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Prevention in adults of transmission of infection with multidrug-resistant organisms: an updated systematic review from Making Healthcare Safer IV

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ABSTRACT

Background Healthcare-associated infections due to multidrug-resistant organisms (MDROs) remain a high priority patient safety topic, despite broad acceptance as standard-of-care safety practices to prevent central line-associated bloodstream infection, catheter-associated urinary tract infection and ventilator-associated pneumonia. Prior editions of Making Healthcare Safer have mixed certainty evidence for various other patient safety practices.

Objectives As part of Making Healthcare Safer IV, we performed an updated systematic review on the certainty of evidence for the following safety practices at reducing in-facility MDRO infections in adult patients: universal gloving, contact precautions, cohorting, environmental decontamination, patient decolonisation and the adverse effects of isolation.

Methods We searched PubMed and the Cochrane Library 2011–May 2023 for systematic reviews and original research studies, both randomised and observational. Settings were limited to high-income countries. Screening and eligibility were done in duplicate, while data extraction was done by one reviewer and checked by a second reviewer. The synthesis of results is narrative. Certainty of evidence was based on the GRADE (Grading of Recommendations Assessment, Development and Evaluation) framework.

Results Three systematic reviews and three original research studies provided moderate certainty evidence that patient decolonisation reduced MDRO infections, although restricted to certain populations and organisms. One systematic review provided low certainty evidence that universal gloving was beneficial, again limited to certain populations. One systematic review and two original research studies provided low certainty evidence of benefit for environmental decontamination. One systematic review and one new original study provided low certainty evidence of benefit for cohorting in outbreak settings, and very low certainty evidence of benefit in endemic settings. Six original research studies provide mixed evidence for benefit of contact precautions. There is very low certainty evidence of a signal of increased non-infectious adverse events under patients in contact isolation.

Conclusion In general, the reviewed patient safety practices reduced MDRO infections, but certainty of evidence was low.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ In-facility transmission in adults of multidrug-resistant organisms (MDROs) is a high-priority patient safety topic.
⇒ Prior Making Healthcare Safer reviews (last done in 2020) have found mixed evidence for various patient safety practices.

WHAT THIS STUDY ADDS

⇒ We found moderate certainty evidence that patient decolonisation can reduce infection with MDROs, although to date the evidence is restricted to certain higher risk patient populations and mostly about methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus*.
⇒ Universal gloving, cohorting and environmental cleaning may be effective, but effect sizes are small and certainty of evidence is low.
⇒ Contact precautions, meaning use of gowns, gloves and single room isolation for infected or colonised patients has mixed evidence, and there is a very low certainty signal that isolation may be associated with some adverse health effects.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ In-facility transmission of MDROs can be reduced, but more research is needed to reach moderate certainty evidence about the most effective practices or combinations of practices for specific organisms and settings.

PROSPERO registration number CRD42023444973.

BACKGROUND

There have been concerted efforts to track and reduce the burden of healthcare-associated infections (HAIs) in the USA over the past several decades. With these efforts, there has been a decrease in hospital-acquired infections and particularly procedure-related and device-related infections, including surgical site infections, catheter-associated urinary tract infection (CAUTI) and central line-associated bloodstream infection (CLABSI), as well as *Clostridioides difficile* infection, although several of these trends have reversed in the short term in the context of the COVID-19 pandemic.[1 2] Meanwhile, the threat of multidrug-resistant organisms (MDROs) has seen more mixed progress; a 2019 report found a decrease in overall and hospital deaths from antibiotic-resistant organisms, with reductions in the burden of some MDROs including vancomycin-resistant *Enterococcus* (VRE), methicillin-resistant *Staphylococcus aureus* (MRSA) and multidrug-resistant *Pseudomonas*, but no change in carbapenem-resistant *Enterobacterales* (CRE) and an increase in several other MDROs including extended-spectrum beta-lactamase (ESBL)-producing *Enterobacterales* (ESBL-E) and *Candida auris*.[3] As with HAI rates, MDRO rates saw a significant setback with the COVID-19 pandemic.[4] For Making Healthcare Safer (MHS) IV, the technical expert panel prioritising topics for review selected patient safety practices for reducing burden and transmission of MDROs within hospital and nursing home environments, including those centering around the patient microbiome (but not including antimicrobial stewardship or surveillance testing, the subjects of other MHS reports). Thus, this systematic review assesses decolonisation, barrier precautions and room decontamination, patient isolation and patient/staff cohorting based on colonisation status, in adult patients for the following organisms: VRE, MRSA, *Clostridioides difficile* (*C. difficile*), multidrug-resistant *Enterobacterales* (including ESBL-producing *Enterobacterales* and carbapenem-resistant *Enterobacterales* (CRE)), and the rare but dangerous invasive yeast, *Candida auris* (*C. auris*).

METHODS

This review is an enlarged version of a review done as part of MHS IV, an AHRQ-supported review of numerous patient safety practices.[5] A protocol was developed for the AHRQ review and posted on the AHRQ website; additionally, it was registered with PROSPERO (CRD42023444973). AHRQ participated in setting the scope of the original review and in reviewing the final results. A multidisciplinary technical expert panel advised the project on scope. This review is reported using the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) criteria. Data have been uploaded to the Systematic Review Data Repository managed by the AHRQ and is publicly accessible.[6]

Data sources and searches

We searched PubMed and the Cochrane Library from 2011 (the time of Making Healthcare Safer II) to May 2023 for English-language studies assessing the effectiveness of a transmission-based intervention to prevent infection with multidrug-resistant organisms. The full search strategy can be found in online supplemental file 1.

Study selection

Two authors independently screened titles, abstracts and full texts. Eligibility criteria were adult patients (paediatric-only studies were excluded) with interventions to reduce transmission-based infections compared with usual care or an alternative transmission-based precaution that reported clinical outcomes (infection and surveillance testing status), provider outcomes, costs or unintended effects, in the inpatient or nursing home setting (outpatient settings were excluded), with outcomes measured up to 24 months after discharge from the index hospitalisation or nursing home stay. Systematic reviews, randomised trials, non-randomised trials and observational studies (including case control, controlled pre-post studies, interrupted time series and repeated measure studies) were included. As this was an update of prior work in the Making Healthcare Safer series, our search for new evidence started with the end of Making Healthcare Safer II in 2011. In keeping with the AHRQ Rapid Review format, we looked first for systematic reviews of interventions and then for new original research studies not included in those reviews. Uncontrolled pre-post studies of infection control practices were excluded from original research studies as they are too prone to bias to support causal conclusions, as witnessed by the results of the English Safer Patients Initiative.[7] Cross-sectional studies were excluded because they cannot account for temporality. Patient safety practices to reduce CLABSI, CAUTI and ventilator-associated pneumonia (VAP), as well as promote hand hygiene, were already identified in Making Healthcare Safer II in 2011 as practices for which the evidence was sufficient to 'strongly encourage' their adoption at that time. Thus, for this new edition of Making Healthcare Safer, the technical expert panel recommended that our review should focus on other safety practices, so we excluded studies measuring safety intervention effectiveness using the outcomes of CLABSI, CAUTI or VAP, along with hand hygiene as an intervention. Studies assessing surveillance testing alone or decontamination of reusable devices are reviewed in other sections of Making Healthcare Safer. Studies of education-only or respiratory precautions or only of surgical site infections

were excluded. Because of the perceived importance of healthcare context, studies outside of Organization for Economic Cooperation and Development high-income countries were excluded.

Data extraction and quality assessment

Data were extracted by one author-reviewer and checked by the other. Data extracted included the study design, condition, intervention type, comparison group, outcome measured, timing and items needed to complete the Risk of Bias Tools. Prospective studies were assumed to be conducted in endemic settings unless a study specified an outbreak setting. For systematic reviews, we used the criteria developed by the US Preventive Services Task Force that assesses reviews as good, fair or poor.[8] Poor systematic reviews as determined by these criteria were excluded.[8]

Data synthesis and grading

The data synthesis first relied on existing good or fair quality systematic reviews, and then eligible original studies published since 2011 and not included in the systematic reviews or prior versions of Making Healthcare Safer. The synthesis is narrative; we did not perform new meta-analyses ourselves (although many of the included systematic reviews were meta-analytic). We used the GRADE system to assess the certainty of evidence for new original studies on an intervention/outcome. Since much of the evidence consisted of systematic reviews and meta-analyses, and not all of these performed their own assessment of the certainty of evidence, we estimated this ourselves for each review using the methods described in Making Healthcare Safer IV, which assesses whether the included studies were randomised controlled trials (RCTs) or observational studies or a mix of both, whether the synthesis of evidence in the systematic review was meta-analytic or narrative, the heterogeneity of the results, what the authors of the systematic review stated as limitations of their review, and lastly, how the authors of the systematic review described their results.

RESULTS

Our search retrieved 715 unique titles and abstracts, from which we reviewed 128 full-text articles for eligibility (figure 1). We found 39 studies that met our eligibility criteria. Details of the included original research studies are in table 1, while details of the included systematic reviews are in table 2, and the overall assessments of the certainty of evidence are in table 3. Risk of bias assessments for original research studies and strength of evidence assessments for included systematic reviews are in online supplemental file 2. A list of studies excluded during full text review is included in online supplemental file 3.

Description of the evidence

We identified nine good or fair quality systematic reviews about interventions of interest,[9–17] and an additional 17 original research studies,[18–34] across all settings. We excluded eight systematic reviews that otherwise met eligibility criteria because they were superseded by a more recent or more relevant systematic review[35–38] or were focused on specific organisms rather than specific interventions.[39–42] We also excluded five original research studies because they were included in a systematic review which we include.[43–47]

Universal gloving

Our literature search identified one new systemic review about the effectiveness of universal gloving on HAIs.[11] This review, which we judged to be good quality, searched through July 2018 and identified eight eligible studies, four of which were RCTs and four were controlled before-and-after studies. Five studies focused on MRSA and VRE, and the remaining three studies assessed all HAIs. Six of the eight studies were done in intensive care units (ICUs). Three studies were in paediatric populations. Random effects pooled analyses of all eight studies yielded an incidence rate ratio of 0.89 (95% CI 0.72, 1.10). Stratified analyses by study design, intervention type (universal gloving alone or as part of multiple interventions), pathogen or ward yielded random effects pooled incidence rate ratios of between 0.75 and 1.01, with 95% CIs that either slightly included or slightly excluded the null. The strongest observed effect was reduction of infections in paediatric ICUs. The authors concluded that 'universal gloving was associated with reduced incidence of HAIs. However, the results were not statistically significant when only RCTs were pooled.' We assessed the certainty of evidence from this review as low that universal gloving reduced HAIs.

Our search did not identify any new original research articles since 2018 related to universal gloving for prevention and control of MDROs.

Contact precautions

Our search identified six original research articles that addressed contact isolation.[19–22 25 26] Bessesen and colleagues performed an observational head-to-head trial comparing different isolation strategies for hospitalised adults known or found to be infected or colonised with MRSA, with one strategy employed at each of two Veterans Affairs (VA) hospitals.[19] One hospital observed contact isolation for MRSA-positive patients with use of gown and gloves for all encounters, while the other hospital observed upgraded standard precautions for MRSA-positive patients including gloves for all encounters with addition of a gown only if anticipating contact with blood, body fluids, secretions or excretions. During the 4-year study, the authors saw no difference in MRSA acquisition nor in MRSA

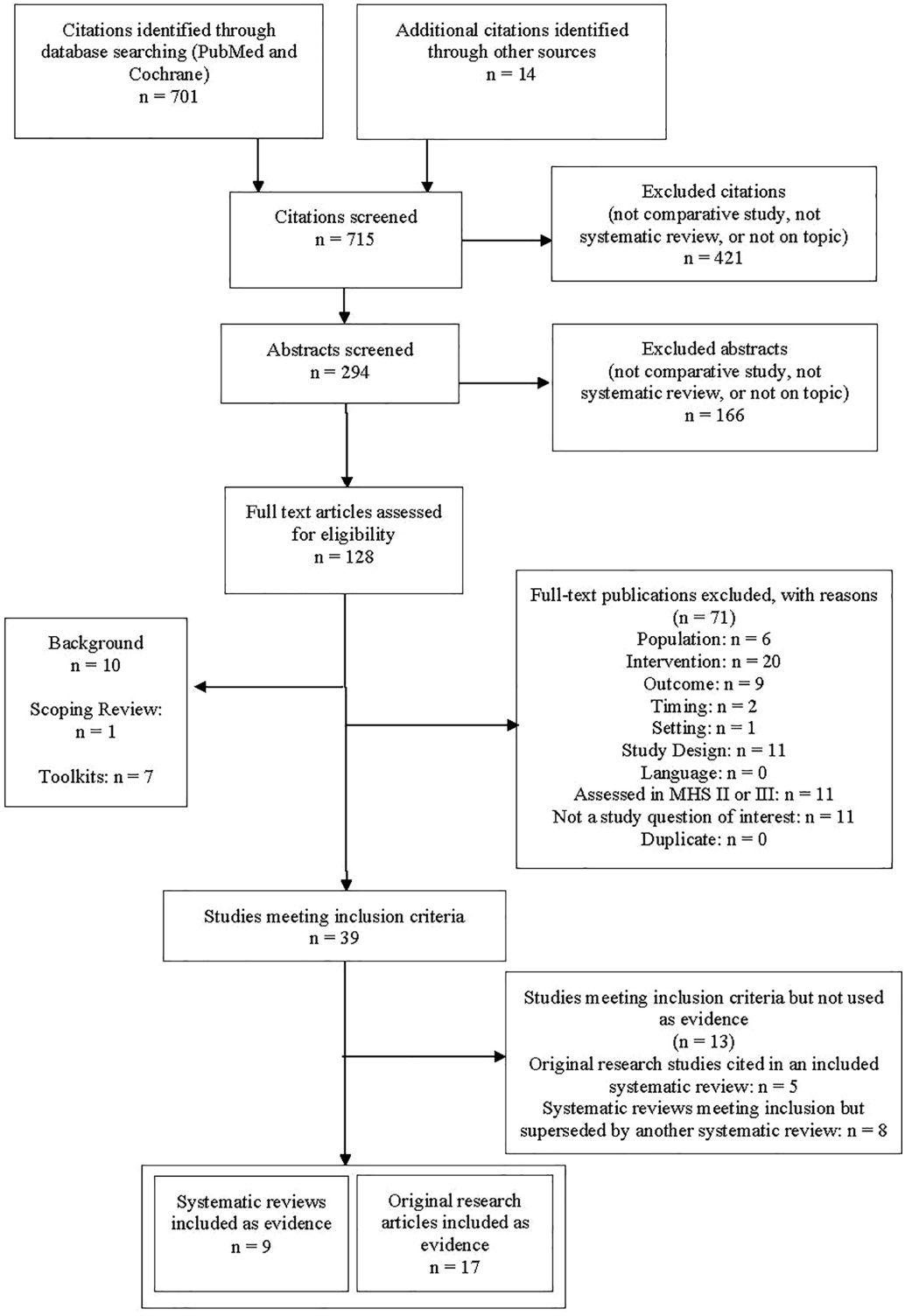

Figure 1 Literature flow. MHS, Making Healthcare Safer.

hospital-acquired infection. Gown costs were estimated from total consumption and a standard unit price, resulting in differences in annual gown costs of $183 609 and $25 812 at the two hospitals.

Four studies examined the effect of single-bed rooms versus multibed rooms. A cluster-randomised trial compared contact precautions (including gloves and gowns before any contact, and single-bed rooms where possible) to standard precautions (gloves and other barriers as needed before contact with wounds or body fluid, hand hygiene) for preventing ESBL-producing *Enterobacterales* in four European university hospitals.[26] Over 2 ½ years, there was no difference in the incidence rate ratio of colonisation or infection (0.99, 95% CI 0.80 to 1.22). Another cluster-randomised RCT in 16 Dutch hospitals found the difference

Table 1 Evidence table for the included original research studies

Author, year Study design	Setting Sample size	Intervention	Outcome
Amirov *et al*, 2017 Controlled before-and-after[18]	Tertiary care hospital geriatric complex continuing care unit n=122	Chlorhexidine bathing 6 days/week	Over 12 months, there was one new case of MRSA acquisition in the intervention group and seven new cases in the control group, this difference was not statistically significant.
Bessesen *et al*, 2013 Non-randomised head-to-head[19]	Two acute care hospitals (one per arm) n=193 300 patient-days across both sites	Contact isolation (gloves+gown for all room entry) vs upgraded standard precautions for patients infected/ colonised with MRSA	No difference in incidence density of MRSA acquisition (1.58 vs 1.56 per 1000 patient-days, p=0.98) or MRSA hospital-acquired infection (0.19 vs 0.16 per 1000 patient-days, p=0.78). Annual gown costs higher with contact isolation strategy ($183 609 vs $25 812).
Biehl *et al*, 2019 Controlled before-and-after[20]	Oncology wards at 4 German hospitals n=2968 patients	Single room contact precautions	No statistically significant effect on acquisition of multidrug-resistant *E. coli*
Biehl *et al*, 2022 Controlled before-and-after[21]	Oncology wards at 4 German hospitals n=3079 patients	Single room contact precautions	VRE acquisition was 4.8% lower in single room contact precaution patients but this was less than the a priori 10% non-inferiority
Camus *et al*, 2011 Randomised trial[22]	2 ICUs in France n=500 patients	Addition of contact precautions (consistent gowns and gloves when entering the room, face masks for close contact) and decontamination to standard precautions	No difference in MRSA acquisition between groups (5.3% vs 6.5%, p=0.58)
Evans *et al*, 2023 Prospective cohort analysis of non-randomised discontinuation of study practices[23]	123 acute care hospitals (all Veterans Affairs hospitals) n=5 225 174 patient-days	Optional discontinuation of any combination of MRSA active surveillance testing (AS), contact precautions for patients colonised with MSRA (CPC) and/or contact precautions for patients infected with MRSA (CPI)	Higher hospital-wide MRSA HAI rate when all three practices were discontinued (no AS or CPC or CPI) compared with continuing any combination of these practices (0.22 vs 0.09-0.12 MRSA HAI per 1000 patient-days, p<0.05). Discontinuing all three practices (no AS or CPC or CPI) showed higher rates of MRSA HAI compared with continuing all three practices (AS+CPC+CPI) both in ICU patients (0.65 vs 0.20 MRSA HAI per 1000 patient-days, p<0.001) and non-ICU patients (0.12 vs 0.07 MRSA HAI per 1000 patient-days, p=0.01).
Huang *et al*, 2019 RCT[24]	24 centres (17 acute care hospitals, 7 nursing homes) n=2121 patients	Post-discharge hygiene education alone vs patient education plus decolonisation protocol (chlorhexidine mouthwash and bathing; nasal mupirocin) repeated in 5 day courses twice per month for 6 months	Over 1-year follow-up, decolonisation arm had 30% lower risk of MRSA infection (HR 0.70; 95% CI 0.52 to 0.96); 29% lower risk of hospitalisation for MRSA infection (HR 0.71; 95% CI 0.51 to 0.99); 17% lower risk of any clinically judged infection (HR 0.83; 95% CI 0.70 to 0.99); 24% lower risk of hospitalisation for any infection (HR 0.76; 95% CI 0.62 to 0.93)
Kluytmans *et al*, 2019 Cluster-randomised crossover trial[25]	16 Dutch hospitals, medical and surgical wards n=10 220	Contact precautions in a single room vs a multiple-bed room	No significant difference in transmission of ESBL producing Enterobacterales to at least one wardmate (3.4%, 90% CI −0.3 to 7.1)
Maechler *et al*, 2020 Cluster-randomised crossover trial[26]	4 European university hospitals n=16 091 patients in contact isolation period vs 16 163 patients in standard precaution	Contact isolation targeting ESBL-E infection or colonisation, vs universal standard precautions	Incidence density of ward-acquired ESBL-E was 6.0 events per 1000 patient-days at risk during periods of targeted contact isolation, vs 6.1 per 1000 patient-days at risk during periods of universal standard precautions (p=0.9710) corresponding to incidence rate ratio of colonisation or infection of 0.99 (95% CI 0.80 to 1.22)
Martin *et al*, 2018 Discontinuation study (before/after)[27]	Single acute care hospital n=50 268 patient-days	De-implementation of routine use of contact isolation precautions for patients infected or colonised with MRSA/VRE	Non-infectious adverse events (postoperative respiratory failure, haemorrhage/haematoma, thrombosis, wound dehiscence, pressure ulcers, falls/ trauma) decreased by 19% (12.3 to 10.0 per 1000 admissions, p=0.022) (infectious outcomes were included in a relevant review)
McConeghy *et al*, 2017 RCT[28]	10 nursing homes (5 per arm, pair-matched) n=861 patients at baseline	Multicomponent infection prevention/ control bundle with staff education, sanitation supplies, and auditing/ feedback dashboard for infection rates and high-touch surface cultures	Total infections 2.9 vs 4.1 per 1000 patient-days (p=0.03), lower respiratory infections 0.8 vs 1.5 per 1000 patient-days (p=0.01); neither reached significance in difference-in-difference analysis. No difference in antibiotic starts or hospitalisation.
Mehta *et al*, 2013 Controlled before-after study[29]	Single orthopaedic acute care hospital; control affiliated university hospital n=128 187 patient-days	Preoperative decolonisation protocol (nasal mupirocin and chlorhexidine) plus screening MRSA nares cultures to determine perioperative antibiotic choice	Clinical MRSA culture prevalence density reduced from 1.23 to 0.83 per 1000 patient-days (p=0.026), while control hospital saw no difference over timeframe (1.27 vs 1.24 per 1000 patient-days, p=0.787)

Continued

Table 1 Continued

Author, year Study design	Setting Sample size	Intervention	Outcome
Miller *et al*, 2023 Cluster RCT[30]	28 nursing homes (14 in each arm) n=3 109 607 patient-days	Routine bathing vs use of chlorhexidine for all bathing/showering plus nasal povidone-iodine twice daily for 5 day periods (at admission then every other week)	Comparing intervention to baseline period, risk ratio for transfer to hospital due to infection was 1.00 in routine care arm vs 0.83 in decolonisation arm (difference in risk ratio 16.6%, 95% CI 11.0 to 21.8), and risk ratio for transfer to hospital for any reason was 1.08 in routine care arm vs 0.92 in decolonisation arm (difference in risk ratio 14.6%, 95% CI 9.7 to 19.2).
Mitchell *et al*, 2019 Stepped wedge randomised trial[31]	11 acute care hospitals in Australia n=4.8 million bed days	A bundle of environmental cleaning strategies	VRE infections were reduced with the intervention (RR 0.63, 95% CI 0.41 to 0.97), there was no statistically significant change in MRSA or *C. difficile* infection
Popiel and Miller, 2014 Time series analysis of discontinuation[32]	Single acute care urban tertiary teaching hospital n=23 000 admissions per year	Change from all admissions screened for VRE to only admissions from endemic hospitals or admitted to high-risk wards; reduced contact tracing, discontinuation of cohorting, no VRE surveillance	Coincident with discontinuation of practices there was an increase in the number of new VRE-colonised patients per quarter from <40 to >100 (statistical testing not performed); definite clinical VRE infections rose from 0 to 5 cases per quarter to 10 cases per quarter
Ray *et al*, 2017 RCT[33]	15 acute care hospitals (one additional hospital dropped out after randomisation) Sample size not reported	Fluorescent marker room cleaning monitoring and feedback for environmental services staff, vs usual care	No difference in hospital-acquired *C. difficile* infection at intervention hospitals before vs after protocol implementation
Salgado *et al*., 2013 RCT[34]	3 intensive care units n=614 patients	Copper vs standard materials for high-touch surfaces in ICU rooms	Hospital acquired infection and/or acquisition of MRSA or VRE colonisation 7.1% vs 12.3% (p=0.02); hospital-acquired infection only 3.4% vs 8.1% (p=0.013)

CDC, Centers for Disease Control and Prevention; ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus*; RCT, randomised controlled trial; VRE, vancomycin-resistant *Enterococcus*.

between isolating ESBL-producing *Enterobacterales*-positive patients in a single-bed room versus leaving such patients in multiple-bed rooms, in terms of acquisition of the organism by a ward mate, to be 4% vs 7% among 693 infected patients and 9527 ward mates.[25] This difference did not exceed the a priori non-inferiority margin of 10%. The third and fourth studies, by the same investigators, were both 12-month controlled before-and-after studies on oncology wards (intervention wards used single rooms with gowns and gloves for patients infected or colonised with the studied MDRO, while control wards allowed shared rooms and did not use gowns and gloves), with one finding a 4.8% difference in VRE acquisition between the single bed and multi-bed strategies, a value that was statistically significant but below the 10% non-inferiority margin[21] and the other finding no difference in multidrug-resistant *E. coli* acquisition rates.[20]

Another RCT in two ICUs in France compared additional contact precautions (the consistent use of gowns and gloves when entering the patient's room, face masks also required for close contact and patient decolonisation, primarily chlorhexidine) to standard precautions in 500 targeted patients over 1 year and found no difference in the acquisition of MRSA between groups (5.3% vs 6.5%, p=0.58).[22]

Studies of the discontinuation of contact precautions

Our literature search identified one recent systematic review and meta-analysis of studies that assess the effect of discontinuing contact precautions,[14] along with two newer studies not included in that systematic review.[23 27]

The systematic review,[14] which we judged to be of good quality, searched through August of 2019 and identified 17 studies meeting eligibility criteria. Eligible studies had to evaluate the discontinuation of routine use of contact precautions for patients infected or colonised with MDROs. Fifteen studies targeted hospital-wide MRSA or VRE or both. All but two studies were from the USA, and 15 of the 17 studies were pre-post assessments. Ten of the studies reported compliance with an alternative intervention after discontinuation of contact precautions, such as hand hygiene, bare-below-the-elbows or chlorhexidine bathing. About half of studies continued active microbial surveillance. In a pooled analysis of data from 11 studies, there was no statistically significant difference in MRSA infection rates (random effects risk ratio=0.84 in favour of stopping contact precautions, 95% CI 0.71, 1.01) with negligible heterogeneity and no evidence of publication bias. We assessed the certainty of evidence from this review as low.

An additional study[27] assessed reportable non-infectious adverse events that can be influenced by provider contact time, which were defined as post-operative respiratory failure, haemorrhage/haematoma, thrombosis, wound dehiscence, pressure ulcers and falls/trauma. Comparing rates prior to and after discontinuation of routine contact precautions, there

Table 2 Characteristics of the included systematic reviews

Author, year Search dates Quality of review	Number of included studies (included study designs)	Healthcare setting(s)	Organisms	Outcomes of interest	Key findings
Abad *et al*, 2020 November 30, 2019 Good[9]	87 (all observational)	Hospital	Cohorting 60 studies cohorted patient and staff, 27 studies cohorted patients alone Multiple MDRO (*C. diff*, MRSA, VRE, CRE, *Acinetobacter*)	Infection or colonisation Infection for *C. diff*, infection for MRSA, infection for VRE. CBE and ESBL and more	Effect of cohorting on *C. diff* and MDRO 77 of 87 studies showed a decline in infection or colonisation rates after a multifaceted approach that included cohorting. 65 of 87 studies were in the setting of an outbreak and thus evidence is less certain for endemic settings
Afonso *et al*, 2013 November 1, 2012 Good[10]	15 (9 RCTs)	Hospital settings included intensive care, hospital and pre-surgical settings (five studies about paediatric populations)	Chlorhexidine wipes Multiple (*Acinetobacter*, *Klebsiella*, *Psuedomonas*, *E. coli*, *C. diff*, other MDRO unspecified)	Infection or colonisation outcomes (HAIs, VAP, CLABSI, BSI)	Most included studies favour the use of chlorhexidine wipes to prevent the spread of pathogens, including MDRO
Chang *et al*, 2019 July 9, 2018 Good[11]	8 (4 RCTs)	Hospital+LTC (mostly ICU, includes two paediatric studies)	Universal gloving Multiple MDRO (MRSA, VRE, *C. diff*)	HAI HAI (mostly but not only MRSA, VRE, *C. diff*)	Pooled analysis of 7 studies of universal gloving showed a reduced incident rate ratio of 0.80 (95% CI 0.67, 0.96). Stratified analyses showed no statistically significant association of the intervention in adult ICUs, whereas results were statistically significant in the paediatric ICU setting. Restricting the analysis to only RCTs resulted in a non-significant result.
Dancer and King, 2021 March 1, 2020 Good[12]	43 (1 RCT)	Hospital+LTC	Decontamination devices (UV, hydrogen peroxide) Multiple (*C. diff*, MRSA, CRE, MDRGN, VRE)	HAI rates Infection	Automated decontamination devices (hydrogen peroxide or UV light) on HAI rates organisms include *C. diff*, MRSA, CRE, etc. Most studies reported either reductions in HAI rates or resolution of an outbreak, but confounding is likely
Huang *et al*, 2016 March 1, 2015 Good[13]	15 (1 RCT)	ICU	Chlorhexidine baths Mixed HAIs (CLABSI, CAUTI, VAP) or MDROs (MRSA, VRE)	Infection or colonisation CLABSI, CAUTI, VAP	Effectiveness of daily chlorhexidine bathing on numerous organisms—restricted to ICU patients. Pooled analysis of results from one RCT and seven observational studies showed a risk ratio of 0.78 (95% CI 0.68, 0.91) for reduction in MRSA acquisition
Kleyman *et al*, 2021 August 1, 2019 Good[14]	12 in quantitative analysis (no RCTs)	Hospital	Contact precautions MRSA, VRE	Infection or colonisation MRSA and VRE Infections	Discontinuation of contact precautions on MRSA and VRE. Pooled analysis of 11 studies showed a risk ratio of 0.84 (95% CI 0.71, 1.01) in HAI from MRSA, favouring stopping contact precautions. Pooled analysis of 7 studies showed a risk ratio of 0.82 (95% CI 0.72, 0.94) in HAI from VRE, favouring stopping precautions.
O'Horo *et al*, 2012 Inception– May 2011 Good[15]	12 (1 RCT)	Mostly ICU (one LTACH study)	Chlorhexidine baths N/A	BSI (mainly CLABSI, some non-CLABSI) Healthcare-associated bloodstream infection incidence, including CLABSI	Inpatient daily chlorhexidine bathing. Pooled analysis of 12 studies showed an OR of 0.44 (95% CI 0.33, 0.59) in reduction in blood stream infections.

Continued

Table 2 Continued

Author, year Search dates Quality of review	Number of included studies (included study designs)	Healthcare setting(s)	Organisms	Outcomes of interest	Key findings
Purssell *et al*, 2020 Inception–2018 Good[16]	26 (no RCTs)	Hospital	Isolation precautions N/A	Non-infectious adverse impacts/mental health/patient experience Psychological (anxiety, depression scores) and non-psychological (non-infectious) outcomes (eg, attention from HCW, errors, falls, ulcers)	Non-infection-related impact of isolation precautions on patients in isolation. Pooled analysis of 8 studies showed an SMD of 1.45 (95% CI 0.56, 2.34) for more anxiety in patients who were isolated. Pooled analysis of 8 studies showed an SMD of 1.28 (95% CI 0.47, 2.09) for more depression in patients who were isolated.
Wong *et al*, 2022 Database inception– 2020 Good[17]	11 studies included in quantitative analysis (5 RCTs)	LTC	Multiple (vertical, eg, decolonisation; horizontal, eg, decontamination, barrier precautions, training/adherence) Multiple MDROs (MRSA, other MDROs)	Infection or colonisation Primary MRSA colonisation; secondary other MDRO colonisation, all MDRO infections	Prevention of MDROs in long-term care setting, with interventions including vertical (decolonisation) as well as horizontal strategies (admin, barrier precautions, training, environmental cleaning, performance improvement, source control). 11 studies included in the meta-analysis showed no statistically significant benefit for MRSA outcomes.

BSI, bloodstream infection; CAUTI, catheter-associated urinary tract infection; *C. diff*, *Clostridioides difficile*; CLABSI, central line-associated bloodstream infection; CRE, carbapenem-resistant *Enterobacterales*; *E. coli*, *Escherichia coli*; HAI, healthcare-associated infection; ICU, intensive care unit; LTACH, long-term acute care hospital; LTC, long-term care; MDRGN, multidrug-resistant Gram-negative bacteria; MDRO, multidrug-resistant organism; MRSA, methicillin-resistant *Staphylococcus aureus*; RCT(s), randomised controlled trial(s); SMD, standardised mean difference; UV, ultraviolet; VAP, ventilator-associated pneumonia; VRE, vancomycin-resistant *Enterococcus*.

was no change in the rate of infectious adverse events whereas the rate of non-infectious adverse events decreased a statistically significant 19%.

Finally, a recently published prospective cohort study compared differences in hospital-acquired MRSA infection in all 123 VA acute-care hospitals nationally, after each facility was given the policy choice to discontinue use of any combination of active surveillance testing for MRSA, contact isolation for patients colonised with MRSA and contact isolation for patients infected with MRSA (in the context of the COVID-19 pandemic, in consideration of need to conserve isolation supplies).[23] Over the 24-month study period and a total of 5 225 174 patient-days, higher facility-wide rates of MRSA HAI were observed when all three of these practices were discontinued (0.22 MRSA HAI per 1000 patient-days with none of these three practices) compared with continued use of any combination (or all) of these practices between 0.09 and 0.12 MRSA HAI per 1000 patient-days depending on which practices were continued. The increase in MRSA HAI infections with discontinuation of safety practices persisted after accounting for facility complexity and current COVID-19 rates.

Overall, we conclude that the evidence is mixed for routine use of contact precautions for reducing MDRO infections, and certainty of evidence is low.

Cohorting

Our literature search identified one new systematic review about the effect of cohorting patients to reduce the incidence of *C. difficile* infections and other MDRs.[9] Cohorting was defined as the practice of grouping together patients who are colonised or infected with the same organism to confine their care to one area, to prevent contact with other susceptible patients. This review, which we judged to be of good quality, searched through November 2019 and identified 87 eligible studies. There were no randomised trials, with 49 studies being retrospective and 35 studies being controlled before-and-after studies. Most studies (74%) were performed in the setting of an outbreak. About 25% of studies were about MRSA, 25% were about CRE or ESBL-E, about 20% were about VRE and 7% were about *C. difficile*. Sixty per cent of studies cohorted both patients and staff. In general, studies reported decreased rates of infection after implementing cohorting, although this was not always the case, and the cohorting was usually implemented along with other infection control practices simultaneously rather than as a single intervention. The authors concluded that cohorting 'may be a reasonable strategy as part of multimodal approach to curtailing MDRO outbreaks,' and we assessed the certainty of evidence from this review as low. They added, 'whether it is an effective strategy in endemic situations is unknown.'

Table 3 Overall assessments of the certainty of evidence

Conclusion from MHS IV	Strength of evidence
Universal gloving has a small effect in reducing MDRO infections (mostly in the ICU setting)	Low
Contact precautions have mixed evidence for effect in reducing MDRO infections	Low
Cohorting may be part of an effective strategy to reduce MDRO infections in the setting of an outbreak	Low
Environmental decontamination may reduce MDRO infections	Low
Patient decolonisation can reduce MDRO infections in certain populations	Moderate
Bundled infection prevention and control practices in long-term care facilities have at most a small effect on rates of MDRO infections in the endemic setting	Low
Infective isolation makes little difference to psychological outcomes, but where it does make a difference this is primarily negative	Low
Non-infectious adverse events may be higher in patients in infective isolation compared with patients who are not isolated	Very Low

ICU, Intensive care unit; MDROs, multidrug-resistant organisms; MHS, Making Healthcare Safer.

Our search identified one new original research article related to patient cohorting for prevention and control of MDRO. A time series study from 2000 to 2013, at an urban tertiary teaching hospital in Montreal, found that on relaxation of screening policies and eliminating cohorting for patients with VRE, there was an immediate large increase in the number of patients colonised with VRE, although the number of patients with clinical infections rose only slightly.[32] This increase in patients colonised with VRE cannot be attributed only to cessation of cohorting (the practice of interest to our review) since this change was made simultaneously with reduction in screening practices.

Environmental decontamination

Our literature search identified one recent systematic review about the effects of different types of environmental decontamination.[12] This review searched through March 2020 to find studies of automated technologies using either hydrogen peroxide or UV light on cleaning and disinfecting hospital surfaces. This review, which was judged to be good quality, identified 43 eligible studies. About half of studies used peroxide and the other half used UV light, although all studies in the setting of an outbreak used peroxide. Almost all studies were before-and-after studies. There was one cluster randomised trial, and four controlled studies. Pathogens were a mix of organisms including MRSA (37% of studies), VRE (33% of studies), *C. difficile* (63% of studies), CRE, MDRO in general and other organisms. The synthesis of results was narrative. The authors discussed in detail a number of methodological and analytical problems with studies, including the use of historical controls, the problem of confounders, the role of industry in funding studies and how data were analysed. While the authors concluded that there were clear benefits from non-touch devices in vitro, they concluded that there was insufficient evidence of benefit with automated room cleaning technologies over-and-above traditional manual cleaning practices, which they recognised as already established as effective. We assessed the certainty of evidence for their conclusions from this review as low.

Our search identified two original research articles addressing environmental decontamination,[31 33] as well as another original research article that used antimicrobial materials to address room contamination.[34] Ray and colleagues performed an RCT[33] in 15 acute care hospitals which compared usual care with a fluorescent-marker-based feedback protocol for staff performing hospital room cleaning, with an emphasis on rooms used for *C. difficile* isolation. The intervention arm showed a marked decrease in post-discharge high-touch surface *C. difficile* culture rates between baseline and intervention periods, but room surface cultures after cleaning did not correlate with rates of *C. difficile* infection. Mitchell and colleagues in a stepped-wedge trial implemented a bundle of environmental cleaning policies (Researching Effective Approaches to Cleaning in Hospitals) in 11 hospitals and a modelled analysis showed the intervention caused a relative risk reduction in VRE of 0.63 (95% CI 0.41, 0.97) but no statistically significant changes in MRSA or *C. difficile* infection.[31]

Salgado and colleagues performed a small RCT[34] in three ICUs, comparing copper versus standard materials for several high-touch surfaces in patient rooms, predicated on the antimicrobial properties of copper as a strategy for environmental self-decontamination. The primary outcome was a composite of any hospital acquired infection or acquisition of MRSA or VRE colonisation, which occurred in 7.1% of patients (21 of 294) in the intervention arm vs 12.8% (41 of 320) in the control arm ($p=0.02$).

Overall, we conclude that certain environmental decontamination practices may reduce MDRO infections, but certainty of evidence is low.

Patient decolonisation

Our literature search identified three systematic reviews of use of chlorhexidine wipes or baths to reduce hospital-acquired infections.[10 13 15] The review with the largest number of included studies, which we judged to be of good quality, searched through 2014 for studies of daily chlorhexidine bathing in the ICU.[13] The search yielded 15 eligible studies, of which 3 were

RCTs. Although primarily focused on the outcomes of CLABSI, CAUTI and VAP, the review did identify one RCT and seven controlled before-and-after studies that measured MRSA acquisition and a pooled analysis resulted in a fixed effects risk ratio of 0.78 (95% CI 0.68, 0.91) favouring chlorhexidine bathing. A pooled analysis of one RCT and four controlled before-and-after studies that measured VRE acquisition showed a random effects pooled risk ratio of 0.56 (95% CI 0.31, 0.99) favouring chlorhexidine bathing. The authors concluded that their data 'suggest that daily chlorhexidine bathing can significantly reduce healthcare associated infections in ICUs.' We assessed the certainty of evidence of this conclusion as Low. Their conclusion was consistent with the conclusions of the two older reviews,[10 15] that also assessed use in long term care and obstetric contexts in addition to the ICU.

Our search identified three original research articles addressing decolonisation[18 24 29] and a fourth study published after our search date was identified during peer review.[30] Two multi-site randomised trials, one that included both acute hospitals and nursing homes and the other limited to nursing homes, both found in decolonised patients statistically significant 15–30% reductions in MRSA infection at 12–18 months follow-up.[24 30] A time series study in a single orthopaedic hospital found a reduction in the prevalence density of clinical MRSA cultures.[29] One small single site controlled before-and-after study in a geriatric complex continuing care unit found one new MRSA infection in the chlorhexidine bathing group and seven new infections in the control group, but this difference was not statistically significant.[18]

Overall, we conclude that patient decolonisation can reduce MDRO infection in certain populations (moderate certainty of evidence).

Adverse effects of isolation

Our literature search identified one newer review on the adverse effects of isolation.[16] This review, which we judged to be fair quality, searched through 2018 for studies assessing the psychological or non-psychological outcomes in adult patients who are in infectious isolation. The search identified 26 studies meeting eligibility criteria. The synthesis was both meta-analytic for the outcome of anxiety and depression, and narrative for all other outcomes. Eight studies reporting anxiety outcomes that were pooled using a random effects model yielded a SMD of 1.45 (95% CI 0.56, 2.34) favouring higher anxiety when isolated. Similarly, for depression, the random effects pooled estimate of 8 studies yielded a standardised mean difference of 1.28 (95% CI 0.47, 2.09), meaning more depression when isolated. For the remaining psychological outcomes, such as confusion, worry and sadness, the authors note that 'infective isolation precautions make little difference to psychological outcomes, [but] where it does make a difference this is primarily negative'. Similarly for non-infectious outcomes like falls, pressure ulcer, 'any adverse event', the authors conclude 'there was a trend' for more 'errors' to occur in those who are isolated. They concluded that 'there are a number of apparently negative aspects to contact precautions'. We assessed the certainty of evidence from this review as Low for their conclusions.

Our search did not identify any new original research articles related to adverse effects of isolation precautions used for prevention and control of MDROs, aside from the study by Martin and colleagues, discussed before, which showed a statistically significant 19% decrease of non-infectious adverse events (including falls, pressure ulcers, haemorrhage, thrombosis, postoperative respiratory failure and wound dehiscence) after halting routine use of isolation precautions for MRSA and VRE.[27] Overall, we conclude that non-infectious, non-psychological adverse events may be higher in patients in infective isolation compared with patients who are not isolated, but certainty of evidence is very low.

Infection prevention and control practices in nursing home settings

We identified one newer systematic review[17] and one new original research study[28] (in addition to the patient decolonisation study[30] discussed earlier). Details are in online supplemental file 4.

Certainty of evidence

The certainty of evidence assessments is almost entirely based on the included systematic reviews. The newly included original research studies supported the conclusions of the systematic reviews. In one instance, we uprated the systematic review strength of evidence from low to medium based on a new large, randomised trials showing benefit for patient decolonisation. See table 2. See the online supplemental appendix for details of our classification of the certainty of evidence for the systematic reviews that did not themselves report this.

DISCUSSION

The principal finding from this review is that there are studies that have found it possible to reduce the transmission of MDROs in patients in hospitals and nursing homes, but with one exception, the certainty of evidence is at best low. The one exception is patient decolonisation, for which there are systematic reviews and two large multi-site RCTs that together are sufficient to conclude with moderate certainty that patient decolonisation, with chlorhexidine bathing and in some cases with nasal antibacterials as well, reduces infection and transmission of MDROs (primarily MRSA and to a lesser extent VRE) in certain patient populations, notably ICU patients and nursing home patients. For other safety practices and organisms, the

evidence is low certainty, meaning we expect future research to change our estimates of effect.

These findings add to the conclusions from earlier versions of Making Healthcare Safer. A review in MHS I (2001) found significant reductions in VRE and *C. difficile* with barrier precautions to prevent HAI with VRE, but noted that in many of the reviewed studies the barrier precautions were part of a bundle, making the independent effect of barrier precautions uncertain. Furthermore, most studies were pre-post studies of limited ability to make causal inferences. In MHS II, again limited to VRE and *C. difficile*, the review noted that as in MHS I most studies were bundles, making causal inferences of any particular component hard to assess. Overall, MHS II concluded that the evidence was mixed in terms of interventions for reducing colonisation or infections. In MHS III (2020), the review concluded that adding peroxide or UV light to standard cleaning was associated with reduced *C. difficile* infections, although study quality was low and the only RCT found no difference in infection rates. The MHS III review also concluded that there was high level evidence supporting the use of chlorhexidine bathing to reduce VRE and MRSA, though the majority of the literature addressed ICU patients.

Perhaps the most controversial aspect of the newer evidence concerns the use of barrier precautions—single room isolation, gowns and gloves—for patients infected or colonised with MDROs. While the causal pathway for why such precautions should be effective is very strong, over the past decade there are numerous published case reports and even a meta-analysis of case reports of institutions discontinuing routine contact precautions and finding no increase in MRSA or VRE infections. Such results are, however, at increased likelihood of publication bias, as institutions whose HAI rates increased may be less likely to publish such results. Counterbalancing these null findings is one of the largest studies of multiple hospitals in a single healthcare delivery system, where the discontinuation of barrier precautions was associated with an increase in MRSA infection rates, with stepwise increases as the number of barrier precautions were discontinued.[23] Interpretation of these results is complicated by the fact that the barrier precautions were relaxed in the face of the COVID pandemic. Analytical attempts to control for pandemic-related hospital-wide disruption yielded results similar to that of the main analysis, but whether hospital-wide COVID rates are a valid proxy for this disruption is not established. Without randomised or high-quality observational studies (eg, a stepped wedge study of de-implementation) it will be impossible to reach strong conclusions about the benefit or lack thereof for barrier precautions for patients infected or colonised with MDROs.

This review is subject to the usual limitations of all such reviews: limitations in the source material and limitation in how we performed the review. With regard to the former, by far the greatest limitation is the reliance on observational data as the evidence for the benefit, or lack of benefit, and potential adverse effects of any of these patient safety practices. Since MHS I there are more randomised trials of MDRO infection prevention interventions, but much more needs to be done—as an example, the question above about barrier precautions. Another limitation of the source literature is that many studies did not specify whether the study was conducted in the endemic or outbreak setting; most were presumed to be performed in the endemic setting. Thus, our conclusions are relevant to the endemic setting, and generalising these results to the outbreak setting should be done with caution. With respect to our conduct of the review, the biggest limitation is that we did not ourselves re-review all the studies included in the existing meta-analyses, in other words we took the results of those reviews 'at face value'. To re-review all of the studies and reach our own independent conclusions was beyond our resources and also negates the supposed contributions of systematic reviews in the advancement of knowledge. A second limitation is that our search was limited to PubMed and Cochrane and restricted to publications in English. A third limitation is that screening and selection of studies was not performed in a blinded fashion between the two authors. Finally, a fourth limitation is that some of the interventions were assessed as part of bundles, and therefore, the decision to include such a study and assign it the category of the most-likely-active component versus excluding the study required judgement, which other experts may decide differently.

In summary, we found moderate certainty evidence that patient decolonisation can reduce infection with MDROs, although to date the evidence is restricted to certain higher risk patient populations and mostly about MRSA and VRE. Universal gloving, cohorting and environmental cleaning may be effective, but effect sizes are small and certainty of evidence is low. Contact precautions, meaning use of gowns, gloves and single room isolation for infected or colonised patients, has mixed evidence, and there is a very low certainty signal that isolation may be associated with some adverse health effects.

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