relevant, patient-centred endpoints aligned with this core outcome set, using standardised definitions rather than composite measures.

Statistical analyses must address data dependency through clustering, with transparent reporting of sample size estimations and correlation coefficients.

Data collection should align with healthcare administrative capacity and standardised surveillance criteria.

Funders should prioritise publicly funded research in low-resource settings and enforce conflict-of-interest policies to mitigate bias in industry-funded studies.

5.8. Implications for research

5.8.1. Overall implications for research derived from this dissertation

By identifying both evidence and methodological gaps specific to non-pharmacological infection control interventions, this thesis offers a roadmap for developing a more rigorous and inclusive research agenda. Strengthening the evidence base in this area requires more than just additional trials. To shift from common sense practices to evidence-informed strategies, the infection control community must engage with the recommendations outlined in this thesis. These provide actionable proposals for future research, including the following.

Adopt adequately powered, non-conventional RCTs—particularly cluster-crossover and stepped-wedge designs—that are well-suited to evaluating infection control interventions, using statistical methods that appropriately account for the clustered nature of infection data. These trials should also include low-resource settings, where context-specific evidence is critically needed.

Adopt core outcome sets that support a shift from biologically plausible surrogates to patient-centred outcomes. Trials should move beyond measuring proxies such as germs killed and instead focus on clinically meaningful endpoints, including the incidence of HAIs, quality of life and lives saved.

Establish clear thresholds for clinical relevance. This will facilitate the interpretation of effect sizes and support more robust assessments of their precision across studies.

5.8.2. Implications for research from study I: SR on decontamination

There is an urgent need to establish optimal decontamination practices driven by the substantial global burden of HAIs and the emerging challenge of antimicrobial resistance. While this review identified four ongoing trials evaluating newer technologies, evidence gaps remain important. New RCTs are needed to define best protocols the best products, technology and practices for decontamination and reduce unnecessary practice variability¹²⁸.

We anticipate that addressing the following research areas will improve infection prevention programs.

5.8.2.1. The effectiveness and safety of the different choices available to decontaminate hospital environmental surfaces are yet to be established

Routine manual decontamination options

Routine cleaning with detergents remains understudied likely due to limited industry sponsorship. Head-to-head comparisons of routine manual decontamination interventions are essential, particularly between detergents and chemical disinfectants (QACs, phenolics). This gap is critical given concerns about antimicrobial resistance and disinfectant safety.

High-risk environmental surfaces

Research must identify which hospital surfaces pose the greatest transmission risk and therefore merit targeted or enhanced decontamination. This requires epidemiological and microbiological investigation linking surface contamination patterns to patient infection outcomes across diverse ward types.

No-touch terminal decontamination modalities

Head-to-head trials comparing terminal decontamination with no-touch devices, that is, ultraviolet light (UV-C, pulsed xenon), high-intensity narrow-spectrum (HINS) light, HPV systems, steam cleaning, chlorine dioxide, ozone, and cold atmospheric pressure plasma, against manual decontamination are needed.

Antimicrobial surfaces

RCTs of copper, silver, and zinc surfaces compared to standard surfaces are required, evaluating both clinical outcomes and cost-effectiveness.

Decontamination of equipment

The effects of the different equipment options for decontamination are uncertain, such as new materials for applying liquid disinfectants to surfaces (microfiber or ultramicrofiber cloths). An important aspect that needs to be clarified is the role of the wiping effect, that is, the physical removal of soil. In this line, the effects of different wipes in the decontamination of high-touch environmental surfaces need further research. Following, we detail some of the comparisons that may be addressed.

1. Evaluation of different forms of using the same wipe, such as the use of one wipe, for one site, and in one direction versus other options
2. Microfiber mops or cloths versus standard ones for routine decontamination
3. Ultramicrofiber mops or cloths versus standard ones for routine decontamination
4. Peracetic acid wipes versus standard wipes for routine decontamination

5. Hydrogen peroxide wipes versus standard wipes for routine decontamination
6. Electrolysed water versus standard mops or cloths for routine decontamination

Frequency and time of decontamination

Controlled comparisons of increased versus standard frequency for routine and terminal decontamination remain unknown, with important implications for resource allocation. An example is evaluating detergent use once versus twice a day for hand-touch sites in the patient zone.

The effects of increasing or reducing the time dedicated to routine or terminal decontamination are still unknown, which is particularly relevant in resource-limited settings.

5.8.2.2. Development of a core outcome set and a core measurement set for decontamination trials

There is an urgent need to develop a core outcome set for decontamination trials that prioritises clinically meaningful, patient-centred outcomes—such as HAIs and adverse effects—rather than surrogate measures like microbial surface burden^{113, 323}.

A core measurement set for HAIs and colonisation outcomes is needed, as infection outcomes often rely on subjective judgment, even when standardised criteria are applied^{323, 335}. Establishing universally accepted microbiological standards for environmental surface cleanliness is also needed to provide a consistent benchmark for evaluating interventions and modeling clinical infection risk^{472, 473}.

Future research should rigorously assess safety and antimicrobial resistance outcomes potentially associated to decontamination. Although ecotoxicological effects and user satisfaction were beyond the scope of this review, they remain critical for the development of sustainable and acceptable interventions³⁷⁹.

5.8.2.3. Reporting guidelines for decontamination trials

There is a need to adapt existing reporting guidelines to better suit decontamination intervention trials, which present distinct methodological and contextual challenges.

First, the ORION statement—developed to enhance transparency in reporting outbreak investigations and intervention studies on nosocomial infections¹¹³—requires updating and broader implementation, as it was not followed in any of the trials included in our review.

Second, while the TIDieR checklist¹⁶⁵ is a valuable tool for reporting interventions, it lacks elements specific to decontamination practices. Its structure appears more suited to interventions such as psychotherapy or surgery, limiting its applicability in the infection control context.

Third, there is currently no established guidance for reporting fidelity in decontamination interventions. This gap may contribute to the inconsistent and often inadequate reporting of intervention compliance. For instance, there is no consensus on the threshold level of surface contamination that should be considered unacceptable, which may reflect adherence. This makes interpretation and comparison across studies difficult.

5.8.2.4. *Overcoming implementation barriers of RCTs in the hospital setting*

Need of pragmatic trials adapted to the local context

Initiating hospital-based decontamination RCTs presents challenges. Staff may resist changes to established routines, blinding may not be feasible, and ward-level randomisation often involves considerable logistical complexity. Strengthening the evidence base will require pragmatic trial designs that align with hospital workflows to minimise disruption to clinical care, patient rest, visiting hours, and routine healthcare activities ^{474, 475}.

Need for funding mechanisms to support decontamination research

There is a critical need for funding mechanisms that support research on decontamination interventions often overlooked by industry, such as basic detergents. Public research funding should extend beyond novel technologies to include basic cleaning practices, particularly in the context of infection prevention.

Collaborative efforts between organisations are essential to conduct RCTs in low-resource settings. Publicly funded studies in these environments, especially in non-Western regions, should be prioritised to generate contextually relevant evidence—including the effectiveness of cleaning without disinfectants—across diverse healthcare and community settings.

5.8.3. *Implications for research from study II: SR on gloves, gowns and masks*

This review is an 'empty review', meaning no studies met the eligibility criteria for inclusion. This underscores the need for well-designed studies to evaluate the effectiveness of gloves, gowns, and/or masks when caring for hospitalised patients with MRSA or when in contact with their immediate environment.

The most robust method to determine if the use of gloves, gowns or masks prevents the transmission of MRSA in hospitals is the randomised controlled design. Researchers should put more effort into conducting cluster-RCTs because they have a number of advantages compared to patient-randomised trials as listed below^{127, 330}. See recommendations for implementing such study designs in section 4.6. Results of study VI: Design recommendations for RCTs.

In settings with high hand hygiene compliance and strong horizontal infection prevention measures, such as universal MRSA decolonisation, discontinuing routine contact precautions for MRSA may not result in an increased incidence of HAIs. However, the impact of de-implementing contact precautions for MRSA warrants careful evaluation.

Given the importance of understanding both the benefits and potential harms, we recommend conducting a separate SR focused specifically on the unintended effects of using gloves, gowns, and masks. Such an effort would contribute to a more balanced and comprehensive evidence base to guide policy and practice. For instance, it is important to determine whether the use of these protective measures is associated with behavioural changes among healthcare workers that may compromise the quality of care—such as spending less time in the rooms of patients under contact precautions. This reduced interaction may lead to adverse outcomes, including falls, delayed medication and less frequent physical assessments.

5.8.4. Implications for research from study III: Sex/gender consideration in Cochrane reviews

Primary studies of interventions to prevent HAIs should systematically incorporate SGBA in their research questions, data collection, analyses, interpretation, and reporting. Adopting this approach will enhance the ability of SRs and meta-analyses to meaningfully consider sex and gender, thereby improving the relevance and equity of evidence synthesis.

The SGAT-SR-2¹¹⁰ may serve as a valuable resource for incorporating sex and gender considerations in SRs. However, further evaluation is needed to determine whether the tool requires additional refinement.

5.8.5. Implications for research from study IV: NRSIs consideration in Cochrane reviews

Future research should focus on developing infrastructure that enables the timely and reliable integration of diverse evidence types in SRs, particularly in the context of pandemics or outbreak scenarios.

Priorities include evaluating AI-assisted tools for the identification and classification of both randomised and non-randomised studies.

In parallel, empirical methodological studies are needed to assess the impact of including NRSIs in infection control SRs, specifically their influence on synthesis decisions, effect estimates, and certainty-of-evidence judgments.

6. Conclusions

Taken together, this thesis demonstrates the need to address persistent methodological challenges in both RCTs and SRs of non-pharmacological hospital infection control interventions. The two SRs conducted as part of this PhD — on environmental surface decontamination and the use of gloves, gowns, and masks — alongside the analysis of Cochrane reviews of interventions to prevent HAIs, reveal a recurrent pattern: limited and inconclusive RCT evidence, insufficient integration of sex and gender in Cochrane reviews and their frequent but suboptimal use of non-randomised studies. In addition, this thesis identifies specific methodological challenges inherent to SRs of infection control interventions and offers targeted recommendations to improve the design and conduct of RCTs in this field.

By identifying these evidence and methodological gaps, this thesis outlines a roadmap toward a more rigorous and inclusive research agenda. Advancing the evidence base for non-pharmacological interventions to prevent HAIs requires more than additional trials. To move from common sense practices to a robust evidence base, the infection control community must prioritise adequately powered, non-conventional RCTs—including cluster-crossover and stepped-wedge RCTs, and those conducted in low-resource settings—adopt core outcome sets that incorporate patient-centred measures, integrate gender-inclusive perspectives, and develop an evidence synthesis framework open to rigorously integrating randomised and non-randomised studies. Ultimately, future review authors and trialists must be equipped to navigate and address the methodological complexities inherent in this field.

The following conclusions drawn from the six studies comprising this PhD collectively chart a path from current evidence gaps toward a more scientifically rigorous and equitable approach to infection control.

RCT evidence on the impact of hospital surface decontamination on patient outcomes remains limited and inconclusive. However, this should not be interpreted as evidence of no effect. Given the substantial burden of HAIs, there is an urgent need for powered, non-industry-funded, multicentre RCTs evaluating cleaning and disinfection interventions—particularly in low-resource settings—to detect meaningful differences in patient-relevant outcomes, including adverse events. The development of reporting guidelines and a core outcome set for RCTs of decontamination interventions would further enhance the clinical relevance of future trials.

No studies were found assessing the impact of wearing gloves, gowns or masks for contact with MRSA hospitalised patients or with their immediate environment on MRSA transmission. Therefore, the evidence remains inconclusive. This absence of evidence should not be interpreted as the evidence of no effect; it means that research that would have been eligible for inclusion in this review has not been conducted.

Consideration of sex and gender in Cochrane reviews of interventions for preventing HAIs is practically absent. This omission limits the applicability of review findings to diverse populations, including women, men, boys, girls, and individuals of diverse gender identities.

Cochrane reviews of interventions to prevent HAIs show considerable room for improvement in their consideration of NRSIs. Although NRSIs are frequently eligible for inclusion, this decision is rarely justified, and the included studies are often poorly described, with limited adherence to *Cochrane Handbook* guidance.

SRs of infection control interventions face distinct methodological challenges, including inconsistencies in study design classification, the absence of tailored risk of bias assessment tools for cluster-crossover and stepped-wedge trials, and limitations in evaluating complex interventions and their integrity.

Future RCTs of infection control interventions should prioritise patient-centred outcomes rather than surrogate measures, adopt a core outcome set informed by standardised infection definitions, and use statistical models that appropriately address data clustering and dependency inherent to communicable diseases.

7. Abbreviations, acronyms and glossary

Abel E González-Vélez	AEG-V
Abelardo Fernández Chávez	AFC
Absolute risk difference	ARD
Adverse effect: Adverse event that occurs during/after an intervention for which the causal relationship between intervention and event is at least a reasonable possibility ³²⁴ .	
Adverse event: Adverse outcome that occurs during/after a drug or other intervention but is not necessarily caused by it ³²⁴ .	
Agency for Healthcare Research and Quality	AHRQ
Airborne precautions: One of the three categories of transmission-based precautions intended to prevent transmission of infectious agents that remain infectious over long distances when suspended in the air (e.g., varicella virus or tuberculosis). Healthcare personnel caring for patients on airborne precautions wear a mask or respirator, depending on the disease-specific recommendations, that is donned prior to room entry ⁷² .	
Ambulatory care facility: Facility which administers health services to individuals who don't require hospitalisation or institutionalisation ¹⁵⁶ .	
Antimicrobial surfaces: Surfaces with components that may protect against bacterial contamination (also known as self-disinfecting surfaces) ⁴¹ .	
As treated analysis: Analysis strategy in which participants are analysed according to the intervention they actually received, even if their randomised allocation was to a different treatment group ²⁰⁶ .	
Available-case analysis: Analysis strategy that excludes participants with missing outcome data. This analysis includes data on only those whose results are known, using as a denominator the total number of people who had data recorded for the particular outcome ²⁰³ . ACA is sometimes called complete case analysis (CCA) or modified intention-to-treat (mITT) analysis.	ACA
Bloodstream infection: Presence of live pathogens in the blood, causing an infection ¹⁶⁰ .	BSI
Bundle: A collection of processes needed to effectively and safely care for patients undergoing particular treatments. Several interventions are bundled together and, when	

combined, significantly improve patient care outcomes⁴⁷⁶.

Carry-over effect: In a cross-over trial, is when the effect of an intervention given in one period persists into a subsequent period, interfering with the effect of the next intervention and biasing the overall effect estimate toward the null¹⁹⁴.

Centers for Disease Control and Prevention

CDC

Cleaning: Removal, usually with detergent and water or enzyme cleaner and water, of adherent visible soil, blood, protein substances, microorganisms and other debris from the surfaces, crevices, serrations, joints, and lumens of instruments, devices, and equipment by a manual or mechanical process that prepares the items for safe handling, further decontamination or both³⁹.

Cluster stepped-wedge RCT

SW-cl-RCT

Cochrane Central Register of Controlled Trials

CENTRAL

Colonisation: Presence of microorganisms (on skin, mucous membranes, in open wounds, or in excretions or secretions) not causing adverse clinical signs or symptoms¹⁶⁰.

Complete case analysis: See ACA above.

CCA

Controlled before-after study: non-randomised study in which the investigators don't decide about allocation to the different comparison groups. Outcomes of interest are measured in both intervention and control groups before and after the intervention is introduced. These studies have a high risk of bias because there may be unidentified differences between the intervention and control groups that may affect changes in the outcome measure¹⁵⁵.

CBA

Controlled clinical trial: Non-randomised study in which the investigator allocates prospectively each participant to an intervention or to a control arm (or more) using methods that are not random. In the quasi-RCTs the allocation methods are also not random, but were intended to produce similar groups when used to allocate participants (see below). The EPOC guidance¹⁵⁵ suggests using the term non-randomised controlled trial (NRCT), instead of CCT or Q-RCT, which are used to mean different things by different authors. Thus, CCTs and Q-RCTs are covered by the label NRCT.

CCT

Controlled cohort before-and-after study: Non-randomised study with

CChBA

allocation to the study arms at the cluster level. The clusters allocated to the intervention group receive an intervention and those in the control group do not. The effect of the intervention is tested by assessment of outcomes within the same group over time both before and after the intervention is introduced, and then, by comparing the control and intervention groups. "Cluster" refers to an entity (an organisation), not necessarily to a group of participants, and 'group' refers to one or more clusters¹⁶⁹. "Cohort" refers to the new sample of individuals drawn from each cluster at each measurement occasion²⁴⁵.

Cluster cross-over randomised clinical trial: Trial in which each cluster is allocated to one sequence for receiving both the experimental and the control interventions. There are two or more sequential interventions in a random order usually separated by a wash-out period⁴⁷⁷.

CRXO-RCT

Cluster randomised controlled trial: RCT in which the investigator allocates prospectively groups of participants (or clusters) to an intervention or to a control arm (or more than one control arm).

CI-RCT

Cochrane Database of Systematic Reviews

CDSR

Conference Proceedings Citation Index - Science

CPCI-S

Confidence interval: Measure of uncertainty around the finding of a statistical analysis. CI represents the range in which a point estimate would fall if multiple experiments were conducted, or the range of values either side of the estimate between which we can be 95% sure that the true value lies^{210, 478}.

CI

Contact precautions: One of the three categories of transmission-based precautions intended to prevent transmission of infectious agents which are spread by direct or indirect contact with the patient or the patient's environment. Healthcare personnel caring for patients on contact precautions wear a gown and gloves for all interactions that may involve contact with the patient or potentially contaminated areas in the patient's environment⁷².

Contamination (in a controlled trial): Application of one of the interventions in participants intended to receive the other¹⁷². Cluster allocation usually reduces the likelihood of contamination.

Critical items: Objects that enter sterile tissue or the vascular system, such as surgical instruments, cardiac and urinary catheters, implants, and ultrasound probes used in

sterile body cavities³⁹.

Cross-over

XO

Cross-over RCT allocated at the individual level

iXO-RCT

Cross-sectional cluster cross-over RCT: CRXO-RCTs with cluster-periods containing a repeated cross-section of different individuals.

Cross-sectional stepped-wedge cluster RCT: SW-cl-RCTs with cluster-periods containing a repeated cross-section of different individuals.

Disability-adjusted life-years

DALYs

Decontamination: Process that removes or destroys contamination so that infectious agents or other contaminants cannot reach a susceptible site in sufficient quantities to initiate infection or any other harmful response. Decontamination removes soil and pathogenic microorganisms from objects to be safe to handle or subject to further processing, use or disposal. The levels of decontamination are either cleaning, cleaning followed by disinfection, or cleaning followed by sterilisation. Cleaning should always precede disinfection and sterilisation^{39, 40}.

Disinfection: Thermal or chemical destruction of pathogenic and other types of microorganisms. Disinfection refers to the elimination of many or most microorganism, and is less lethal than sterilisation because it destroys most recognised pathogenic microorganisms but not necessarily all microbial forms (*e.g.*, bacterial spores)⁴⁰.

Droplets: Solid or liquid particles suspended in the air, whose motion is governed principally by gravity and whose particle size is greater than 10 µm. Droplets are generated primarily as the result of an infected source coughing, sneezing or talking⁴⁷⁹.

Droplet precautions: One of the three categories of transmission-based precautions intended to prevent pathogens spread through close respiratory or mucous membrane contact with respiratory secretions. Healthcare personnel wear a mask (a respirator is not necessary) for close contact with infectious patient; the mask is generally donned upon room entry³⁹.

Elena Jiménez Tejero

EJT

Elena Stallings

ES

Environmental decontamination (also known as environmental cleaning or environmental hygiene): Process that removes hazardous substances, including chemicals or microorganisms, from the hospital environment³⁹.

European Centre for Disease Prevention and Control

ECDC

Experimental study: Study in which an intervention is deliberately introduced by the researcher to observe its effects²⁴⁵.

U.S Food & Drug Administration

FDA

Gender: Socially constructed roles, behaviours and identities of female, male and gender diverse people⁴⁸⁰. It influences how people perceive themselves and each other, how they behave and interact and the distribution of power and resources in society. Gender is usually incorrectly conceptualised as a binary factor (female/male). However, In reality, there is a spectrum of gender identities and expressions defining how individuals identify themselves and express their gender. Definition taken from SAGER guidelines⁴⁸¹.

Gender-based analysis: Analytical tool that systematically integrates a gender perspective into the development of policies, programmes and legislation, as well as planning and decision-making processes. It helps to identify and clarify the differences between women and men and boys and girls and demonstrates how these differences affect health status, access to, and interaction with, the health care system ^{481, 482}.

Grading of Recommendations Assessment, Development and

Evaluation: a common, sensible and transparent approach to grading **GRADE** quality (or certainty) of evidence and strength of recommendations¹⁵¹.

Gemma Villanueva

GV

Gowns: Protective garments made of impervious materials, worn to shield the wearer's clothing from microorganisms and exposure to blood, body fluids, secretions, and excretions⁷⁵. Gowns should be used once per patient and either discarded or laundered as appropriate⁷³.

Health equity: Absence of avoidable and unfair differences in health. The term "inequity" is used when an inequality is deemed unjust. Thus, inequity is the presence of avoidable and unfair health inequalities (differences) across socioeconomic, demographic and geographic factors⁴⁸³.

Health inequality: Measurable differences in health status or the distribution of health determinants between different population groups. It is an objective, descriptive term referring to any observed difference between groups. Not all inequalities are considered "inequities". For example, a difference in health outcomes based solely on biological age (like higher rates of Alzheimer's in the elderly) is an inequality, but not necessarily an inequity because it is not always avoidable or considered "unfair" in a social justice

context⁴⁸³.

Healthcare-associated infection (formerly known as nosocomial infection): Infection acquired as a result of the delivery of healthcare, and therefore, not present or incubating at the time of admission to the healthcare facility. For most bacterial infections, this means that the infection usually becomes evident 48 hours (the typical incubation period) or more after admission. Because the incubation period varies with the type of pathogen and to some extent with the patient's underlying condition, each infection must be assessed individually¹.

Hospital: Institution with an organised medical staff which provides medical care to patients¹⁵⁶

Hospital-acquired colonisation: Colonisation is the presence of microorganisms (on skin, mucous membranes, in open wounds, or in excretions or secretions) that are not causing adverse clinical signs or symptoms. Hospital-acquired colonisation is a colonisation that was not present at the time of admission to the hospital¹.

Hospital-acquired infection: Infection acquired in the hospital as a result of the delivery of healthcare (not present or incubating at the time of admission to the healthcare facility)¹. **HAI**

Hospital environmental surfaces: Hospital surfaces that generally don't come into direct contact with patients during care. Can be further divided into 'medical equipment surfaces', such as knobs or handles on haemodialysis machines, x-ray machines, instrument carts, or dental units, and 'housekeeping surfaces', such as floors, walls, bed rails, tabletops or computer keyboards³⁹.

Hospital outpatient: Patient admitted to the hospital setting for the purpose of observation, care, diagnosis or treatment without receiving board and room, such as patients attending haemodialysis sessions¹⁵⁶.

Hospital outpatient clinic: Organised services in a hospital which provide medical care on an outpatient basis, that is, without providing board and room¹⁵⁶.

Housekeeping surfaces: Environmental surfaces (e.g., floors, walls, ceilings, and tabletops) that are not involved in direct delivery of patient care in healthcare facilities³⁹.

Hartung-Knapp-Sidik-Jonkman **HKSJ**

Hydrogen peroxide **HP**

Hydrogen peroxide vapour **HPV**

Identification bias (also known as recruitment bias): Bias that can occur when

participants (those on whom we seek to collect outcome data) are identified and/or recruited to the trial after the clusters have been randomised. It happens because the knowledge of whether each cluster is an 'intervention' or 'control' cluster could affect the types of participants recruited or identified¹⁷².

Improved hydrogen peroxide	IHP
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Incidence: Number of new occurrences of events (e.g., infections) in a population over a time period. HAls incidence is often presented as number of HAls per 100 patients.

Incidence rate ratio	IRR
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Individual randomised controlled trial: RCT in which the investigator allocates prospectively individual participants to an intervention or to a control arm (or more than one control arm).

i-RCT

Infection: Local or systemic condition that results from an adverse reaction to the presence of an infectious agent or its toxins¹.

Inpatient: Person admitted to health facilities which provide board and room for the purpose of observation, care, diagnosis or treatment¹⁵⁶.

Intensive care unit	ICU
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In-situ decontamination study: Study conducted in a healthcare environment with the sole objective of assessing the antimicrobial activity on a surface.

Intention-to-treat analysis: Analysis strategy that meets the following principles^{171, 203 206, 207}: a) To analyse participants in the intervention groups to which they were randomised, regardless of the intervention they received, whether the interventions were implemented as intended, and the adherence to the intervention; b) To include all randomised participants in the analysis; and c) To measure outcome data on all participants. This means that all randomised participants need to be included in the analysis, and analysed in the arm to which they were allocated. The advantages of ITT analysis are that it allows determining the effect of the assignment to the intervention, and that ensures that the benefits of randomisation (similar groups concerning measured and unmeasured prognostic factors) are maintained¹⁷¹.

ITT

International Clinical Trials Registry Platform	ICTRP
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Interrupted time series design: Study that uses observations at multiple time points before and after an intervention (the 'interruption'). The design

ITS

attempts to detect whether the intervention has had an effect significantly greater than any underlying trend over time¹⁵⁵.

Intraclass correlation co-efficient: Proportion of the total variance of the outcome that can be explained by the variation between clusters¹⁶⁴. **ICC**

In-vitro decontamination study: Study assessing in vitro antimicrobial activity of the decontamination agent, that is, studies that are performed outside their biological context.

Isolation gowns: Non-sterile gowns designed primarily to prevent microbial transfer and exposure to small volumes of body fluids⁷⁵.

Iván Sola **IS**

Jesús López-Alcalde **J-LA**

Laminar airflow: Ventilation systems designed to move air in a single pass, usually through a bank of high-efficiency particulate air (HEPA) filters either along a wall or in the ceiling, in a one-way direction through a clean zone with parallel streamlines³⁹.

Length of hospital stay: Days spent by a patient in a ward or hospital. **LOS**

Low and middle-income country **LMIC**

Lucieni Oliveira-Conterno **LOC**

Manual decontamination: Manual application of the decontamination agent to the surface.

Marta Mateos Mazón **MM-M**

Masks: Items worn over the nose and mouth to reduce the risk of inhaling or transmitting infectious agents. Several types of masks exist (procedure masks and particulate respirators⁷⁵).

Mean difference **MD**

Methodological Expectations of Cochrane Intervention Reviews **MECIR**

Medical equipment surfaces: Examples are knobs or handles on haemodialysis machines, x-ray machines, instrument carts, dental units, monitor manual screen, controls and cables, ventilator control panel, oxygen flow meter and suction regulator, intravenous pump control and pole, and supply carts⁶⁵.

Medical gloves: Disposable medical devices made from natural rubber latex or synthetic materials, designed to be worn on the hands as a barrier against potentially infectious materials and other contaminants. Medical gloves are used during tasks

involving contact with patients or bodily fluids and are intended for single use only. Medical gloves include patient examination gloves, surgical gloves, and gloves specifically designed for handling chemotherapy agents⁷⁵.

Methicillin-resistant <i>Staphylococcus aureus</i>	MRSA
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Missing participant data: Outcome data of a participant in a trial that is not available for the review authors and therefore cannot be analysed for a specific effect estimate in the review ^{173, 174} . MPD is specific to the outcome.	MPD
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Modified intention-to-treat analysis: expression used in different ways ²⁰⁹ . It may refer to an analysis that excludes participants who did not receive a specified minimum amount of the intended intervention. Our use of the term refers to missing data rather than to adherence (see ACA above).	mITT
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Multidrug-resistant organism	MDRO
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Naïve PP analysis: Analysis strategy that is restricted to individuals who adhered to their assigned interventions ²⁰⁶ .	
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Non-critical items: Medical or surgical instruments or devices that come in contact with intact skin but not with mucous membranes. The risk of infection from these devices is low. Examples are blood pressure cuffs, stethoscopes, tourniquets, ophthalmoscopes, reflex hammers, pulse oximeter, thermometer, glucometer, venipuncture tourniquets, or probes used for ultrasonography ⁴⁰ .	
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Non-randomised controlled trial: Experimental study in which people are allocated to different interventions using methods that are not random ¹⁵⁵ . This covers quasi-randomised methods or methods that are clearly not random, e.g., allocation by clinician's judgement or by patient's preference.	NRCT
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Non-randomised study of intervention	NRSI
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Nosocomial: Likely to have been acquired during the hospital stay, without any evidence that was incubating or present on admission ⁴ .	
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No-touch decontamination ('automated decontamination'): Stand-alone machine applies the chemical agents, instead of the manual application.	
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Observational study: Study in which the investigators do not seek to intervene, and simply observe the course of events. Differences in one characteristic (e.g. whether or not people received the intervention of interest) are studied in relation to changes or differences in other characteristic(s) (e.g. whether or not they died), without action by the investigator. There is a greater risk of selection bias than in experimental studies ²⁴⁵ .	
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Odds ratio	OR
Outbreak report: Description of outbreaks and the subsequent interventions adopted for its control ¹¹³ .	
Particulate respirators (such as the N95 respirator): Personal protective devices used by healthcare personnel to protect against airborne pathogens $\leq 5 \mu\text{m}$ in size. These include droplet nuclei from infectious patients (e.g., <i>Mycobacterium tuberculosis</i>) and airborne particles containing fungal spores (e.g., <i>Aspergillus</i> spp.). The N95 disposable particulate respirator is the most commonly used type in healthcare settings ⁵ .	
Personal protective equipment	PPE
Peracetic acid	PA
Performance decontamination study: Study aiming to establish documented evidence that a decontamination process removes or inactivates pathogens from inanimate objects.	
Per-protocol analysis: Analysis that excludes participants that didn't receive the intended intervention in accordance with the protocol ¹⁷¹ .	PP analysis
Procedure masks: Masks intended for use in general patient care ⁷⁵ .	
Quaternary ammonium compounds ("quats")	QACs
Quasi-randomised controlled trial: Non-randomised study in which the investigator allocates prospectively each participant to an intervention or to a control arm (or more) using methods of allocating people to a trial that are not random, but were intended to produce similar groups when used to allocate participants. Examples of quasi-random methods include allocation by the person's date of birth or by the day of the week ¹⁴¹ .	Q-RCT
Randomised controlled trial: Experimental study in which people are allocated prospectively to a study arm using a process of random allocation (e.g., random number generation or coin flips) which theoretically ensures that intervention/control groups differ only in the exposure to the treatment.	RCT
Rate: Number of new occurrences of events (for example, infections or colonisations) occurring per unit of time. Rate of MRSA infection or colonisation usually is presented as number of MRSA infections or colonisations per 1000 patients-days of hospital stay.	
Recruitment bias: see identification bias.	
Restricted maximum likelihood	REML

Rehabilitation centre: Facility which provides programs for rehabilitating the mentally or physically disabled individuals¹⁵⁶.

Relative risk	RR
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Residential facility: Long-term care facility which provide supervision and assistance in activities of daily living with medical and nursing services when required. Residential facilities include assisted living facilities, group homes, halfway houses homes for the aged, nursing homes or orphanages¹⁵⁶.

Routine practices (also known as standard precautions): Measures that have been developed for use in the routine care of all patients at all times in all healthcare settings.

Seasonality (also known as seasonal bias): The seasonal (period in the year) effects may provide alternative explanations for an observed effect of an infection control intervention. For example, there may be more imported MRSA cases in winter as more elderly patients are admitted, so the higher MRSA transmitted cases might be due to the season period and not to the intervention ^{74, 113}.

Semi-critical items: Medical or surgical instruments or devices that come in contact with contact mucous membranes or non-intact skin, such as endoscopes⁴⁰.

Sex: A set of biological attributes in humans and animals that are associated with physical and physiological features including chromosomes, gene expression, hormone function and reproductive/sexual anatomy⁴⁸⁰. Sex is usually categorised as female or male, although there is variation in the biological attributes that constitute sex and how those attributes are expressed. Definition taken from SAGER guidelines⁴⁸¹.

Sex/Gender: A “domain of complex phenomena that are simultaneously biological and social [...]” ⁴⁸⁴. This term has been used “to highlight this socio-biological intertwinement [...]”⁴⁸⁵ or “to acknowledge the interrelationships among [...]” sex and gender⁴⁸⁶.

Sex/Gender based analysis: Analytical approach that integrates a sex and gender perspective into the development of health research, policies and programmes, as well as health planning and decision-making processes. It helps to identify and clarify the differences between women and men and boys and girls, and demonstrates how these differences affect health status, access to, and interaction with, the health care system^{102, 481}.

SGBA

Sex-disaggregated data: Data collected and presented separately on males and females^{481, 487}.

Sex and Gender Appraisal Tool for Systematic Reviews	SGAT-SR
Sheila Cabir Nunes	SCN
Stephanie Dancer	SD
Stepped-wedge RCT allocated at the individual level	iSW-RCT
Society for Healthcare Epidemiology of America	SHEA
Standard deviation	sd
Stepped-wedge design: Study design where the intervention is rolled-out sequentially to the trial participants (either individuals or clusters) over a number of periods. All sequences start with the control intervention in the first period, and the order in which the different allocation units receive the intervention is determined at random. By the end of the allocation, all units will have received the intervention. These designs incorporate data collection at each point where a new group (step) receives the intervention¹³³.	
Sterilisation: Validated process used to render a product free of all forms of viable microorganisms. The microorganisms presence can be expressed in terms of probability. Although this probability can be reduced to a very low number, it can never be zero⁴⁰.	
Surgical gowns: Gowns made from fluid-resistant materials to minimise the transfer of body fluids during surgery. They can be disposable or reusable⁷⁵.	
Surgical masks: Masks worn in operating theatres to protect both the patient and surgical staff from microbial and fluid exposure⁷⁵.	
Study Within A Review	SWAR
Systematic review	SR
Terminal (or 'deep') cleaning: Cleaning of a room between occupying patients.³⁹	
Ultraviolet C light	UV-C
Ultraviolet light	UV
Vancomycin-resistant <i>Enterococci</i>	VRE
Web of Science	WoS
Within-cluster between-period correlation: Measure of the similarity of outcome data within each cluster across different cluster-periods^{153, 359, 360}.	
Within-cluster within-period correlation: Measure of the similarity of the outcome data within the same cluster-period ¹⁵³ .	WPC
95% confidence interval	95% CI

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9. Annexes

Annex 1. Publications of the PhD studies

Annex 1.1. Study I: Manuscript submission and acceptance

Manuscript accepted in *Infection Prevention in Practice*. Number: IPIP-D-25-00265. Submission date: 10th December 2025. Title: Decontamination of environmental surfaces in hospitals to reduce hospital acquired infections: systematic review.

Infection Prevention in Practice: Impact factor (2024): 1.9. Rank (2024): third quartile (Q3); 231/421 Public, Environmental and Occupational health.

1/30/26, 10:22 AM

Your submission IPIP-D-25-00265R1 has been accepted - [EMID:248a5b8f8c373c76] - Cochrane Madrid - Outlook

 Outlook

Your submission IPIP-D-25-00265R1 has been accepted - [EMID:248a5b8f8c373c76]

From em.ipip.0.990e8b.6fb96c15@editorialmanager.com <em.ipip.0.990e8b.6fb96c15@editorialmanager.com>
on behalf of
Infection Prevention in Practice <em@editorialmanager.com>

Date Tue 27/01/2026 10:21

To Cochrane Madrid <cochrane.madrid@ufv.es>

ATENCIÓN: Este mensaje proviene de una fuente EXTERNA a UFV. Por favor, sea cuidadoso especialmente con los enlaces y los archivos adjuntos que contenga.

Ref.: Ms. No. IPIP-D-25-00265R1
Decontamination of environmental surfaces in hospitals to reduce hospital acquired infections:
systematic review
Infection Prevention in Practice

Dear Dr Lopez-Alcalde,

I am pleased to tell you that your work has been accepted for publication in Infection Prevention in Practice.

Annex 1.2. Study II: Systematic review publication

López-Alcalde J, et al. Gloves, gowns and masks for reducing the transmission of meticillin-resistant *Staphylococcus aureus* (MRSA) in the hospital setting. *Cochrane Database of Systematic Reviews* 2015, Issue 7. Art. No.: CD007087. DOI: 10.1002/14651858.CD007087.pub2.

Cochrane Database of Systematic Reviews: Impact factor (2015): 6.103. Rank (2010): first quartile (Q1); 12/155 *Medicine, General & Internal*.



**Cochrane
Library**

Cochrane Database of Systematic Reviews

Gloves, gowns and masks for reducing the transmission of meticillin-resistant *Staphylococcus aureus* (MRSA) in the hospital setting (Review)

López-Alcalde J, Mateos-Mazón M, Guevara M, Conterno LO, Solà I, Cabir Nunes S, Bonfill Cosp X

López-Alcalde J, Mateos-Mazón M, Guevara M, Conterno LO, Solà I, Cabir Nunes S, Bonfill Cosp X.
Gloves, gowns and masks for reducing the transmission of meticillin-resistant *Staphylococcus aureus* (MRSA) in the hospital
setting.
Cochrane Database of Systematic Reviews 2015, Issue 7. Art. No.: CD007087.
DOI: 10.1002/14651858.CD007087.pub2.

www.cochranelibrary.com

Gloves, gowns and masks for reducing the transmission of meticillin-resistant *Staphylococcus aureus* (MRSA) in
the hospital setting (Review)

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Annex 1.3. Study III: Methodology study publication

López-Alcalde J, et al. Consideration of sex and gender in Cochrane reviews of interventions for preventing healthcare-associated infections: a methodology study. *BMC Health Serv Res*. 2019 Mar 15;19(1):169. doi: 10.1186/s12913-019-4001-9.

BMC HEALTH SERVICES RESEARCH: Impact factor (2019): 1.987. Rank: second quartile (Q2); 57/102 Health care sciences & Services.

López-Alcalde et al. *BMC Health Services Research* (2019) 19:169
<https://doi.org/10.1186/s12913-019-4001-9>

BMC Health Services Research

RESEARCH ARTICLEOpen Access



Consideration of sex and gender in Cochrane reviews of interventions for preventing healthcare-associated infections: a methodology study

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Abstract

Background: Healthcare-associated infections (HAIs) are common and increase morbidity, mortality, and healthcare costs. Their control continues to be an unresolved issue worldwide. HAIs epidemiology shows sex/gender differences. Thus the lack of consideration of sex/gender in Cochrane reviews will limit their applicability and capacity to support informed decisions. This study aims to describe the extent to which Cochrane reviews of interventions for preventing HAIs consider sex and gender.

Methods: Methodology study appraising Cochrane reviews of interventions to prevent HAIs. Search methods: *Cochrane Database of Systematic Reviews* from 1995 (launch of the journal) to 31 December 2016. Two authors independently extracted data with *EPPI-Reviewer 4* software, and independently appraised the sex/gender content of the reviews with the *Sex and Gender Appraisal Tool for Systematic Reviews (SGAT-SR)*.

Results: This study included 113 reviews assessing the effects of interventions for preventing HAIs. 100 reviews (88%) used at least one sex or gender-related term. The terminology used was heterogeneous, being "sex" the term used in more reviews (51%). No review defined neither sex nor gender. Thus we could not assess the definitions provided. Consideration of sex and gender was practically absent in the included reviews; in fact, no review met all the applicable items of the SGAT-SR, and 51 reviews (50%) fulfilled no item. No review provided a complete description of the sex and the gender of the samples of the included studies. Only ten reviews (10%) planned to perform sex- and gender-based analysis and only three (3%) could complete the analysis. The method chosen was always the subgroup analysis based on sex (one review) or gender (two reviews). Three reviews (3%) considered sex or gender-related findings in the conclusions.

Conclusion: Consideration of sex and gender in Cochrane reviews of interventions for preventing HAIs was practically absent. This lack of attention to sex and gender reduces the quality of Cochrane reviews, and their applicability for all people: women and men, boys and girls, and people of diverse gender identities. Cochrane should attempt to address the shortfalls detected.

Keywords: Systematic reviews, Data extraction, Sex, Gender, Sex/gender, Equity, Cochrane, Gender bias, Healthcare-associated infection

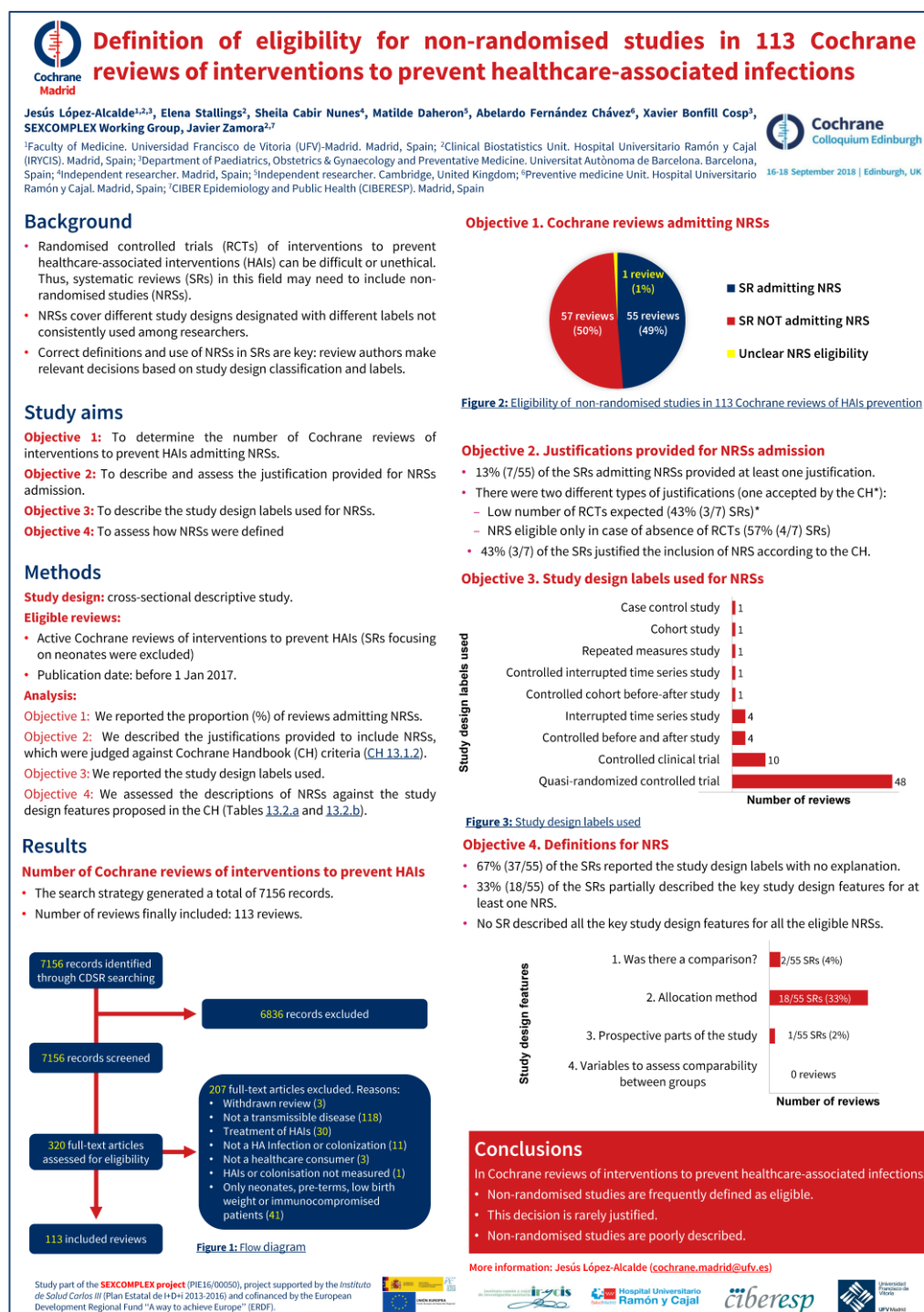
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Annex 1.4. Study IV: Poster presentation

López-Alcalde J, et al. Definition of eligibility for non-randomised studies in 113 Cochrane Reviews of interventions to prevent healthcare-associated infections (Poster 151). In: Abstracts of the 25th Cochrane Colloquium, Edinburgh, UK. **Cochrane Database of Systematic Reviews** 2018;(9 Suppl 1):160-161. <https://doi.org/10.1002/14651858.CD201801>.



Annex 2. Supplementary material for Study I

Annex 2.1. Differences between the protocol and the review

The review team judged that an updated protocol was not necessary because the changes were mainly methodological and reflect advances in review standards (*e.g.*, updated Cochrane Handbook, RoB 2, GRADE, MECIR). The clinical question remained the same. Below we describe the main changes between the protocol and the review.

Eligible study designs. The protocol initially allowed non-randomised studies (including quasi-RCTs, controlled before–after studies, controlled cohort before–after studies, and ITS), anticipating few RCTs. However, as the review ultimately included eleven RCTs, we excluded non-randomised designs because of their higher risk of bias. This decision was taken in agreement with the Cochrane Wounds Editorial Group.

Eligible interventions. Sterilisation had originally been listed as eligible, but we later excluded because it is not used to decontaminate hospital environmental surfaces.

Eligible outcomes. The protocol did not make explicit that we would exclude composite outcomes that combine colonisation and infection and HAIs caused by specific microorganisms.

Resistance outcomes. The protocol did not distinguish resistance to antibiotics from resistance to disinfectants, nor indicated that resistance data should come from human samples. Thus, we excluded studies based only on environmental sampling.

Search sources removed. We did not search sources that were no longer maintained or were already covered elsewhere (Cochrane EPOC register, DARE, OpenSIGLE, www.clinicalstudyresults.org, Current Controlled Trials, EU Clinical Trials Register, IFPMA Clinical Trials Portal). For dissertations, we searched ProQuest Dissertations & Theses Global instead of ProQuest Dissertations & Theses A&I. We did not handsearch journals as relevant journals had been handsearched for CENTRAL.

Additional sources not planned in the protocol. We searched the COVID-19 Study Register, EMBASE conference proceedings, WoS Core Collection, international infection prevention conference materials, Google, publisher websites, PubPeer for retractions/comments, bibliographies of guidelines, and contacted manufacturers.

Risk of bias. We used RoB 2 instead of the earlier Cochrane RoB tool.

Certainty of evidence. We assessed certainty using GRADE, which was not specified in the original protocol.

Annex 2.2. Search strategies

We combined the MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision). We combined the Embase search with the Embase filter developed by the UK Cochrane Centre. MEDLINE and Embase also had filters added for identifying Controlled Before and After studies (CBA) and Interrupted Time Series (ITS). We combined the CINAHL Plus searches with the trial filters developed by the Scottish Intercollegiate Guidelines Network. We applied no methodological filter in Web of Science.

a. Searching electronic databases

1. Ovid MEDLINE(R) ALL. Date searched: February 24, 2025

1exp Hospitals/
2exp Hospital Units/
3exp Outpatient Clinics, Hospital/
4exp Patients' Rooms/
5exp Equipment Contamination/
6exp Equipment/ and Supplies, Hospital/
7exp Health Facilities/
8exp *Nursing Homes/
97 not 8
10hospital*1.ti,ab.
11or/1-6,9-10
12exp "Floors and Floorcoverings"/
13surface*1.ti,ab.
14(furniture or furnishing*).ti,ab.
15hand touch site*.ti,ab.
1612 or 13 or 14 or 15
17and/11,16
18exp Housekeeping, Hospital/
19exp Disinfection/
20exp Infection Control/
21exp Disinfectants/
22exp Detergents/
23exp Decontamination/
24(housekeeping or house keeping or hygien* or sanitary engineering or sanitation or bundling or antiseptic* or asepsis or biocid* or germicid* or microbicid* or bactericid* or fungicid* or tuberculocid* or virucid* or sanitiz* or sanitis* or decontaminat*).ti,ab.

25(cleaning or domestic services or soap*1 or detergent* or surfactant* or surface active agent* or cleaner* or mop*1 or vacuum* or steam clean* or spray clean* or wet scrub* or mechanical scrub* or dry wip* or damp wash*).ti,ab.

26(disinfect* or inactivation or alcohol* or chlorine* or hypochlorite* or aldehyde* or formaldehyde or glutaraldehyde or peroxide* or peroxygen compound* or benzalkonium chloride or iodophor* or ortho-phthalaldehyde or peracetic acid or phenolic* or quaternary ammonium compound* or QUAT or orthobenzyl parachlorophenol or ortho-benzyl para-chlorophenol or active oxygen-based compound* or glycol derivative* or alkylamine*).ti,ab.

27or/18-26

28and/17,27

29randomized controlled trial.pt.

30controlled clinical trial.pt.

31randomi?ed.ab.

32placebo.ab.

33clinical trials as topic.sh.

34randomly.ab.

35trial.ti.

36non-randomized controlled trials as topic/

37interrupted time series analysis/

38controlled before-after studies/

39((before adj5 after) or (pre adj5 post) or ((pretest or pre test) and (posttest or post test)) or quasiexperiment* or quasi experiment* or pseudo experiment* or pseudoexperiment* or evaluat* or time series or time point? or repeated measur*).ti,ab. 4862887

40or/29-39

41exp animals/ not humans.sh.

4240 not 41

4328 and 42

2. EMBASE (ELSEVIER) Date searched: February 24, 2025

#1 'hospital'/exp

#2 'outpatient department'/exp

#3 'hospital equipment'/exp

#4 'health care facility'/exp

#5 'nursing home'/exp/mj

#6 #4 NOT #5

#7 hospital\$:ab,ti

#8 #1 OR #2 OR #3 OR #6 OR #7

#9 surface\$:ab,ti

#10 furniture OR furnishing\$:ab,ti

#11 "hand touch site\$":ab,ti

#12 #9 OR #10 OR #11
 #13 #8 AND #12
 #14 'hospital hygiene'/exp
 #15 'disinfection'/exp
 #16 'infection control'/exp
 #17 'disinfectant agent'/exp
 #18 'detergent'/exp
 #19 housekeeping:ab,ti OR 'house keeping':ab,ti OR hygien*:ab,ti OR 'sanitary engineering':ab,ti
 OR sanitation:ab,ti OR bundling:ab,ti OR antiseptic*:ab,ti OR asepsis:ab,ti OR biocid*:ab,ti OR
 germicid*:ab,ti OR microbicid*:ab,ti OR bactericid*:ab,ti OR fungicid*:ab,ti OR tuberculocid*:ab,ti
 OR virucid*:ab,ti OR sanitiz*:ab,ti OR sanitis*:ab,ti OR decontaminat*:ab,ti
 #20 disinfect*:ab OR inactivation:ab OR alcohol*:ab OR chlorine*:ab OR hypochlorite*:ab OR
 aldehyde*:ab OR formaldehyde:ab OR glutaraldehyde:ab OR peroxide*:ab OR 'peroxygen
 compound*':ab OR 'benzalkonium chloride':ab OR iodophor*:ab OR 'ortho phthalaldehyde':ab OR
 'peracetic acid':ab OR phenolic*:ab OR 'quaternary ammonium compound*':ab OR quat:ab OR
 'orthobenzyl parachlorophenol':ab OR 'ortho-benzyl para-chlorophenol':ab OR 'active oxygen-
 based compound*':ab OR 'glycol derivative*':ab OR alkylamine*:ab
 #21 #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20
 #22 'randomized controlled trial'/de
 #23 'controlled clinical trial'/de
 #24 'quasi experimental study'/de
 #25 ((double OR single OR doubly OR singly) NEXT/1 (blind OR blinded OR blindly)):ab,ti
 #26 random*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR 'cross over*':ab,ti OR placebo*:ab,ti
 OR assign*:ab,ti OR allocat*:ab,ti OR volunteer*:ab,ti
 #27 'pretest posttest control group design'/de
 #28 'time series analysis'/de
 #29 randomis*:ab,ti OR randomiz*:ab,ti OR randomly:ab,ti
 #30 ((before NEXT/5 after):ab,ti) OR ((pre NEXT/5 post):ab,ti) OR ((pretest:ab,ti OR 'pre
 test':ab,ti) AND (posttest:ab,ti OR 'post test':ab,ti)) OR quasiexperiment*:ab,ti OR 'quasi
 experiment*':ab,ti OR 'pseudo experiment*':ab,ti OR pseudoexperiment*:ab,ti OR evaluat*:ab,ti
 OR 'time series':ab,ti OR 'time point?':ab,ti OR 'repeated measur*':ab,ti
 #31 #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30
 #32 'animal'/exp
 #33 'invertebrate'/exp
 #34 'animal experiment'/exp
 #35 'animal model'/exp
 #36 'animal tissue'/exp
 #37 'animal cell'/exp
 #38 'nonhuman'/exp
 #39 #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38

#40 'human'/exp
 #41 'normal human'/exp
 #42 'human cell'/exp
 #43 #40 OR #41 OR #42
 #44 #39 AND #43
 #45 #39 NOT #44
 #48 #46 AND #47
 #46 #31 NOT #45
 #47 #13 AND #21

**3. The Cochrane Central Register of Controlled Clinical Trials (CENTRAL) (CENTRAL).
 COCHRANE LIBRARY. Date searched: February 24, 2025**

#1MeSH descriptor: [Hospitals] explode all trees
 #2MeSH descriptor: [Hospital Units] explode all trees
 #3MeSH descriptor: [Outpatient Clinics, Hospital] explode all trees
 #4MeSH descriptor: [Patients' Rooms] explode all trees
 #5MeSH descriptor: [Equipment and Supplies, Hospital] explode all trees
 #6MeSH descriptor: [undefined] explode all trees
 #7MeSH descriptor: [Health Facilities] explode all trees
 #8MeSH descriptor: [Nursing Homes] explode all trees
 #9#7 NOT #8
 #10hospital*:ti,ab,kw
 #11#1 or #2 or #3 or #4 or #5 or #6 or #9 or #10
 #12MeSH descriptor: [Floors and Floorcoverings] explode all trees
 #13surface*:ti,ab,kw
 #14(furniture or furnishing*):ti,ab,kw
 #15hand next touch next site*:ti,ab,kw
 #16#12 or #13 or #14 or #15
 #17MeSH descriptor: [Housekeeping, Hospital] explode all trees
 #18MeSH descriptor: [Disinfection] explode all trees
 #19MeSH descriptor: [Infection Control] explode all trees
 #20MeSH descriptor: [Disinfectants] explode all trees
 #21MeSH descriptor: [Detergents] explode all trees
 #22MeSH descriptor: [Decontamination] explode all trees
 #23(housekeeping or "house keeping" or hygien* or "sanitary engineering" or sanitation or
 bundling or antiseptic* or asepsis or biocid* or germicid* or microbicid* or bactericid* or fungicid*
 or tuberculocid* or virucid* or sanitiz* or sanitis* or decontaminat*):ti,ab,kw
 #24(cleaning or "domestic services" or soap*1 or detergent* or surfactant* or (surface next active
 next agent*) or cleaner* or mop*1 or vacuum* or (steam next clean*) or (spray next clean*) or (wet
 next scrub*) or (mechanical next scrub*) or (dry next wip*) or (damp next wash*)):ti,ab,kw

#25(disinfect* or inactivation or alcohol* or chlorine* or hypochlorite* or aldehyde* or formaldehyde or glutaraldehyde or peroxide* or (peroxygen next compound*) or "benzalkonium chloride" or iodophor* or ortho-phthalaldehyde or "peracetic acid" or phenolic* or (quaternary next ammonium next compound*) or QUAT or "orthobenzyl parachlorophenol" or "ortho-benzyl para-chlorophenol" or (active next oxygen-based next compound*) or (glycol next derivative*) or alkylamine*):ti,ab,kw

#26#17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25

4. CINAHL COMPLETE (EBSCO). Date searched: February 24, 2025

S1 (MH "Hospitals+")

S2 (MH "Hospital Units+")

S3 (MH "Patients' Rooms+")

S4 (MH "Equipment Contamination")

S5 (MH "Equipment and Supplies+")

S6 (MH "Health Facilities+")

S7 (MM "Nursing Homes+")

S8 S6 not S7

S9 TI (hospital or hospitals) or AB (hospital or hospitals)

S10 (S1 or S2 or S3 or S4 or S5 or S8 or S9)

S11 (MH "Floors and Floorcoverings")

S12 TI surface* or AB surface*

S13 TI (furniture or furnishing*) or AB (furniture or furnishing*)

S14 TI hand touch site* or AB hand touch site*

S15 (S11 or S12 or S13 or S14)

S16 S10 and S15

S17 (MH "Housekeeping Department")

S18 (MH "Infection Control+")

S19 (MH "Disinfectants")

S20 (MH "Detergents+")

S21 TI housekeeping or house keeping or hygien* or sanitary engineering or sanitation or bundling or antiseptic* or asepsis or biocid* or germicid* or microbicid* or bactericid* or fungicid* or tuberculocid* or virucid* or sanitiz* or sanitis* or decontaminat*

S22 AB housekeeping or house keeping or hygien* or sanitary engineering or sanitation or bundling or antiseptic* or asepsis or biocid* or germicid* or microbicid* or bactericid* or fungicid* or tuberculocid* or virucid* or sanitiz* or sanitis* or decontaminat*

S23 TI cleaning or domestic services or soap or detergent* or surfactant* or surface active or agent* or cleaner* or mop or vacuum or steam clean* or spray clean* or wet scrub* or mechanical scrub* or dry wip* or damp wash*

S24 AB cleaning or domestic services or soap or detergent* or surfactant* or surface active or agent* or cleaner* or mop or vacuum or steam clean* or spray clean* or wet scrub* or mechanical scrub* or dry wip* or damp wash*

S25 TI disinfect* or inactivation or alcohol* or chlorine* or hypochlorite* or aldehyde* or formaldehyde or glutaraldehyde or peroxide* or peroxygen compound* or benzalkonium chloride or iodophor* or ortho-phthalaldehyde or peracetic acid or phenolic* or quaternary ammonium compound* or QUAT or orthobenzyl parachlorophenol or ortho-benzyl para-chlorophenol or active oxygen-based compound* or glycol derivative* or alkylamine*

S26 AB disinfect* or inactivation or alcohol* or chlorine* or hypochlorite* or aldehyde* or formaldehyde or glutaraldehyde or peroxide* or peroxygen compound* or benzalkonium chloride or iodophor* or ortho-phthalaldehyde or peracetic acid or phenolic* or quaternary ammonium compound* or QUAT or orthobenzyl parachlorophenol or ortho-benzyl para-chlorophenol or active oxygen-based compound* or glycol derivative* or alkylamine*

S27 S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26

S28 S16 and S27

S29 MH "Clinical Trials+"

S30 PT Clinical trial

S31 TI clinic* N1 trial* or AB clinic* N1 trial*

S32 TI (singl* or doubl* or trebl* or tripl*) and TI (blind* or mask*)

S33 AB (singl* or doubl* or trebl* or tripl*) and AB (blind* or mask*)

S34 TI randomi?ed control* trial* or AB randomi?ed control* trial*

S35 MH "Random Assignment"

S36 TI random* allocat* or AB random* allocat*

S37 MH "Placebos"

S38 TI placebo* or AB placebo*

S39 MH "Quantitative Studies"

S40 TI allocat* random* or AB allocat* random*

S41 (MH "Interrupted Time Series Analysis")

S42 (MH "Controlled Before-After Studies")

S43 (MH "Pretest-Posttest Design+")

S44 TI (before N5 after or pre N5 post or ((pretest or "pre test") and (posttest or "post test"))) or quasiexperiment* or quasi W0 experiment* or pseudo experiment* or pseudoexperiment* or evaluat* or "time series" or time W0 point* or repeated W0 measur*) OR AB (before N5 after or pre N5 post or ((pretest or "pre test") and (posttest or "post test"))) or quasiexperiment* or quasi W0 experiment* or pseudo experiment* or pseudoexperiment* or evaluat* or "time series" or time W0 point* or repeated W0 measur*)

S45 S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44

S46 S28 AND S45

5. ProQuest Dissertations & Theses Global

Date searched: February 24, 2025

all(hospital*) AND all(surface* OR furniture OR furnishing* OR hand touch) AND (all(housekeeping OR "house keeping" OR hygiene* OR "sanitary engineering" OR sanitation OR bundling OR antiseptic* OR asepsis OR biocide* OR germicide* OR microbic* OR bactericide* OR fungicide* OR tuberculoid* OR virucide* OR sanitize* OR sanitise* OR decontaminate* OR cleaning OR "domestic services" OR soap* OR detergent* OR surfactant* OR cleaner* OR mop* OR vacuum* OR disinfect* OR inactivation OR alcohol* OR chlorine* OR hypochlorite* OR aldehyde* OR formaldehyde OR glutaraldehyde OR peroxide* OR "benzalkonium chloride" OR iodophor* OR ortho-phthalaldehyde OR "peracetic acid" OR phenolic* OR QUAT) OR all(surface near/1 active near/1 agent*) OR all(steam near/1 clean*) OR all(spray near/1 clean*) OR all(wet near/1 scrub*) OR all(mechanical near/1 scrub*) OR all(dry near/1 wip*) OR all(damp near/1 wash*) OR all("orthobenzyl parachlorophenol" OR "ortho-benzyl para-chlorophenol" OR alkylamine* OR (peroxygen near/1 compound*) OR (quaternary near/1 ammonium near/1 compound*) OR (active near/1 oxygen-based near/1 compound*) OR (glycol near/1 derivative*)))

6. Web of Science (WoS) Core Collection: Science Citation Index Expanded (SCI-EXPANDED); Conference Proceedings Citation Index - Science (CPCI-S). Date searched: March 3, 2025

1 TOPIC: ((hospital*) OR TITLE: (hospital*))

2 TOPIC: ((surface*) OR TITLE: (surface*))

3 TOPIC: (furniture OR furnishing* OR TITLE: (furniture OR furnishing*))

4 TOPIC: ((hand NEAR/1 manual NEAR/1 site*) OR TITLE: (hand NEAR/1 manual NEAR/1 site*))

5 #4 OR #3 OR #2

6 TOPIC: (housekeeping OR "house keeping" OR hygien* OR "sanitary engineering" OR sanitation OR bundling OR antiseptic* OR asepsis OR biocid* OR germicid* OR microbicid* OR bactericid* OR fungicid* OR tuberculocid* OR virucid* OR sanitiz* OR sanitis* OR decontaminat*)

7 TITLE: (housekeeping OR "house keeping" OR hygien* OR "sanitary engineering" OR sanitation OR bundling OR antiseptic* OR asepsis OR biocid* OR germicid* OR microbicid* OR bactericid* OR fungicid* OR tuberculocid* OR virucid* OR sanitiz* OR sanitis* OR decontaminat*)

8 TOPIC: (cleaning OR "domestic services" OR soap* OR detergent* OR surfactant* OR cleaner* OR mop* OR vacuum*)

9 TITLE: (cleaning OR "domestic services" OR soap* OR detergent* OR surfactant* OR cleaner* OR mop* OR vacuum*)

10 TOPIC: ((surface NEAR/1 active NEAR/1 agent*) OR TITLE: (surface NEAR/1 active NEAR/1 agent*))

11 TOPIC: ((steam NEAR/1 clean*) OR TITLE: (steam NEAR/1 clean*))

12 TOPIC: ((spray NEAR/1 clean*) OR TITLE: (spray NEAR/1 clean*))

13 TOPIC: ((wet NEAR/1 scrub*) OR TITLE: (wet NEAR/1 scrub*))

14 TOPIC: ((mechanical NEAR/1 scrub*) OR TITLE: (mechanical NEAR/1 scrub*))

15 TOPIC: ((dry NEAR/1 wip*) OR TITLE: (dry NEAR/1 wip*))

16 TOPIC: ((damp NEAR/1 wash*) OR TITLE: (damp NEAR/1 wash*))

17 TOPIC: ((disinfect* OR inactivation OR alcohol* OR chlorine* OR bleach* OR aldehyde* OR formaldehyde OR glutaraldehyde OR peroxide* OR "benzalkonium chloride" OR iodophor* OR ortho-phthalaldehyde OR "peracetic acid" OR phenolic* OR QUAT OR "orthobenzyl parachlorophenol" OR "ortho-benzyl para-chlorophenol" OR alkylamine*) OR TITLE: (disinfect* OR inactivation OR alcohol* OR chlorine* OR bleach* OR aldehyde* OR formaldehyde OR glutaraldehyde OR peroxide* OR "benzalkonium chloride" OR iodophor* OR ortho-phthalaldehyde OR "peracetic acid" OR phenolic* OR QUAT OR "orthobenzyl parachlorophenol" OR "ortho-benzyl para-chlorophenol" OR alkylamine*))

18 TOPIC: ((peroxygen NEAR/1 compound*) OR TITLE: (peroxygen NEAR/1 compound*))

19 TOPIC: ((quaternary NEAR/1 ammonium NEAR/1 compound*) OR TITLE: (quaternary NEAR/1 ammonium NEAR/1 compound*))

20 TOPIC: ((active NEAR/1 oxygen-based NEAR/1 compound*) OR TITLE: (active NEAR/1 oxygen-based NEAR/1 compound*))

21 TOPIC: ((glycol NEAR/1 derivative*) OR TITLE: (glycol NEAR/1 derivative*))

22 #21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6#

23 #22 AND #5 AND #1

7. British Nursing Index and Archive via ProQuest. Date searched: February 29th, 2012

(TI(hospital* OR room* OR surface* OR furniture OR furnishing* OR "hand manual") OR AB(hospital* OR room* OR surface* OR furniture OR furnishing* OR "hand manual")) AND (TI(housekeeping OR house keeping OR hygiene* OR sanitary engineering OR sanitation OR bundling OR antiseptic* OR asepsis OR biocide* OR germicide* OR microbic* OR bactericide* OR fungicide* OR tuberculoid* OR virucide* OR sanitize* OR sanitise* OR decontaminate* OR cleaning OR domestic services OR soap*1 OR detergent* OR surfactant* OR surface active agent* OR cleaner* OR mop*1 OR vacuum* OR steam clean* OR spray clean* OR wet scrub* OR mechanical scrub* OR dry wip* OR damp wash*) OR AB(housekeeping OR house keeping OR hygiene* OR sanitary engineering OR sanitation OR bundling OR antiseptic* OR asepsis OR biocide* OR germicide* OR microbic* OR bactericide* OR fungicide* OR tuberculoid* OR virucide* OR sanitize* OR sanitise* OR decontaminate* OR cleaning OR domestic services OR soap*1 OR detergent* OR surfactant* OR surface active agent* OR cleaner* OR mop*1 OR vacuum* OR steam clean* OR spray clean* OR wet scrub* OR mechanical scrub* OR dry wip* OR damp wash*))

8. OpenGrey (www.opengrey.eu). Date searched: December 10th, 2020

discipline:(06E - Medicine) decontaminat* OR detergent* OR disinfect*

9. US National Institutes of Health Ongoing Trials Register (ClinicalTrials.gov). Date searched: 3 March 2025

Hospital Infection OR Healthcare Associated Infection OR Nosocomial Infection | surface OR housekeeping OR house keeping OR hygiene OR antiseptic OR surfactant OR clean OR cleaning OR decontamination OR mop OR vacuum OR disinfect OR alcohol | Interventional studies

10. World Health Organization International Clinical Trials Registry Platform (WHO ICTRP). Date searched: 3 March 2025

Condition: Hospital Infection OR Healthcare Associated Infection OR Nosocomial Infection
Intervention: surface OR housekeeping OR house keeping OR hygiene OR antiseptic OR surfactant OR clean OR cleaning OR decontamination OR mop OR vacuum OR disinfect OR alcohol

b. Searching other resources

Searching reference lists of included trials and relevant reviews

We searched the bibliographies of the following reports for further studies:

- Abreu AC, *et al.* Current and emergent strategies for disinfection of hospital environments. *Journal of Antimicrobial Chemotherapy* 2013;68:2718-32.
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Searching conferences

We searched for conference abstracts from 2008 to 2024 using conference websites or associated journals.

1. Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) 2008 to 2017.
2. American Society for Microbiology (ASM) microbe 2020,2021,2024 (2022, 2023 not celebrated).
3. ASM/European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Joint Conference on Drug Development to Meet the Challenge of Antimicrobial Resistance 2024.
4. European Congress of Clinical Microbiology and Infectious Diseases (ESCMID) 1997 to 2021 (1998 not celebrated, 2000 not available).
5. European Society of Clinical Microbiology and Infectious Diseases (ECCMID) 2022-2024.
6. Annual Conference on Antimicrobial Resistance - Bethesda (ACAR): 2002-2010 (2009 not celebrated).
7. Society for Healthcare Epidemiology of America (SHEA): 2012-2024.
8. International Conference on Prevention and Infection Control (ICPIC): 2011, 2013, 2015, 2017, 2019, 2021, 2022-2024.
9. Healthcare Cleaning Forum: 2018, 2019, 2022, 2024 (2020 and 2021 not celebrated).

Contacting individuals or organisations, citation tracking and retractions

We contacted authors of key papers on the topic to identify further published or non-published studies eligible for inclusion.

We contacted companies for further eligible studies: Diversey, Steris, Micronova, E-mist, Medivators, Acuro, Synergyheath, B. Braun and Striker (only Steris replied). We also screened the studies reported at the website of the action AMiCI (Anti-Microbial Coating Innovations to prevent infectious disease: <http://amici.lifescienceopenspace.pl/>).

We tracked the included studies and relevant systematic reviews in ISI Science Citation Index. We looked for retraction and errata notices on the articles' pages and in specialised retraction databases (PubPeer and Retraction Watch).

Annex 2.3. Unit-of-analysis errors and re-analyses

This table details the unit-of-analysis errors identified for each review effect estimate and our approaches to address them. It also presents the description of the study outcomes according to the scheme proposed by Mayo-Wilson and Saldanha (PMIDs: 28529187; 25329377).

Outcome	HA-colonisations		HAIs				BSIs		All-cause mortality	LOS	AEs
	Wilson 2011	Rock 2022	Danforth 1987	LAMP trial 2024	KARMIN 2023	Salgado 2013	Danforth 1987	Salgado 2013	Salgado 2013	Salgado 2013	Kundrapu 2012
Study design	CRXO cross-sectional RCT					iRCT	CRXO cross-sectional RCT	iRCT			
Transmissible event											
Transmissible	Yes								No		
Statistical test used	Generalised linear model	Poisson regression model	Chi-square	Poisson regression model	Cox-proportional hazard regression analysis	▪ Chi-square ▪ Fisher	No test	▪ Chi-square ▪ Fisher		NR	No test used
UAE ¹	No ²	Yes	Yes	Yes	No	Yes	NA (no test)	Yes	NA (not infection/colonisation data)		
Reviewer's analysis	re-	No									
Impact	NA	▪ Underestimates variability in data ▪ Too narrow CI			NA	Infraestimate variability Narrow CI	NA	Infraestimate variability Narrow CI	NA		
Cluster crossover RCT											
	HA-colonisations		HAIs				Bloodstream infections		All-cause mortality	LOS	AEs
	Wilson 2011	Rock 2022	Danforth 1987	LAMP trial 2024	KARMIN 2023	Salgado 2013	Danforth 1987	Salgado 2013	Salgado 2013	Salgado 2013	Kundrapu 2012
CRXO study	Yes					No	Yes	No			
UAE ³	No ²	No ⁴	Yes ⁵	Yes ⁶	No ⁷	NA	NA (no test)	NA			
Wash-out period	1 week	5 weeks	Absent	6 months	1 month	NA	Absent	NA			
Types of UAE	NA	NA	▪ Cluster	▪ Cluster	NA	NA	▪ Cluster	NA			

			design ▪ XO design	design ▪ XO design but minimised due to wash- out period			design ▪ XO design				
Reviewer's reanalysis	NA	NA	Yes ⁸	Yes ⁸	NA	NA	No	NA			
Correlations	NA	NA	a. M=368 b. WPC=0.19 ⁹ c. BPC=0.15 d. DE=14.78 e. SE _{UAE} =0.09 f. SE _{inflated} =0.35	a. M=647 b. WPC=0.19 ⁹ c. BPC=0.15 d. DE=26.69 e. SE _{UAE} =0.08 f. SE _{inflated} =0.42	NA	NA	NA (no statistical analysis)	NA			
Effect _{UAE}	NA	NA	HAIs: RR 1.12 [0.94 to 1.35]	HAIs: RaR 1.10 [0.94, 1.29]	NA	NA	NA (no estimate)	NA			
Effect _{AA}	NA	NA	HAIs: RR 1.13 [0.57 to 2.24]	HAIs: RaR 1.10 (0.48, 2.51]	NA	NA	NA (no estimate)	NA			
Impact	NA	NA	No	No	NA	NA	NA	NA			
Analysis of events that may re-occur in the same participant											
	HA-colonisations		HAIs				BSIs		All-cause mortality	LOS	AEs
	Wilson 2011	Rock 2022	Danforth 1987	LAMP trial 2024	KARMIN 2023	Salgado 2013	Danforth 1987	Salgado 2013	Salgado 2013	Salgado 2013	Kundrapu 2012
Outcome can re- occur	Yes							No		Yes	
Numbers per arm: a. Nr. participants with outcome b. Nr. cases e. Nr. participants analysed	Intervention a. NR b. NR e. 1252 Comparator a. NR b. NR e. 1331	Intervention a. NR b. VRE colonisation: 149 cases CD colonisation: 42 cases e. 3543	Intervention ¹¹ a. NR b. 229 e. 2876 Comparator ¹¹ a. NR b. 213 e. 3007	Intervention a. NR b. 303 e. 9,117 Comparator a. NR b. 298 e. 10,296	Disinfection a. NR b. 72 e. 4,535 Probiotic a. NR b. 72 e. 4,653 Soap	Intervention a. 17 b. NR e. 294 Comparator a. 29 b. NR e. 320	NR	Intervention a. 3 b. 3 e. 294 Comparator a. 11 b. 11 e. 320	Intervention a. 42 b. 42 e. 294 Comparator a. 50 b. 50 e. 320	Intervention a. NA b. NA e. 294 Comparator a. NA b. NA e. 320	NR

		admissions ¹⁰ Comparator: a. NR b. VRE colonisation: 150 cases CD colonisation: 26 cases e. 3629 admissions ¹⁰			a. NR b. 78 e. 4,708						
UAE ¹²	No ¹³	No ^{14, 15}	Unknown ¹⁶	No ^{14, 17}	No ¹⁴	No ¹⁸	Unknown ¹⁶	No ¹⁸	No (event cannot re-occur)	No ¹⁹	
Reviewer's reanalysis	No										
Impact of the UAE	NA	NA	Unknown	NA	NA	NA	Unknown	NA	NA	NA	NA
Repeated observations on participants for the same outcome											
	HA-colonisations		HAIs				BSIs		All-cause mortality	LOS	AEs
	Wilson 2011	Rock 2022	Danforth 1987	LAMP trial 2024	KARMIN 2023	Salgado 2013	Danforth 1987	Salgado 2013	Salgado 2013	Salgado 2013	Kundrapu 2012
Multiple observations	No										
UAE	No ²⁰										
Reviewer's reanalysis	NA										
Impact	NA										
Multi-arm studies											
Multi-arm study ²¹	No	No	No	No	Yes	No	No	No	No	No	No
UAE	NA				No	NA					
Reviewer's reanalysis	NA										
Impact	NA										
Outcomes definition											
1. Domain	HA-colonisations		HAIs				BSIs		All-cause mortality	LOS	AEs
	Wilson 2011	Rock 2022	Danforth 1987	LAMP trial 2024	KARMIN 2023	Salgado 2013	Danforth 1987	Salgado 2013	Salgado 2013	Salgado 2013	Kundrapu 2012

Definition	Reported ²²	Reported ²³	CDC 1972 ²⁴	CDC 2022 ²⁵	CDC 1992 ²⁶	CDC 2008 ²⁷	CDC 1972 ²⁴	CDC 2008 ²⁷	Reported ²⁸	NR	
Microorganism	MRSA	VRE C. difficile	Any (NR)						NA		
Infection/colonisation location	Surperficial sites ²⁹	Surperficial sites ²³	Any				Blood		NA		
Infection origin	NA		Any (NR)				Blood		NA		
Outcome re-definition by reviewer	No					Yes ³⁰	No				
2. Measurement tool	Wilson 2011	Rock 2022	Danforth 1987	LAMP trial 2024	KARMIN 2023	Salgado 2013	Danforth 1987	Salgado 2013	Salgado 2013	Salgado 2013	Kundrapu 2012
Reporting	Reported								NA	NA	NR
Tool	PCR Nasal or perineum screening swabs	Perianal surveillance samples ▪ VRE: perianal Eswabs ▪ C. difficile: PCR	Laboratory test, radiological and clinical judgement						Clinical judgement		Self-report
Developer	Reported ²²	Reported ²³	CDC 1972 ²⁴	CDC 2022 ²⁵	CDC 1992 ²⁶	CDC 2008 ³¹	CDC 1972 ²⁴	CDC 2008 ³¹	Reported ²⁸	NA	NR
Time: admission / from discharge	> 48 h / ICU Discharge ³²	▪ VRE: > 48 h / NR ▪ C difficile: > 48 h / NR	> 48 h / NR	> 72 h / < 72 h ³³	> 48 h / Discharge ³⁴	> 48 h / < 48 h after ICU discharge ³⁵	> 48 h / NR	> 48 h / < 48 h after ICU discharge ³⁵	In the ICU	LOS at the ICU	During stay
Assessment skills	Microbiological		Clinical and microbiological						Clinical		
Data collection: temporal sequence	Prospective										
Data collection: person	Routine infection control team	Pre-existing surveillance staff	NR	Centrally managed by study team	Routine infection control team	Clinician	NR	Clinician	NR	NR	Self-report (patient or nursing staff)
Data collection: system	NR	Pre-existing surveillance systems	NR	Hospital databases & electronic medical records	Routine infection control team ³⁶	Web-based tool	NR	Web-based tool	NR	NR	NR
Outcome assessment: temporal sequence	Prospective	Prospective	NR	Prospective	Prospective	Retrospective	NR	Retrospective	Retrospective	Retrospective	Retrospective (self-reported)
3. Outcome metric	Wilson 2011	Rock 2022	Danforth 1987	LAMP trial 2024	KARMIN 2023	Salgado 2013	Danforth 1987	Salgado 2013	Salgado 2013	Salgado 2013	Kundrapu 2012

Event of interest	MRSA colonisation	• VRE colonisation • C difficile colonisation	Any HAI				Any BSI		Death	NA	Any adverse effect
Meaning	Undesirable, lower is better										
Data value	Endpoint										
4. Data format	Wilson 2011	Rock 2022	Danforth 1987	LAMP trial 2024	KARMIN 2023	Salgado 2013	Danforth 1987	Salgado 2013	Salgado 2013	Salgado 2013	Kundrapu 2012
Type of study data	Dichotomous	Count	Dichotomous	Count	Count	Dichotomous	Dichotomous	Dichotomous	Dichotomous	Continuous	Dichotomous
Aggregation per study arm	n/N	Incidence rate	n/N	Incidence rate	Incidence rate	n/N	Range ³⁷	n/N	n/N	Median, IQR NR	n
Type of data for MA	Contrast level	Contrast level	Contrast level	Contrast level	Contrast level	Arm level	NA, no analysis	Arm level	Arm level	NA, no analysis	NA, no analysis
Type of data - review	Contrast level	Contrast level	Contrast level	Contrast level	Contrast level	Arm level	NA, no analysis	Arm level	Arm level	NA, no analysis	NA, no analysis
Reviewer's conversion	No	No	Re-analysed	Re-analysed	No	No	No	No	No	No	No
5. Analysis time point (from intervention start)	Wilson 2011	Rock 2022	Danforth 1987	LAMP trial 2024	KARMIN 2023	Salgado 2013	Danforth 1987	Salgado 2013	Salgado 2013	Salgado 2013	Kundrapu 2012
Analysis time-point (review)	Any										
Planned analysis time-point (study)	Any (during stay in the unit)										
Observed follow-up (study)	NR	NR (> 3 days) ³⁸	NR	NR (at least 4 days) ³⁹	Median 6 days (IQR of 4–10 days)	Median 4 days for both study arms	NR	Median 4 days for both study arms	Median 4 days for both study arms	Median 4 days for both study arms	Mean range 5 to 7 days
6. Analysis population	Wilson 2011	Rock 2022	Danforth 1987	LAMP trial 2024	KARMIN 2023	Salgado 2013	Danforth 1987	Salgado 2013	Salgado 2013	Salgado 2013	Kundrapu 2012
Reporting	NR	NR	NR	NR	Reported	Reported	NR	Reported	Reported	Reported	NR
Study analysis population	ITT	Unknown	Unknown ⁴⁰	Unknown	ITT	ITT	Unknown ⁴⁰	ITT	ITT	ITT	Unknown ⁴⁰
Review analysis population	As reported										
Reviewer's re-analysis	No										
7. Handling of MPD	Wilson 2011	Rock 2022	Danforth 1987	LAMP trial 2024	KARMIN 2023	Salgado 2013	Danforth 1987	Salgado 2013	Salgado 2013	Salgado 2013	Kundrapu 2012

Reporting	NR										
Study strategy	ACA	ACA	Unknown ⁴¹	ACA	ACA	ACA ⁴²	Unknown ⁴¹	ACA ⁴²	ACA ⁴²	ACA ⁴²	Unknown ⁴¹
Review strategy	As reported										
Reviewer's re-analysis	No										
8. Re-analysis of UAEs	Wilson 2011	Rock 2022	Danforth 1987	LAMP trial 2024	KARMIN 2023	Salgado 2013	Danforth 1987	Salgado 2013	Salgado 2013	Salgado 2013	Kundrapu 2012
Reviewer's re-analysis	No		Yes	Yes	No		Yes	No			
9. Data used in the review											
Raw/adjusted data	Adjusted	Adjusted	Raw	Adjusted	Adjusted	Raw	Raw	Raw	Raw	Raw	Raw
10. Data completeness for the review analysis											
Data completeness	Complete		Complete			Incomplete	Complete	Complete	Incomplete	Incomplete	Incomplete
Missing data	NA		NA			n/N per arm	NA	NA	MD, CI 95%	n/N per arm	
Abbreviations: AA: approximate analysis. ACA: available case analysis. BPC: within-cluster between-period correlation. C: comparator. CI: confidence interval. ci-RCT: cluster RCT. CRXO: cluster cross-over design. DE: design effect. Effect _{AA} : effect estimate with approximate analysis. Effect _{UAE} : effect estimate with UAE. HAI: hospital-acquired infections. I: intervention. ICC: intracluster correlation coefficient.i-RCT: parallel RCT allocated at the individual level. ITT: intention-to-treat. LOCF: last observation carried forward. M: average cluster size: total number of participants in the intervention and control groups / total number of clusters. NR: not reported. PCR: polymerase chain reaction. PP: per protocol. RCT: randomised controlled trial. RR: relative risk. RaR: rate ratio.SE: standard error. SE _{inflated} : Inflated SE to correct for the UAE (SE x √ DE). SE _{UAE} : standard error with unit of analysis error. UAE: unit of analysis error. VRE: Vancomycin Resistant Enterococcus. WPC: within-cluster within-period correlation. XO: cross-over.											
Footnotes 1. Presence of UAE: the statistical test assumes outcome data independency for transmissible events. 2. "Acquisition data were analysed using a generalised linear model (GLM); daily acquisitions were assumed to be binomially distributed, with the number of trials equal to the number of patients not having MRSA the previous day. Using a logit link function, independent variables included cleaning intervention, hospital, and MRSA colonisation pressure on the three previous days". Thus, the analysis took into account the colonisation, cluster and crossover designs correlations. 3. Presence of UAE: the statistical test assumes independent outcome data, ignoring the dependencies introduced by clustering and crossover design. 4. Analysis approach: This study used a two-stage statistical approach specifically recommended for cluster-randomized trials with fewer than 15 clusters per arm. They had 5 units total, which clearly falls into this small-cluster category. Statistical method: Stage 1: Poisson regression on unit-month data to compute expected events. Stage 2: Two-way ANOVA on log(observed/expected) ratios, accounting for clustering. Assessment: No unit of analysis error. The authors explicitly recognised the clustering and used an appropriate statistical method designed for small cluster trials. Their approach properly accounts for the correlation within clusters. 5. The statistical test overlooks for dependencies in the outcome data (it assumes independence of individual outcomes). 6. The paper reports using "Poisson regression" but does not specify whether clustering was addressed. With 15 units across 2 hospitals, statistical adjustment for clustering is essential. The LAMP study appears to treat individual patients as independent, without adequately accounting for within-cluster correlation. This is concerning because: 1) 47% of HAI cases involved patient transfers between units; 2) environmental interventions naturally operate at the cluster level; and 3) failing to adjust for clustering can produce overly narrow confidence intervals and incorrect p-values. 7. The study used of a CRXO design with wash-in periods and Cox-proportional hazard regression for time-dependent outcomes. This seems to provide a robust framework for analysing longitudinal data while implicitly addressing temporal dependencies within wards. Outcomes are measured at the ward-period level, and data analysis is performed per arm, which is the correct approach for avoiding a unit of analysis error in cluster designs. 8. Inflated SE by DE.											

9. Hess AS, Shardell M, Johnson JK, Thom KA, Roghmann MC, Netzer G, et al. A randomised controlled trial of enhanced cleaning to reduce contamination of healthcare worker gowns and gloves with multidrug-resistant bacteria. *Infect Control Hosp Epidemiol*. 2013;34(5):487–93.
10. This number does not necessarily represent unique individual patients, as a patient could have had multiple admissions during the study period.
11. Eight nursing units (clusters) were allocated with two cluster-periods per nursing unit. This makes a total of sixteen cluster-periods in the study (eight per arm).
12. Events that re-occurred were erroneously analysed as dichotomous data.
13. The outcome was new MRSA acquisition, defined as the first positive MRSA screen after 48 hours in the ICU, following at least 1 earlier negative screen and without previous MRSA isolates. This definition treats MRSA acquisition as a first-event only outcome, not accounting for possible multiple acquisitions or infections per patient.
14. Colonisations/Infections were analysed as count data (incidence density), not as dichotomous data. This correctly takes into account the possibility that some patients may experience more than one event within their at-risk time.
15. The study design explicitly censored a patient's "at-risk" time after their initial infection event: re-occurrences in the same patient were not counted as new primary outcomes.
16. The outcome may have recurred, but the analysis approach was not reported. Since follow-up duration was also unspecified, we cannot determine whether recurrences were common. Thus, it is unclear whether the analysis was inappropriate or what impact this might have had.
17. Any eiHAI where the patient had a previous infection with the same organism within 14 calendar days prior was removed from the analysis.
18. The outcome measures were defined as "incident HAI or colonization", which typically refers to the first new occurrence.
19. Outcomes may have re-occurred, but they did not as there were no events.
20. The studies reported effect measures that combined all time points, such as total events or incidence rates.
21. More than 2 arms relevant for the review.
22. MRSA colonisation: presence of pathogens at superficial sites not causing adverse clinical signs or symptoms.
23. New VRE infection during the hospital stay: a VRE growth from either a clinical culture (e.g., blood, sputum, or wound sample) or a surveillance culture (perianal sample) on or after day 3 of unit admission. New *C. difficile* infection during the hospital stay: a positive PCR result for *C. difficile* from either a clinical stool sample or a surveillance perianal sample on or after day 3 of unit admission.
24. Centers for Disease C. Outline for surveillance and control of nosocomial infections. US Department of Health and Human Services, Atlanta, Georgia 1972.
25. Centers for Disease C. CDC 2022 Centers for Disease Control and Prevention. National Healthcare Safety Network (NHSN) Patient Safety Component Manual 2022.
26. Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG. CDC definitions of nosocomial surgical site infections, 1992: a modification of CDC definitions of surgical wound infections. *Infect Control Hosp Epidemiol*. 1992;13(10):606–8
27. Centers for Disease C. Guideline for disinfection and sterilisation in healthcare facilities, 2008 (update May 2019).
28. Died in the ICU.
29. Nose, groin, sputum, wound or other sites.
30. We re-defined the outcome. The trial registry entry stated that the objective was "Determine whether placement of copper-alloy surfaced objects in an ICU reduce risk of HAI". However, the frequency of HAIs wasn't reported in the article. Its table 2 reported patients with "HAI and/or colonization" and patients with "HAI only". As these outcomes excluded patients with both HAI and colonisation, we re-calculated the relevant outcome "patients that had at least one HAI" as suggested in Harbarth 2013.
31. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control*. 2008;36(5):309–32.
32. "Acquisition was defined as any MRSA-positive specimen taken after the first 48 hrs from admission, either for screening or diagnosis provided 1) no previous MRSA isolates were documented and 2) there was at least one earlier negative screen result during the current study phase. Acquisition was assumed to occur at the midpoint between the last negative and first positive sample. Once discharged from ICU, patients were exposed to varying risks of acquisition of MRSA on other wards, so further analysis was not attempted".
33. "Infections were categorized as eiHAIs if they occurred on or after calendar day 4 of admission or within 3 calendar days of discharge from the study unit. For unit transfers within a study hospital, the eiHAIs were attributed to the unit the patient was on 2 calendar days prior to the date of the infection" "Any eiHAIs in which the patient had a previous infection with the same organism within 14 calendar days prior were removed".
34. Article: "Only infections that provided signs or symptoms after the second day of admission to a study ward were classified as HAIs. Only patients that stayed ≥ 3 days on the study wards were included in the analysis." Protocol: "If a patient leaves the hospital the surveillance for HAIs ends with the day of discharge."
35. "HAI or colonization was attributed to the ICU if it occurred more than 48 hours after ICU admission or within 48 hours after ICU discharge".
36. Study personnel were not allowed to be involved in the routine clinical workup. The HAI analysis was conducted twice, with each analysis performed by a different study nurse trained

in infection control.

37. BSIs risk ranged from 0 to 1.3% in the eight intervention wards.

38. Admissions were included in the analysis only when the LOS was more than 3 days.

39. Infections were categorised as eiHAIs if they occurred on or after calendar day 4.

40. Numbers randomised and analysed per arm NR.

41. We couldn't infer the strategy to handle MPD as the numbers and reasons of MPD per arm were not reported.

42. Article's figure 1: 36 randomised patients weren't analysed due to primary outcome or the study room was missing. Thus, there was no imputation.

Annex 2.4. Excluded studies in decontamination systematic review

This appendix provides the primary exclusion reason for studies excluded at full-text assessment that readers might consider as eligible.

1. Al-Said 2009

Al-Said J, *et al.* Infection-free hemodialysis: can it be achieved? Saudi Journal of Kidney Diseases & Transplantation 2009;20(4):677-80.

Not possible to disentangle the effects of decontamination. Several infection control interventions were implemented in a dialysis unit.

2. Apisarnthanarak 2008

Apisarnthanarak A, *et al.* A multifaceted intervention to reduce pandrug-resistant *Acinetobacter baumannii* colonization and infection in 3 intensive care units in a Thai tertiary care center: a 3-year study. Clin Infect Dis 2008;47(6):760-7.

ITS study. Not possible to disentangle the effects of decontamination. The study aimed to determine the long-term effect of a multifaceted infection-control intervention to reduce the incidence of *Acinetobacter baumannii* infection in a Thai tertiary care centre. During periods 2 and 3 the following interventions were performed: contact isolation, hand hygiene, active surveillance, and cohorting patients who were colonised or infected with multidrug-resistant *Acinetobacter baumannii*. During the first six months of period 2 daily environmental cleaning was performed with 1:100 sodium hypochlorite solution; from the seventh month of period 2 until the end of period 3 the environmental cleaning solutions were changed to detergent and phenolic agents for surface contaminated with body fluid, blood or both. Thus, the comparison of HAI rates of period 3 versus period 2 did not allow to isolate the effects of decontamination.

3. ASCOT trial 2017

Anderson DJ, *et al.* The Antimicrobial Scrub Contamination and Transmission (ASCOT) Trial: a three-arm, blinded, randomized controlled trial with crossover design to determine the efficacy of antimicrobial-impregnated scrubs in preventing healthcare provider contamination. Infect Control Hosp Epidemiol 2017;38(10):1147-1154. 2017;38(10):1147-5.

Cluster crossover RCT. Not possible to disentangle the effects of decontamination. The impact of an infection control bundle was evaluated.

4. ASEPTIC trial 2024

Cheng L, *et al.* Antimicrobial surface coating in the emergency department as protective technology for infection control (ASEPTIC): a pilot randomized controlled trial. Antimicrobial Resistance and Infection Control 2024;13(1):129.

RCT. Evaluation of decontamination performance.

5. Ayliffe 1962

Ayliffe GA, Beard MA. A system of air recirculation and antibacterial surface treatment in a surgical ward. *Journal of Clinical Pathology* 1962;15:242-6.

Not eligible design: CCT. Cluster design with less than two sites per study arm.

6. Barbut 2013

* Barbut F, *et al.* Reducing the spread of *Acinetobacter baumannii* and methicillin-resistant *Staphylococcus aureus* on a burns unit through the intervention of an infection control bundle including hydrogen peroxide vapour decontamination. *Clinical Microbiology and Infection* 2011;17(Suppl 4):S371-S372.

Barbut F, *et al.* Reducing the spread of *Acinetobacter baumannii* and methicillin-resistant *Staphylococcus aureus* on a burns unit through the intervention of an infection control bundle. *Burns* 2013;39(3):395-403.

Not possible to disentangle the effects of decontamination. The impact of an infection control bundle was evaluated.

7. Batra 2010

Batra R, *et al.* Efficacy and limitation of a chlorhexidine-based decolonization strategy in preventing transmission of methicillin-resistant *Staphylococcus aureus* in an intensive care unit. *Clin Infect Dis* 2010;50(2):210-7.

ITS study. Not eligible intervention. The study does not assess the effects of environmental decontamination. It assesses the effects of an antiseptic skin protocol.

8. Brite 2018

Brite J, McMillen T, Robilotti E, *et al.* Effectiveness of ultraviolet disinfection in reducing hospital-acquired *Clostridium difficile* and vancomycin-resistant *Enterococcus* on a bone marrow transplant unit. *Infect Control Hosp Epidemiol*. 2018;39(11):1301-1306

Not eligible design: ITS study

9. Brown 1977

Brown DG, *et al.* Reservoirs of *Pseudomonas* in an intensive care unit for newborn infants: mechanisms of control. *The Journal of Pediatrics* 1977;90(3):453-7.

Not eligible intervention. The study does not assess the effects of environmental decontamination. It evaluates factors responsible for gram-negative agents transmission in a high-risk unit.

10. Bryce 2022

Bryce EA, *et al.* Antimicrobial efficacy and durability of copper formulations over one year of hospital use. *Infect Control Hosp Epidemiol* 2022; 43: 79-87.

RCT. Evaluation of decontamination performance.

11. Carlisle 2023

Carlisle MG, et al. A randomized trial of ultraviolet-C (UV-C) light versus sodium hypochlorite delivered by an electrostatic sprayer for adjunctive decontamination of hospital rooms. *Infect Control Hosp Epidemiol* 2023; 44: 1025-1028.

RCT. Evaluation of decontamination performance.

12. CLEEN trial 2024

Browne K, White NM, Russo PL, et al. Investigating the effect of enhanced cleaning and disinfection of shared medical equipment on health-care-associated infections in Australia (CLEEN): a stepped-wedge, cluster randomised, controlled trial. *Lancet Infect Dis.* 2024;24(12):1347-1356.

Stepped-wedge RCT. Not possible to disentangle the effects of decontamination. The study evaluated the effects of an environmental cleaning bundle.

13. CLEAN FRONTLINE trial 2023

Gon C. O28. Improving environmental cleaning: a stepped wedge cluster trial across thirteen Cambodian hospitals. *International Conference on Prevention and Infection Control 2023. Antimicrob Resist Infect Control* 12 (Suppl 1), 81 (2023).

Stepped-wedge RCT. Not possible to disentangle the effects of decontamination. The study evaluated the effects of an environmental cleaning bundle.

14. Dancer 2009

* Dancer SJ, *et al.* Measuring the effect of enhanced cleaning in a UK hospital: a prospective cross-over study. *BMC Medicine* 2009;7:28.

Dancer SJ, *et al.* P1644 Measuring the effect of enhanced cleaning in a UK hospital: a prospective cross-over study. In: 19th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID); 2009 May 16-19; Finland. www.congrex.ch/2009/eccmid2009/, 2009.

Not eligible design: CCT.

15. Datta 2011

Datta R, *et al.* Environmental cleaning intervention and risk of acquiring multidrug-resistant organisms from prior room occupants. *Archives of Internal Medicine* 2011;171(6):491-4.

Not eligible design: retrospective cohort study.

16. Debast 1996

Debast SB, *et al.* Use of interrepeat PCR fingerprinting to investigate an *Acinetobacter baumannii* outbreak in an intensive care unit. *Scandinavian Journal of Infectious Diseases* 1996;28(6):577-81.

Not eligible intervention. The study does not assess the effects of environmental surfaces decontamination. It assesses the use of PCR to differentiate *A. baumannii* strains during an outbreak.

17. Dharan 1999

Dharan S, *et al.* Routine disinfection of patients' environmental surfaces. Myth or reality? *The Journal of Hospital Infection* 1999;42(2):113-7.

Not eligible design: CCT. Cluster design with less than two sites per study arm.

18. Ebbehøj 2002

Ebbehøj N E, *et al.* Building-related symptoms and molds: a two-step intervention study. *Indoor Air* 2002;12(4):273-7.

Not eligible setting. Not a healthcare setting.

19. Engelhart 2002

Engelhart S, *et al.* *Pseudomonas aeruginosa* outbreak in a haematology-oncology unit associated with contaminated surface cleaning equipment. *Journal of Hospital Infection* 2002;52(2):93-8.

Not possible to disentangle the effects of decontamination. Several interventions were implemented to control an outbreak.

20. Exner 2004

Exner M, *et al.* Household cleaning and surface disinfection: new insights and strategies. *The Journal of Hospital Infection* 2004;56 Suppl 2:S70-5.

Not eligible intervention. The study does not assess the effects of environmental decontamination. It assesses a new experimental model for characterising the cleaning and disinfection properties of detergents and disinfectants under practical conditions.

21. Feigel 2012

Feigel J, *et al.* Expanding the *Clostridium difficile* infection prevention bundle to include patient hand hygiene. *Am J Infect Control* 2012;40(5):e77-8.

Not possible to disentangle the effects of decontamination. Several infection control interventions grouped into an "evidence-based bundle" were evaluated.

22. Ferrari 2014

Ferrari M, *et al.* Efficacy of Hyperdrymist® micro-nebulized hydrogen peroxide in reducing hospital acquired infections. In: 24th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID); 2014 May 10-13th; Barcelona. <http://2014.eccmid.org/>, 2014.

Not eligible design: CCT.

23. Fickenscher 2023

Fickenscher M-C, *et al.* Operating room disinfection: operator-driven ultraviolet C' vs. chemical treatment. *Infection Prevention in Practice* 2023;5(3):100301.

RCT. Evaluation of decontamination performance.

24. Fournel 2010

Fournel I, *et al.* Airborne Aspergillus contamination during hospital construction works: efficacy of protective measures. *Am J Infect Control* 2010;38(5):189-94.

Not eligible intervention. The study does not assess the effects of environmental decontamination. It assesses the impact of outdoor hospital construction work on Aspergillus air contamination in the immediate environment of patients at high risk for aspergillosis in the presence of protective measures.

25. Friedmann 1998

Friedmann PS, *et al.* Mite elimination - clinical effect on eczema. *Allergy* 1998;53(s48):97-100.

Not eligible setting. Not a healthcare setting.

26. Gan 2017

Gan T, *et al.* Sequential enhanced cleaning eliminates multidrug-resistant organisms in general intensive care unit of a traditional Chinese medicine hospital. *Journal of Critical Care* 2017;41:216-21.

Not eligible design: CCT.

27. Gavalda 2016

Gavalda L, *et al.* Control of endemic extensively drug-resistant *Acinetobacter baumannii* with a cohorting policy and cleaning procedures based on the 1 room, 1 wipe approach. *Am J Infect Control* 2016;44(5):520-4.

Not possible to disentangle the effects of decontamination. The intervention was a screening and cohorting policy with new cleaning techniques.

28. Goto 2023

Goto M, et al. Effectiveness of ultraviolet-C disinfection on hospital-onset gram-negative rod bloodstream infection: a nationwide stepped-wedge time-series analysis. *Clinical Infectious Diseases* 2023; 76: 291-298.

Not eligible design: ITS study

29. Grayson 2011

Grayson ML, *et al.* Marked reductions in rates of vancomycin-resistant enterococci (VRE) colonization and disease associated with introduction of a routine hospital-wide bleach cleaning program. *BMC Proceedings* 2011;5(Suppl 6):P24.

Not possible to disentangle the effects of decontamination. A multimodal hospital-wide bleach-based cleaning program that included a new product (sodium hypochlorite 1000ppm + detergent), new standardised (routine and detailed) cleaning practices and modified glove/gown protocols were implemented.

30. Haider 2014

Haider S, et al. Impact of OxyCide™ use on environmental contamination and infection rates compared to standard cleaning practice. *Open Forum Infectious Diseases* 2014;1(suppl 1):S363.

Not eligible design. The study was a non-randomised cross-over study. It was unclear if there was a prospective intervention allocation. We unsuccessfully tried the author (Dr. Haider) to confirm that this was a CCT or a quasi-RCT but we did not obtain any reply (contacted via Research Gate).

31. Hakawi 2014

Hakawi AM. Multiple approaches to decrease the rate of MDROs colonization in intensive care unit at tertiary care hospital in Saudi Arabia. *International Journal of Infectious Diseases* 2014;21(Suppl 1):404-5.

Not possible to disentangle the effects of decontamination. An environmental hygiene stewardship program was implemented.

32. Hakim 2019

Hakim H, *et al.* Effect of a shielded continuous ultraviolet-C air disinfection device on reduction of air and surface microbial contamination in a pediatric oncology outpatient care unit. *Am J Infect Control* 2019;47(10):1248-54.

Not eligible design: non-randomised controlled clinical trial (CCT)

33. Heredia-Rodríguez 2018

* Heredia-Rodríguez M, *et al.* Impact of an ultraviolet air sterilizer on cardiac surgery patients, a randomized clinical trial. *Medicina Clínica* 2018;151(8):299-307.

Bustamante Munguira J, *et al.* An ultraviolet air sterilizer, can it be reduced the rate of infections in patients underwent to cardiac surgery? *European Heart Journal* 2010;31(Suppl 1):F296.

RCT. Not eligible intervention. The study does not assess the effects of environmental decontamination. It evaluated the impact of an ultraviolet air sterilizer on cardiac surgery patients.

34. Hinsaleasure 2016

Hinsaleasure SM, *et al.* Copper alloy surfaces sustain terminal cleaning levels in a rural hospital. *Am J Infect Control* 2016;44(11):e195-203.

Not eligible design: CCT.

35. Hughes 2013

Hughes GJ, *et al.* Impact of cleaning and other interventions on the reduction of hospital-acquired *Clostridium difficile* infections in two hospitals in England assessed using a breakpoint model. *The Journal of Hospital Infection* 2013;84(3):227-34.

'Breakpoint time series analysis model'. Not possible to disentangle the effects of decontamination.

36. IMPACT trial 2018

Lautenbach E, *et al.* A randomized controlled trial of the effect of accelerated copper textiles on healthcare-associated infections and multidrug-resistant organisms: The "Investigating Microbial Pathogen Activity of Copper Textiles" (IMPACT) Study. *Open Forum Infectious Diseases* 2018;5(suppl 1):S568.

RCT. Not eligible intervention. Copper-impregnated linens.

37. Jolly 2021

Jolly J. A study into the use of Surfacide® UV-C emitters in reducing hospital acquired infection rates at Royal Manchester Children's Hospital. *Infection, Disease and Health* 2021; 26: S8. Conference Abstract.

Not eligible design. Not a RCT.

38. Knochen 2010

Knochen H, *et al.* [Influence of floor disinfection on microbial and particulate burden measured under low turbulence air flow in ophthalmological operation theatres] [Einfluss der Fussbodendesinfektion auf die mikrobielle und partikuläre Belastung der Raumluft in Augen-OP-Räumen mit Verdrängungsluftungsbereichen.]. *Klinische Monatsblätter für Augenheilkunde* 2010;227(11):871-8.

Not eligible design: CCT. Cluster design with less than two sites per study arm.

39. Kochar 2009

Kochar S, *et al.* Success of an infection control program to reduce the spread of carbapenem-resistant *Klebsiella pneumoniae*. *Infect Control Hosp Epidemiol* 2009;30(5):447-52.

Not possible to disentangle the effects of decontamination. The study assessed the effect of enhanced infection control measures with screening for gastrointestinal colonisation on limiting the spread of carbapenem-resistant *Klebsiella pneumoniae*.

40. Koo 2011

Koo HS, *et al.* The effectiveness of the infection control program for methicillin-resistant staphylococcus aureus in an intensive care unit of a tertiary hospital. *American Journal of Infection Control. Conference: 38th Annual Educational Conference and International Meeting of the Association for Professionals in Infection Control and Epidemiology, Inc., APIC.* 2011;39(5):E17.

Not possible to disentangle the effects of decontamination. An infection control program, including the use of contact precautions along with environmental decontamination, was implemented.

41. Kovach 2017

Kovach C R, *et al.* Evaluation of an ultraviolet room disinfection protocol to decrease nursing home microbial burden, infection and hospitalization rates. *BMC Infectious Diseases* 2017;17(1):186.

Not eligible design: ITS study. Long term care facility.

42. Larson 2004

Larson EL, *et al.* Effect of antibacterial home cleaning and handwashing products on infectious disease symptoms: a randomized, double-blind trial. *Annals of Internal Medicine* 2004;140(5):321-9.

RCT. Not eligible setting. Not a healthcare setting.

43. Lee 2009

Lee YJ, *et al.* Reduction of MRSA and VRE acquisition by bundling daily 2% chlorhexidine gluconate (CHG) bath and active surveillance culture (ASC) for MRSA at a tertiary care hospital. *Am J Infect Control* 2009;37(5):E85-6.

Not possible to disentangle the effects of decontamination. A bundle consisting of several interventions was implemented.

44. Lewis 2014

Lewis VR, *et al.* Reducing healthcare-associated infections in an ambulatory dialysis unit: Identification and alignment of work system factors. *Am J Infect Control* 2014;42(Suppl 10):S284-90.

Not possible to disentangle the effects of decontamination. The intervention was based on the identification and alignment of work system factors to decrease healthcare-associated infections.

45. Ley 2014

Ley C, *et al.* Household products with triclosan and triclocarban reduce infectious disease symptoms in newborns - preliminary data from an ongoing randomized trial. *Open Forum of Infectious Diseases* 2014;1(Suppl 1):S278.

RCT. Not eligible setting. Not a healthcare setting.

46. Lin 2015

Lin JC, *et al.* Evaluation of using disposable wipes and real time adenosine triphosphate bioluminescence monitoring: A new intensive care unit cleaning program. *Wei mian yu gan ran za zhi [Journal of microbiology, immunology, and infection]* 2015;48(2 Suppl 1):S101-2.

Not possible to disentangle the effects of decontamination. The intervention included an infection control education program, use of disposable wipes rather than a reusable microfiber towel, and feedback the monitoring result.

47. Litwin 2017

Litwin AS, *et al.* Superbugs versus outsourced cleaners: employment arrangements and the spread of health care-associated infections. *Industrial and Labor Relations Review* 2017;70(3):610-41.

Not eligible intervention. The study does not assess the effects of environmental decontamination. It assesses the effects of the externalisation of cleaning.

48. Loftus 2020

Loftus RW, *et al.* The effect of improving basic preventive measures in the perioperative arena on *Staphylococcus aureus* transmission and surgical site infections: a randomized clinical trial. *Jama Network Open.* 2020;3(3):e201934.

RCT. Not possible to disentangle the effects of decontamination. Several infection control interventions were implemented.

49. Marcus 2017

Marcus E L, *et al.* Reduction of health care-associated infection indicators by copper oxide-impregnated textiles: Crossover, double-blind controlled study in chronic ventilator-dependent patients. *Am J Infect Control* 2017;45(4):401-3.

Not eligible design: CCT.

50. Marik 2020

Marik PE, *et al.* The effect of copper-oxide-treated soft and hard surfaces on the incidence of healthcare-associated infections: a two-phase study. *Journal of Hospital Infection* 2020;105(2):265-71.

Cluster crossover RCT. Not eligible intervention. Surface (bed linens)

51. Martin 2018

Martin ET, *et al.* Cleaning high touch surfaces of patients' rooms: make It easier, and It simply gets cleaner. *Open Forum Infectious Diseases* 2018;5(Suppl 1):S346.

Not eligible design: not randomised crossover trial.

52. McConeghy 2017

McConeghy KW, *et al.* Implementing a Pilot Trial of an Infection Control Program in Nursing Homes: Results of a Matched Cluster Randomized Trial. *Journal of the American Medical Directors Association* 2017;18(8):707-12.

RCT. Not eligible setting. Long term care facility.

53. Mody 2019

Mody L, *et al.* O1084: A multicomponent intervention including chlorhexidine bathing in reducing multidrug-resistant organisms in six post-acute care facilities in Michigan, USA. In: 29th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID); 2019 April 13-16; Amsterdam. 2019.

Not possible to disentangle the effects of decontamination

54. Molaeb 2019

Molaeb B. How to successfully manage multi-drug-resistant *Acinetobacter baumannii* transmissions in intensive care unit? *Journal of Infection and Public Health* 2019;12(1):129.

Not possible to disentangle the effects of decontamination

55. Mosci 2017

Mosci D, *et al.* Automatic environmental disinfection with hydrogen peroxide and silver ions versus manual environmental disinfection with sodium hypochlorite: a multicentre randomized before-and-after trial. *J Hosp Infect* 2017;97(2):175-79.

RCT. Evaluation of decontamination performance

56. Muhlebach 2017

Muhlebach MS, *et al.* Microbiological efficacy of early MRSA treatment in cystic fibrosis in a randomised controlled trial. *Thorax* 2017;72(4):318-26.

RCT. Not possible to disentangle the effects of decontamination. The study aim was to evaluate microbiological effectiveness of an eradication protocol (including environmental decontamination for 21 days) compared with observation in cystic fibrosis participants with newly positive methicillin resistant *Staphylococcus aureus* cultures.

57. Muzslay 2009

Muzslay M, *et al.* P1645: Results of a 6-month in-use efficacy trial of AzoMaxActive cleaning products compared to hypochlorite. In: 19th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID). Helsinki, May 16-19 2009.

Not eligible design: CCT.

58. Nadimpalli 2023

Nadimpalli G, *et al.* Efficacy of a continuously active disinfectant wipe on the environmental bioburden in the intensive care unit: A randomized controlled study. *Infect Control Hosp Epidemiol* 2023; 44: 2036-2043.

RCT. Evaluation of decontamination performance.

59. NCT00560599

NCT00560599. A randomized clinical trial to prevent recurrent CA-MRSA Infection (PRIMO). <https://clinicaltrials.gov/ct2/show/NCT00560599>.

Not eligible setting. Not a healthcare setting.

60. NCT00566306

NCT00566306. Influence of a new polycationic disinfectant on *Clostridium difficile* incidence and environmental colonisation. <https://clinicaltrials.gov/ct2/show/record/NCT00566306>.

Not possible to disentangle the effects of decontamination. The study evaluated the use of disinfectant polyhexamethyleneguanidine for hand hygiene and environmental disinfection in rooms with patients with *Clostridium difficile* associated disease, as compared with the use of alcohol-based disinfectants for handwashing and quaternary ammonium compounds/chloramines for environmental cleaning.

61. Ojajarvi 1974

Ojajarvi J, et al. An evaluation of two cleaning and disinfection methods of surfaces in hospital. Zentralblatt fur Bakteriologie, Parasitenkunde, Infektionskrankheiten und Hygiene. Erste Abteilung Originale. Reihe B: Hygiene, praventive Medizin 1974;158(5):479-85.

Not eligible design: CCT. Cluster design with less than two sites per study arm.

62. PACTR202402531001186 2020

PACTR202402531001186. The impact of enhanced cleaning of the environmental surfaces on the bacterial contamination at the intensive care units, <https://trialsearch.who.int/Trial2.aspx?TrialID=PACTR202402531001186>.

RCT. Not possible to disentangle the effects of decontamination. Several infection control interventions were delivered, but the main intervention evaluated was an educational programme.

63. Passaretti 2013

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

Not eligible design: CCT. Dr. Perl (one of the study investigators) confirmed us by email that this was an experimental study with prospective allocation of the intervention and prospective measurement of outcomes.

64. Pavia 2018

Pavia M, *et al.* The effect of ultraviolet-C technology on viral infection incidence in a pediatric long-term care facility. Am J Infect Control 2018;46(6):720-2.

Not eligible setting. Long term care facility (uncontrolled study)

65. Pedersen 2005

Pedersen LK, *et al.* Short-term effects of alcohol-based disinfectant and detergent on skin irritation. *Contact Dermatitis* 2005;52(2):82-7.

Not eligible intervention. The study does not assess the effects of environmental decontamination. It assessed short-term effects of hands alcohol-based disinfectant and detergent on skin irritation.

66. Peterson 2016

Peterson LR, *et al.* Reduction of methicillin-resistant *Staphylococcus aureus* infection in long-term care is possible while maintaining patient socialization: A prospective randomized clinical trial. *Am J Infect Control* 2016;44(12):1622-7.

RCT. Not eligible intervention. The study does not assess the effects of environmental decontamination. Long-term care facility. The objective was to demonstrate that a novel, minimally invasive program not interfering with activities of daily living or socialisation could lower methicillin-resistant *Staphylococcus aureus* disease.

67. Pulliam 2015

Pulliam JR. Lower infection rates after introduction of a photocatalytic surface coating. *Am J Infect Control* 2015;43(2):180-1.

Not eligible setting. Long term care facility.

68. Ray 2015

Ray AJ, *et al.* A multicenter randomized trial to determine the effect of an environmental disinfection intervention on the incidence of healthcare-associated *Clostridium difficile* infection. *Infect Control Hosp Epidemiol* 2017;38(7):777-83.

RCT. Not possible to disentangle the effects of decontamination. The study evaluated the effects of an environmental cleaning bundle that included monitoring of environmental services (EVS) personnel with feedback to EVS and infection control staff.

69. REACH study 2019

* Mitchell BG, *et al.* An environmental cleaning bundle and health-care-associated infections in hospitals (REACH): a multicentre, randomised trial. *The Lancet. Infectious diseases* 2019;19(4):410-8.

Hall L, *et al.* Researching effective approaches to cleaning in hospitals: protocol of the REACH study, a multi-site stepped-wedge randomised trial. *Implementation Science* 2016;44(11):1-10.

Hall L, on behalf of the Researching Effective Approaches to Cleaning in Hospitals (REACH) Study team. O3 Improving real world evidence around hospital cleaning – the role of a pragmatic, implementation focused trial. *Antimicrobial Resistance and Infection Control* 2017;6(Suppl 3):52.

Mitchell BG, *et al.* Evaluating bio-burden of frequently touched surfaces using Adenosine Triphosphate bioluminescence (ATP): Results from the Researching Effective Approaches to Cleaning in Hospitals (REACH) trial. *Infection, Disease & Health* 2020;25(3):168-174.

Stepped-wedge RCT. Not possible to disentangle the effects of decontamination. The study evaluated the effects of an environmental cleaning bundle, with five interdependent, evidence-based components (training, technique, product, audit and communication) implemented with environmental services staff to enhance hospital cleaning practices.

70. Rivero 2014

Rivero P, *et al.* [Impact of copper in the reduction of hospital-acquired infections, mortality and antimicrobial costs in the Adult Intensive Care Unit] [Impacto del cobre en la reduccion de infecciones intrahospitalarias, mortalidad y gasto en antimicrobianos en una Unidad de Cuidados Intensivo de adultos.]. *Revista Chilena de Infectologia : Órgano Oficial de la Sociedad Chilena de Infectologia* 2014;31(3):274-9.

Not eligible design: Quasi-RCT.

71. Ruiz 2017

Ruiz J, *et al.* Silver-embedded screens in the intensive care unit. A new tool to control multi-drug resistant bacterial cross-transmission. *European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology* 2017;36(8):1505-9.

Not eligible design. The study was a prospective observational study.

72. Sampathkumar 2016

Sampathkumar P, *et al.* A trial of pulsed xenon ultraviolet disinfection to reduce *C. difficile* infection. *Am J Infect Control* 2016;44:S30–S31.

Not eligible design: CCT.

73. Sattar 1994

Sattar SA, *et al.* Interruption of rotavirus spread through chemical disinfection. *Infect Control Hosp Epidemiol* 1994;15(12):751-6.

Not eligible setting. Not a healthcare setting. Measurement of the transfer of viruses from disk to the fingers of healthy volunteers in a controlled setting.

74. Schandel 2010

Schandel JM, *et al.* Clean sweep reducing healthcare-associated infections, employee absenteeism, healthcare cost and hospital readmissions in a long term care facility. *Am J Infect Control* 2010;38(5):E71-2.

Not eligible setting. Long term care facility.

75. Semret 2016

Semret M, *et al.* Cleaning the grey zones of hospitals: A prospective, crossover, interventional study. *Am J Infect Control* 2016;44(12):1582-8.

Not eligible design: CCT.

76. Sifri 2016

Sifri C D, *et al.* Reduced health care-associated infections in an acute care community hospital using a combination of self-disinfecting copper-impregnated composite hard surfaces and linens. *Am J Infect Control* 2016;44(12):1565-71.

Not eligible design: CCT.

77. Souli 2017

Souli M, *et al.* Reduction of environmental contamination with multidrug-resistant bacteria by copper-alloy coating of surfaces in a highly endemic setting. *Infect Control Hosp Epidemiol* 2017;38(7):765-71.

Weber DJ, *et al.* Can copper-coated surfaces prevent healthcare-associated infections? *Infect Control Hosp Epidemiol* 2017;38(7):772-6.

Not eligible design: CCT.

78. Struelens 1991

Struelens MJ, *et al.* Control of nosocomial transmission of *Clostridium difficile* based on sporadic case surveillance. *American Journal of Medicine* 1991;91(3B):138S-44S.

Not possible to disentangle the effects of decontamination. The intervention included: (a) gas-liquid chromatography screening of inpatients' diarrhoeal stools; (b) enteric isolation precautions, cohorting and terminal room disinfection in wards with a cluster of two or more nosocomial *Clostridium difficile* disease cases per month.

79. von Dessauer 2016

von Dessauer B, *et al.* Potential effectiveness of copper surfaces in reducing health care-associated infection rates in a pediatric intensive and intermediate care unit: A nonrandomized controlled trial. *Am J Infect Control* 2016;44(8):e133-9.

Not eligible design: CCT.

80. von Kohn 2012

Von Kohn B. Closing the gap of inconsistent hand and surface sanitation. *Am J Infect Control* 2012;40(5):e114-5.

Not possible to disentangle the effects of decontamination. The study determined if using a persistent antimicrobial hand sanitizing lotion and surface disinfectant would reduce healthcare associated infection rates.

81. Warren 2022

Warren BG, et al. An enhanced strategy for daily disinfection in acute care hospital rooms: a randomized clinical trial. *JAMA network open* 2022; 5: e2242131.

RCT. Evaluation of decontamination performance.

82. Williams 2009

Williams VR, *et al.* Utility of environmental sampling for the prevention of transmission of vancomycin resistant enterococci (VRE) in hospitals. *The Canadian Journal of Infection Control : the Official Journal of the Community & Hospital Infection Control Association-Canada = Revue Canadienne de Prevention des Infections* 2009;24(2):119-24.

Not eligible intervention. The study does not assess the effects of environmental decontamination. It assesses the effects of a policy of environmental sampling and room closure as compared to visual inspection without culturing in preventing the transmission of vancomycin-resistant *Enterococcus* to the next admitted patient.

83. Zhao 2014

Zhao H, *et al.* [Monitoring and control of pan-drug resistant *Acinetobacter baumannii* colonization and infection in a medical intensive care unit]. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue* 2014;26(7):464-7.

Not possible to disentangle the effects of decontamination. Several environmental control interventions were assessed: on-the-spot investigation, isolation of patients with XDRABA colonisation and infection, tubes terminal environment disinfection.

84. Ziegler 2022

Ziegler MJ, *et al.* Stopping Hospital Infections With Environmental Services (SHINE): A cluster-randomized trial of intensive monitoring methods for terminal room cleaning on rates of multidrug-resistant organisms in the intensive care unit. *Clin Infect Dis* 2022; 75: 1217-1223.

RCT. Not eligible intervention. The study assesses the effects of monitoring of terminal cleaning effectiveness.

