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RESEARCH

Infection prevention and control measures for multidrug-resistant organisms: a systematic review and network meta-analysis

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Abstract

Background The effectiveness of infection prevention and control measures combating multidrug-resistant organisms (MDROs) in healthcare settings remains controversial.

Methods PubMed, Embase, MEDLINE, Cochrane Library, and CINAHL were searched from inception to June 1, 2024. The interventions encompassed standard precautions (SP), contact precautions (CP), hand hygiene (HH), environmental cleaning (ENV), antimicrobial stewardship programs (ASP), decolonization (DCL), and chlorhexidine baths (CHG). The primary outcome were the acquisition, infection, and colonization of MDROs. Secondary outcomes were all-cause mortality and MDROs-associated bacteraemia. Effect indicators were expressed as rate ratios (RRs) with 95% confidence intervals (CIs).

Results The study included a total of 97 articles, comprising 19 RCTs and 78 non-RCTs. The results showed that the most effective combination interventions for the acquisition, infection, and colonization of MDROs compared to SP varied as follows: CP+CHG (RR, 0.38 [0.18, 0.79]), SP+CP+ENV (RR, 0.04 [0.02, 0.08]), and SP+CHG (RR, 0.28 [0.14, 0.56]). In subgroup analyses, CP+CHG (RR, 0.36 [0.20,0.64]) was the most effective intervention for the acquisition of MDROs in the ICU setting, whereas SP+CP+ASP (RR, 0.35 [0.14,0.92]) was the most effective hospital-wide. Across subgroups, SP+CP+ENV (RR, 0.04 to 0.09 [95% CI, 0.01 to 0.99]) was identified as the most effective intervention for MDROs infections. In the ICU setting, SP+CHG (RR, 0.28 [0.14,0.56]) demonstrated the highest effectiveness in reducing the colonization of MDROs, whereas SP+CP+ENV+CHG (RR, 0.15 [0.06,0.38]) was the most effective on a hospital-wide scale. SP+CP+DCL (RR, 0.28 [0.24, 0.32]) was associated with reduced CRE colonization. The results of this study were robust according to the sensitivity analysis. None of the analyses related to secondary outcomes were statistically significant. In terms of article quality assessment, 94.7% of the RCTs were medium to high risk, while 92.31% of the non-RCTs. The primary limitation of the RCTs were related to the randomization process, whereas the non-RCTs were primarily affected by confounding bias.

Conclusions Effective interventions differ based on carriage status, intervention setting, and the resistant strain. Additionally, contact precautions is a crucial component of these combinations. Consequently, healthcare organizations can select appropriate interventions based on their unique resistance profiles to optimize precision and resource efficiency.

Keywords Multidrug-resistant · Network meta-analysis · Standard precautions · Infection prevention and control (IPC)

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Introduction

Multidrug-resistant organisms (MDROs) are primarily bacteria that exhibit resistance to three or more classes of antimicrobial drugs currently in clinical use [1]. These highly resistant bacteria include Methicillin-resistant *Staphylococcus aureus* (MRSA), Vancomycin-resistant *Enterococci* (VRE), and certain gram-negative bacilli (GNB). In recent years, MDROs have emerged as significant pathogens in hospital-acquired infections, limiting therapeutic options and increasing the length of hospital stays, mortality rates, and healthcare costs [2]. The ongoing emergence and spread of MDROs in healthcare settings are attributed to several factors, including antibiotic misuse, low patient immunity, genetic variation among bacteria, inadequate sterilization of environments, carriage by healthcare workers (HCWs), and cross-contamination. These factors collectively position MDROs as a significant threat to global public health [3].

Infection prevention and control (IPC) measures are a set of strategies designed to prevent or halt the spread of infections in healthcare settings. In 2006, the Centers for Disease Control and Prevention (CDC) published guidelines for the management of MDROs in healthcare environments, with an update released in 2022 (https://www.cdc.gov/infection-control/hcp/mdro-management/index.html). Additionally, the World Health Organization (WHO) published guidelines in 2016 outlining the core elements of IPC programs at both the national and acute healthcare facility levels (https://www.who.int/publications/i/item/9789241549929). Although authorities have implemented appropriate response strategies [1], the effectiveness of these interventions remains a subject of debate.

Previous meta-analyses have concentrated on the effectiveness of specific interventions targeting MDROs or have focused exclusively on the intensive care unit (ICU) environment [4, 5]. However, control measures that focus solely on one resistant organism are less feasible, as immunocompromised patients may continue to be infected with other resistant organisms. Additionally, the presence of multiple pathogens in healthcare settings complicates the situation [6]. Therefore, IPC measures must be tailored to suit various environments and resistance profiles in order to more effectively control the spread of MDROs.

We conducted a systematic review and network meta-analysis to evaluate the impact of various interventions on MDROs in hospitalized patients, both in the ICU and across the whole hospital environment. Our assessment focused on the effectiveness of IPC measures in preventing MDROs acquisition, infection, and colonization, as well as their effects on all-cause mortality and MDROs-associated bacteremia.

Methods

Search strategy and selection criteria

We searched PubMed, Embase, MEDLINE, Cochrane Library, and CINAHL databases for English-language articles published from inception to June 1, 2024 (Table S3). We defined eligible participants as patients who were hospitalized in a healthcare facility, specifically those who were admitted and received care, diagnosis, or treatment within that facility. Consequently, we excluded studies conducted in outpatient clinics, rehabilitation centers, and nursing homes. The included articles involved comparisons of at least two different groups of IPC measures. These interventions included hand hygiene (HH), standard precautions (SP), contact precautions (CP), antimicrobial stewardship programs (ASP), environmental cleaning (ENV), decolonization (DCL), and chlorhexidine gluconate baths (CHG; appendix 4). The control group could consist of usual care, placebo, or other interventions. The study types included randomized controlled trials (RCTs), cohort studies, before-and-after controlled studies, and interrupted time-series studies (ITS), excluded case-control studies, case series, and case reports. The definition of drug-resistant microorganisms is delineated according to the guidelines established by the European Centre for Disease Prevention and Control and the CDC [7]. The resistant strains included were MRSA, VRE, Extended-spectrum β-lactamase-producing *Enterobacteriaceae* (ESBL-E), Carbapenem-resistant *Enterobacteriaceae* (CRE), Multidrug-resistant *Acinetobacter baumannii* (MDR-AB), and Multidrug-resistant *Pseudomonas aeruginosa* (MDR-PA). The study was registered with PROSPERO (CRD42024564114), and a systematic review and network meta-analysis were conducted in accordance with PRISMA guidelines [8].

Data extraction and quality assessment

At least two reviewers (Liu Z, Dang J, Zhang P and Chen C) independently screened the search results, and if there was any doubt, they consulted a third reviewer. Two reviewers (Ma X and Pan T) independently extract relevant data for input into a standardized form. All extracted data were cross-checked by two additional reviewers. The Risk of Bias 2 (RoB 2) tool [9] was used to assess the methodological quality of the included RCT studies. The quality of non-RCT studies was assessed using the Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) tool [10]. Quality assessments were conducted independently by two reviewers (Pan D and Chen M), and any disagreements were resolved through discussion.

Outcomes

The primary outcome measures assessed were the acquisition, infection, and colonization of MDROs. Colonization was defined as a positive result from a screening swab or clinical specimen culture, without any clinical signs or symptoms of infection caused by MDROs. Infection was defined as the isolation of MDROs from a patient's clinical specimen, accompanied by the development of appropriate clinical signs and symptoms. Acquisition was defined as a patient who tested negative on specimens collected within 48 h of admission, with clinical cultures that were positive either 48 h after admission or at the time of discharge, regardless of the presence of clinical evidence of MDROs infection. Secondary outcomes included all-cause mortality and MDROs-associated bacteraemia. All-cause mortality refers to the total number of deaths from all causes within a specific population over a defined period, irrespective of the underlying cause of death. MDROs-associated bacteraemia refer to the invasion of the bloodstream by multidrug-resistant bacteria, leading to systemic infection. This condition is typically manifested by symptoms such as fever, chills, and low blood pressure, among others.

Data analysis

We performed paired meta-analysis. Heterogeneity was evaluated using the I^2 statistic, which was categorized as low ($I^2 \leq 50\%$), moderate (I^2 = 50-75%), and high ($I^2 \geq 75\%$) [11]. Effect sizes were estimated using a random-effects model, with the intervention's effect expressed as a rate ratio (RR) and 95% confidence interval (CI). A network meta-analysis was performed using a random effects model, with SP serving as the common comparison group. The outcome variables of the study were all categorical, therefore, the effects were expressed using combined RR and 95% CI. The network inconsistency test was utilized to assess the differences in effect sizes of interventions across various study designs. We evaluated global inconsistency by using the difference between the effect values of direct and indirect comparisons, finding no global inconsistency when $P>0.05$. Local inconsistency was assessed using the inconsistency test for loops, which we evaluated by calculating the inconsistency factor (IF) and the 95% CI for each loop. There was no loop inconsistency at $P>0.05$ [12]. We investigated potential sources of heterogeneity by performing subgroup analyses based on different ranges of intervention implementation and different mechanisms of resistance. We predefined various subgroups while making minor adjustments during the literature review. The range of intervention implementation was categorized into the Intensive Care Unit (ICU) and the whole hospital environment. With the exception of the ICU-only study, all other articles were included in the hospital-wide study. The various resistant strains included MRSA, VRE, ESBL-E, CRE, MDR-AB and MDR-PA. For sensitivity analyses, we focused on high-quality studies and excluded those in which interventions were implemented only in specialty wards.

In the network meta-analysis, we ranked the effects of the interventions by plotting the surface under the cumulative ranking (SUCRA) curves for each intervention, with larger SUCRA values indicating a greater effect. Comparison-adjusted funnel plots were used to assess publication bias [13]. All analyses were conducted using Stata 17.0 software, and P values less than 0.05 were considered statistically significant.

Results

The search identified 9,742 articles and excluded 2,100 duplicates. After screening based on titles and abstracts, we excluded 7,303 ineligible articles. A full-text assessment of 365 articles resulted in the inclusion of 97 studies, which consisted of 19 RCTs and 78 non-RCTs (Fig. 1).

Among the study participants, the median age was 63.0 years (interquartile range [IQR], 58.5–66.1), and 59% (IQR, 50.7–63.4) of the participants were male. Of the articles included in the review, 50 articles focus on ICU wards, 29 articles examine the hospital-wide, and the remaining 18 targeted specialized wards, such as medical and surgical units. Among multi-resistant Gram-positive bacteria, the majority of studies concentrated on MRSA (55 articles), while studies on multi-resistant Gram-negative bacteria primarily focused on ESBL-E (21 articles) and CRE (11 articles; Table S5.1).

Risk of bias assessment

Of the 19 RCTs included in the analysis, one article was assessed to be at high risk of bias, primarily due to missing outcome events. 13 articles were assessed to be at moderate risk of bias, primarily due to the effects of non-concealment of study population subgroups and the presence of missing outcome data. Among the 78 non-RCT studies, 72 were rated as medium risk and six as high risk. The high risk of bias was primarily attributed to confounding bias, as these articles did not adequately control for baseline confounding using appropriate methods (Table S6, Fig. S6).

Pairwise meta-analysis

A paired meta-analysis was conducted to compare the effects of interventions on different outcome indicators. Among the interventions to prevent the acquisition of

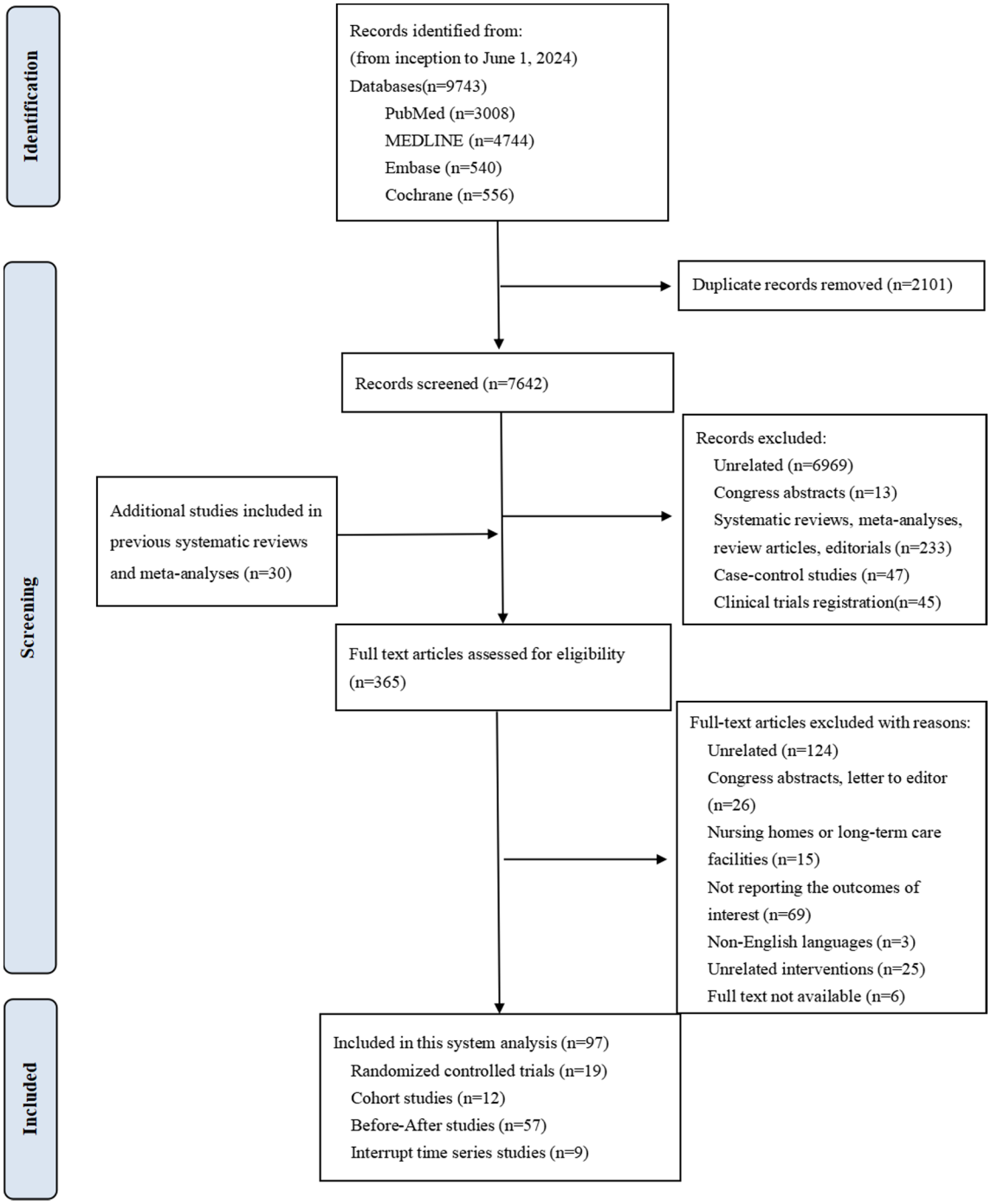

Fig. 1 Flow diagram for study selection

MDROs, the combinations of SP+CHG (RR, 0.67 [0.51, 0.89]) and SP+CP+ASP (RR, 0.33 [0.15,0.76]) demonstrated a positive effect when compared to the control SP. Among the various strategies to prevent the colonization of MDROs, the following combination measures were found to be statistically significant: SP+CHG (RR, 0.61 [0.41, 0.89]), SP+DCL (RR, 0.47 [0.29, 0.74]), SP+CP+CHG (RR, 0.47 [0.24, 0.90]), SP+CP+DCL (RR, 0.33 [0.29, 0.38]), and SP+CP+DCL+CHG (RR, 0.39 [0.25, 0.61]). In addition, the combination measures of SP+CP (RR, 0.55 [0.47, 0.64]), SP+ENV (RR, 0.24 [0.17, 0.32]), SP+ASP (RR, 0.58 [0.37, 0.93]), SP+CP+ENV (RR, 0.17 [0.10, 0.27]), and SP+CHG+DCL (RR, 0.05 [0.01, 0.22]) were all associated with a reduction in infection of MDROs. This study identified significant heterogeneity ($I^2 \geq 75\%$) among

the comparison groups, which exhibited varying outcome measures in the direct comparison meta-analysis (Table S7).

Network meta-analysis

Network evidence maps were created for each outcome measure, and the results indicated that continuous network evidence maps were established between interventions for all outcome measures (Fig. 2, Fig. S9.1 and Fig. S9.2). After testing for global inconsistency and loop inconsistency, all networks demonstrated no global inconsistency or loop inconsistency (Table S8.1-S8.4).

In the network meta-analysis, a total of 78 studies evaluated the effectiveness of 14 different combinations of intervention strategies aimed at preventing the acquisition of MDROs. In the standard analysis, using SP as the control group, CP+CHG (RR, 0.38 [0.18, 0.79]) was the most effective strategy for preventing the acquisition of MDROs, followed by SP+CP+ASP (RR, 0.58 [0.37, 0.92]) (Fig. 3). The studies were categorized into RCT and non-RCT, with the RCT studies not forming a continuous network. Among the non-RCT studies, the four-component intervention SP+CP+CHG+ASP (RR, 0.25 [0.08, 0.77]) was the most effective, and the SP+CP+ASP (RR, 0.41 [0.25,0.69]) strategy was the second most effective (Table S10.1).

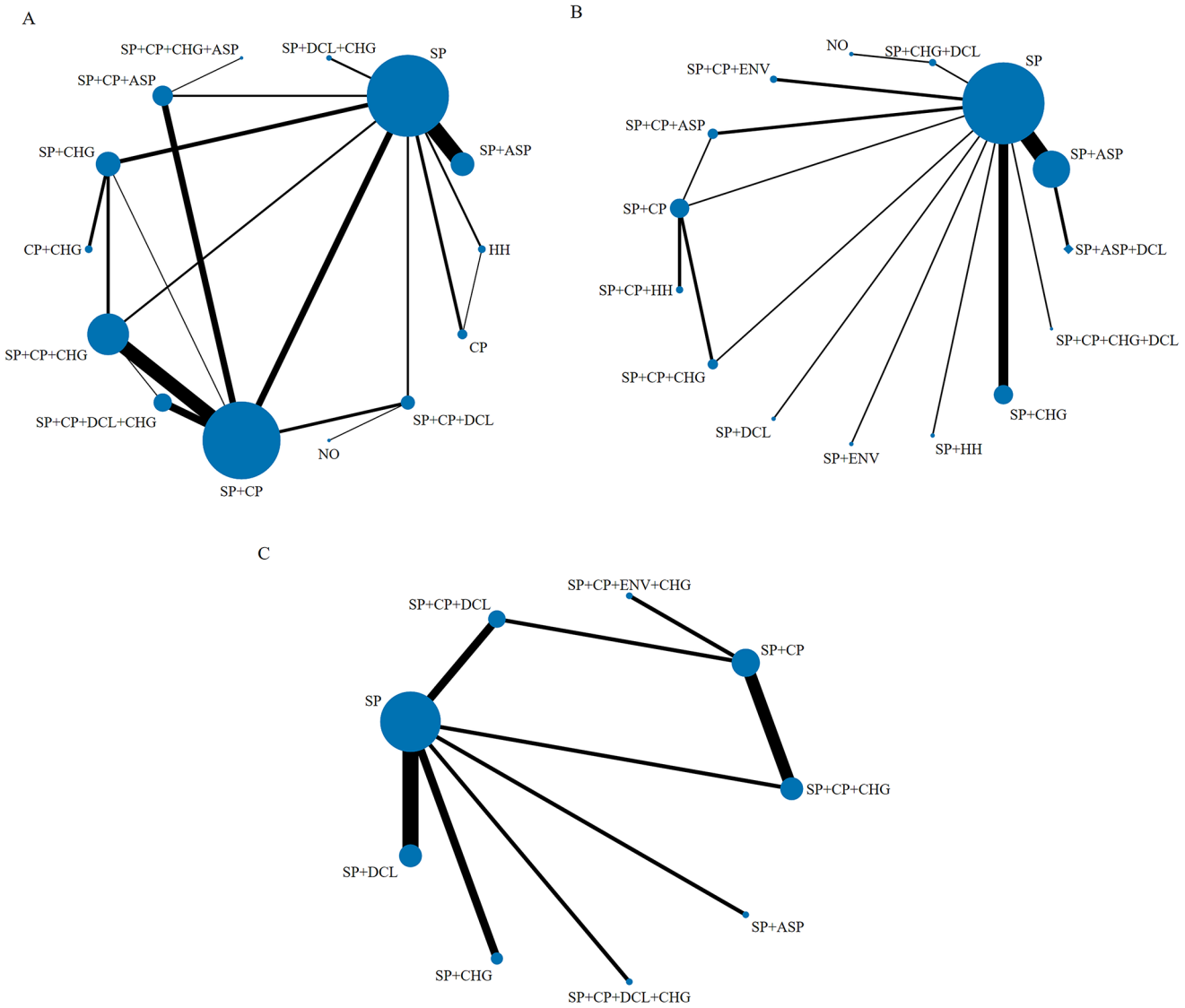

Fig. 2 Network plot of network meta-analyses. **a**, Acquired of multidrug-resistant organism (MDRO). **b**, Infection of MDRO. **c**, Colonization of MDROs. The lines are direct comparisons of the interventions in the study, and the thickness of the lines represents the number of studies. The size of the nodes represents the number of patient days receiving the intervention. Abbreviations: SP=standard precautions. CP=contact precautions. HH=hand hygiene. ENV=environmental cleaning. ASP=antimicrobial stewardship program. DCL=decolonization. CHG=chlorhexidine gluconate baths. NO=no intervention

SP+CP+CHG +ASP	NA	NA	NA	NA	**0.35 (0.26, 0.47)**	NA	NA	NA	NA	NA	NA	NA	NA
3.01 (0.95, 9.48)	SP+CP+DCL+ CHG	NA	0.45 (0.12, 1.63)	NA	NA	NA	NA	NA	0.84 (0.53, 1.32)	NA	NA	NA	NA
2.09 (0.58, 7.54)	0.69 (0.30, 1.63)	SP+DCL+CHG	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	1.19 (0.95, 1.48)
2.47 (0.82, 7.40)	0.82 (0.50, 1.34)	1.18 (0.55, 2.53)	SP+CP+CHG	NA	NA	NA	**1.49 (1.17, 1.91)**	NA	0.79 (0.36, 1.73)	NA	NA	NA	1.38 (0.39, 4.88)
2.72 (0.84, 8.79)	0.90 (0.47, 1.74)	1.30 (0.55, 3.07)	1.10 (0.63, 1.92)	SP+CP+DCL	NA	NA	NA	NA	0.84 (0.67, 1.06)	0.63 (0.28, 1.42)	NA	NA	0.63 (0.20, 1.96)
1.67 (0.62, 4.52)	**0.56 (0.31, 0.98)**	0.80 (0.36, 1.80)	0.68 (0.43, 1.07)	0.61 (0.33, 1.14)	SP+CP+ASP	NA	NA	NA	0.47 (0.22, 1.03)	NA	NA	NA	**0.33 (0.15, 0.76)**
1.08 (0.30, 3.97)	**0.36 (0.15, 0.85)**	0.52 (0.19, 1.41)	**0.44 (0.21, 0.92)**	**0.40 (0.17, 0.96)**	0.65 (0.28, 1.49)	CP+CHG	**1.71 (1.34, 2.18)**	NA	NA	NA	NA	NA	NA
2.06 (0.65, 6.51)	0.69 (0.37, 1.27)	0.99 (0.44, 2.20)	0.84 (0.54, 1.28)	0.76 (0.40, 1.44)	1.23 (0.69, 2.19)	**1.90 (1.04, 3.47)**	SP+CHG	NA	1.09 (0.15, 7.68)	NA	NA	NA	**0.67 (0.51, 0.89)**
2.07 (0.65, 6.51)	0.69 (0.37, 1.29)	0.99 (0.46, 2.11)	0.84 (0.51, 1.38)	0.76 (0.40, 1.43)	1.24 (0.70, 2.19)	1.90 (0.84, 4.32)	1.00 (0.57, 1.75)	SP+ASP	NA	NA	NA	NA	0.92 (0.31, 2.70)
4.17 (1.43, 12.15)	1.39 (0.91, 2.11)	2.00 (0.95, 4.21)	**1.69 (1.29, 2.22)**	1.53 (0.93, 2.53)	**2.50 (1.70, 3.68)**	**3.85 (1.81, 8.18)**	**2.02 (1.28, 3.19)**	**2.02 (1.26, 3.24)**	SP+CP	NA	NA	NA	0.85 (0.34, 2.14)
4.95 (0.82, 29.75)	1.64 (0.36, 7.42)	2.37 (0.48, 11.79)	2.00 (0.46, 8.68)	1.82 (0.47, 7.06)	2.96 (0.67, 13.17)	4.56 (0.90, 23.00)	2.40 (0.53, 10.78)	2.39 (0.54, 10.71)	1.19 (0.28, 5.04)	NO	NA	NA	NA
2.76 (0.75, 10.10)	0.92 (0.38, 2.20)	1.32 (0.50, 3.49)	1.12 (0.51, 2.44)	1.01 (0.42, 2.43)	1.65 (0.72, 3.80)	2.54 (0.92, 7.04)	1.34 (0.59, 3.04)	1.33 (0.61, 2.92)	0.66 (0.31, 1.42)	0.56 (0.11, 2.80)	HH	0.87 (0.42, 1.80)	1.14 (0.54, 2.37)
2.78 (0.80, 9.69)	0.92 (0.41, 2.06)	1.33 (0.54, 3.29)	1.12 (0.56, 2.27)	1.02 (0.46, 2.28)	1.66 (0.78, 3.54)	2.56 (0.98, 6.66)	1.35 (0.64, 2.84)	1.34 (0.67, 2.71)	0.67 (0.34, 1.32)	0.56 (0.12, 2.72)	1.01 (0.46, 2.22)	CP	0.94 (0.57, 1.55)
0.35 (0.12, 1.04)	1.05 (0.62, 1.77)	0.73 (0.37, 1.43)	0.86 (0.61, 1.23)	0.95 (0.56, 1.61)	**0.58 (0.37, 0.92)**	**0.38 (0.18, 0.79)**	0.72 (0.47, 1.11)	0.72 (0.51, 1.02)	**1.46 (1.06, 2.00)**	1.73 (0.40, 7.41)	0.96 (0.48, 1.94)	0.97 (0.53, 1.78)	SP

Fig. 3 Effectiveness values for the comparison of interventions for MDROs acquisition. The results of the network meta-analysis are in the lower left section and the results of the pairwise meta-analysis are in the upper right section. Comparison groups corresponding to effect values are read from left to right (intervention group on the left, control group on the right). Bolded type indicates statistically significant results. Effect values in the grid are rate ratio (RR) and 95% confidence intervals (CI). Abbreviations: SP=standard precautions. CP=contact precautions. HH=hand hygiene. ASP=antimicrobial stewardship program. DCL=decolonization. CHG=chlorhexidine gluconate baths. NO=no intervention. NA=not available

SP+CP+CHG +DCL	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	1.24 (0.61, 2.51)
1.36 (0.37, 5.07)	SP+ASP+DC L	NA	NA	NA	NA	NA	NA	NA	NA	2.07 (0.44, 9.84)	NA	NA	NA	NA
0.41 (0.12, 1.46)	0.30 (0.09, 1.07)	SP+CHG+DC L	NA	NA	NA	NA	NA	NA	NA	NA	NA	1.35 (0.69, 2.63)	**0.05 (0.01, 0.22)**
0.03 (0.01, 0.11)	**0.02 (0.01, 0.08)**	**0.08 (0.03, 0.24)**	SP+CP+ENV	NA	NA	NA	NA	NA	NA	NA	NA	NA	**0.17 (0.10, 0.27)**
0.54 (0.19, 1.55)	0.39 (0.14, 1.14)	1.30 (0.48, 3.52)	16.21 (6.76, 38.84)	SP+CP+CHG	NA	NA	NA	NA	NA	NA	NA	0.25 (0.02, 3.60)	NA	0.66 (0.39, 1.11)
0.38 (0.14, 1.06)	**0.28 (0.10, 0.78)**	0.92 (0.36, 2.40)	11.55 (5.07, 26.31)	0.71 (0.38, 1.33)	SP+CP+ASP	NA	NA	NA	NA	NA	NA	1.02 (0.44, 2.38)	NA	0.15 (0.01, 3.50)
0.29 (0.09, 0.88)	**0.21 (0.07, 0.65)**	0.69 (0.24, 2.01)	8.61 (3.31, 22.35)	**0.53 (0.29, 0.97)**	0.75 (0.36, 1.54)	SP+CP+HH	NA	NA	NA	NA	NA	1.52 (0.15, 15.32)	NA	NA
0.50 (0.16, 1.55)	0.37 (0.12, 1.14)	1.20 (0.41, 3.52)	15.05 (5.77, 39.25)	0.93 (0.41, 2.12)	1.30 (0.60, 2.83)	1.75 (0.70, 4.35)	SP+ENV	NA	NA	NA	NA	NA	NA	**0.24 (0.17, 0.32)**
0.37 (0.07, 2.05)	0.27 (0.05, 1.51)	0.90 (0.17, 4.77)	11.23 (2.27, 55.46)	0.69 (0.15, 3.18)	0.97 (0.22, 4.33)	1.30 (0.27, 6.27)	0.75 (0.15, 3.59)	SP+DCL	NA	NA	NA	NA	NA	0.53 (0.15, 1.95)
0.52 (0.18, 1.54)	0.38 (0.13, 1.13)	1.26 (0.46, 3.50)	15.78 (6.44, 38.69)	0.97 (0.46, 2.07)	1.37 (0.68, 2.75)	1.83 (0.79, 4.28)	1.05 (0.45, 2.46)	1.41 (0.30, 6.53)	SP+CHG	NA	NA	NA	NA	0.63 (0.38, 1.03)
0.64 (0.24, 1.72)	0.47 (0.20, 1.10)	1.54 (0.61, 3.89)	19.21 (8.70, 42.42)	1.19 (0.63, 2.22)	1.66 (0.95, 2.90)	2.23 (1.07, 4.65)	1.28 (0.61, 2.68)	1.71 (0.39, 7.50)	1.22 (0.63, 2.35)	SP+ASP	NA	NA	NA	**0.58 (0.37, 0.93)**
0.23 (0.03, 1.54)	0.17 (0.02, 1.13)	0.55 (0.08, 3.59)	6.87 (1.12, 42.16)	0.42 (0.07, 2.44)	0.59 (0.11, 3.34)	0.80 (0.13, 4.78)	0.46 (0.08, 2.74)	0.61 (0.07, 5.53)	0.44 (0.07, 2.53)	0.36 (0.06, 1.98)	SP+HH	NA	NA	0.27 (0.06, 1.30)
0.61 (0.22, 1.72)	0.45 (0.16, 1.26)	1.48 (0.56, 3.90)	18.47 (7.96, 42.86)	1.14 (0.77, 1.69)	1.60 (0.91, 2.82)	2.15 (1.37, 3.36)	1.23 (0.55, 2.71)	1.64 (0.37, 7.40)	1.17 (0.57, 2.40)	0.96 (0.54, 1.72)	2.69 (0.48, 15.22)	SP+CP	NA	**0.55 (0.47, 0.64)**
1.17 (0.25, 5.45)	0.86 (0.18, 4.00)	2.82 (1.17, 6.81)	35.24 (8.54, 145.41)	2.17 (0.57, 8.24)	3.05 (0.83, 11.20)	4.09 (1.02, 16.38)	2.34 (0.58, 9.39)	3.14 (0.48, 20.73)	2.23 (0.58, 8.59)	1.83 (0.51, 6.60)	5.13 (0.64, 40.87)	1.91 (0.51, 7.08)	NO	NA
1.21 (0.48, 3.07)	1.66 (0.65, 4.20)	0.50 (0.21, 1.18)	**0.04 (0.02, 0.08)**	0.65 (0.39, 1.09)	**0.47 (0.30, 0.71)**	**0.35 (0.18, 0.66)**	0.61 (0.32, 1.16)	0.45 (0.11, 1.90)	0.64 (0.37, 1.10)	0.77 (0.54, 1.11)	0.28 (0.05, 1.47)	0.74 (0.47, 1.18)	1.42 (0.42, 4.85)	SP

Fig. 4 Effectiveness values for the comparison of interventions for MDROs infection. The results of the network meta-analysis are in the lower left section and the results of the pairwise meta-analysis are in the upper right section. Comparison groups corresponding to effect values are read from left to right (intervention group on the left, control group on the right). Bolded type indicates statistically significant results. Effect values in the grid are rate ratio (RR) and 95% confidence intervals (CI). Abbreviations: SP=standard precautions. CP=contact precautions. HH=hand hygiene. ENV=environmental cleaning. ASP=antimicrobial stewardship program. DCL=decolonization. CHG=chlorhexidine gluconate baths. NO=no intervention. NA=not available

A total of 35 studies evaluated the effectiveness of 15 different combinations of interventions in preventing the infection of MDROs. In the standardized analysis, SP+CP+ENV (RR, 0.04 [0.02, 0.08]) was found to be the best intervention using SP as the control group, followed by SP+CP+HH (RR, 0.35 [0.18, 0.66]) and SP+CP+ASP (RR, 0.47 [0.30, 0.71]). No other combinations yielded statistically significant results (Fig. 4). When the analysis was restricted to non-RCTs, the findings remained consistent (Table S10.2).

A total of 16 studies evaluated the efficacy of six different combinations of interventions for the colonization of MDROs. In standardized analyses, it was found that SP+CHG (RR, 0.28 [0.14, 0.56]) achieved the most

significant intervention effect. This was followed by SP+CP+CHG (RR, 0.34 [0.15, 0.74]), SP+CP+DCL (RR, 0.37 [0.20, 0.68]), and SP+DCL (RR, 0.49 [0.29, 0.81]) (Fig. 5). When restricting the analysis to RCTs it was found that SP+CP+DCL+CHG (RR, 0.39 [0.17, 0.87]) had the best intervention effect, followed by SP+DCL (RR, 0.45 [0.29, 0.72]). Non-RCT studies did not form a continuous network (Table S10.3).

Subgroup analysis

The implementation of interventions was restricted to ICU wards, the most effective strategies for preventing the acquisition, infection, and colonization of MDROs unchanged compared to the standard analysis. The most effective intervention for the acquisition of MDROs was CP+CHG (RR, 0.36 [0.20, 0.64]), followed by SP+CP+CHG+ASP (RR, 0.46 [0.21, 0.98]), and SP+ASP (RR, 0.67 [0.47, 0.95]). The strategy associated with reduced MDROs infection was SP+CP+ENV (RR, 0.09 [0.01,0.99]). Statistical analysis revealed that SP+CHG and SP+DCL were associated with a statistically significant difference in the reduction of MDROs colonization (Tables 1, 2 and 3). Effective interventions to prevent the acquisition, infection, and colonization of MDROs were changed by restricting the study to the whole hospital setting. Only SP+CP+ASP (RR, 0.35 [0.14, 0.92]) was significantly associated with a reduced acquisition of MDROs. The most effective intervention for reducing the colonization of MDROs was SP+CP+ENV+CHG (RR, 0.15 [0.06,0.38]). The most effective intervention for reducing the infection of MDROs was unchanged and remained SP+CP+ENV (RR, 0.04 [0.02,0.06]). In addition, there was an increase in the number of combination interventions that were effective in reducing the MDROs infection and colonization, the details of which are shown in Tables 1, 2 and 3.

Subgroup analysis was conducted based on various resistant strains, some of which did not form a continuous network. SP+CP+ASP (RR, 0.43 [0.24, 0.74]) was the most effective intervention for reducing MRSA acquisition. Other effective interventions included SP+CHG (RR, 0.63 [0.46, 0.86]), SP+CP+DCL+CHG (RR, 0.71 [0.51, 0.99]), and SP+CP+CHG (RR, 0.78 [0.63, 0.96]). However, no interventions were shown to be effective in reducing VRE and CRE acquisition. SP+CP+ENV was an effective intervention for preventing MRSA (RR, 0.04 [0.02, 0.06]), as well as for MDR-AB and MDR-PA infection (RR, 0.09 [0.01, 0.81]). In colonization with drug-resistant bacteria, only the SP+CP+DCL intervention (RR, 0.28 [0.24, 0.32]) was effective in reducing CRE. For specific information, see S12.6 (Fig. 6).

Secondary outcomes

24 studies evaluated the effectiveness of interventions in reducing all-cause mortality, while 12 studies focused on the reduction of MDROs-associated bacteremia. The findings were not statistically significant in either the standard analysis or the non-RCT studies (Table S12.1, Table S12.2).

SP+CP+ENV +CHG	NA	NA	NA	NA	NA	NA	0.49 (0.22, 1.09)	NA
1.42 (0.26, 7.87)	SP+CP+DCL+ CHG	NA	NA	NA	NA	NA	NA	**0.39 (0.25, 0.61)**
1.36 (0.35, 5.23)	0.95 (0.30, 3.05)	SP+CP+DCL	NA	NA	NA	NA	0.94 (0.75, 1.17)	**0.33 (0.29, 0.38)**
1.23 (0.35, 4.31)	0.87 (0.24, 3.08)	0.91 (0.41, 1.99)	SP+CP+CHG	NA	NA	NA	0.44 (0.07, 2.75)	**0.47 (0.24, 0.90)**
1.04 (0.22, 4.92)	0.73 (0.22, 2.45)	0.77 (0.31, 1.91)	0.84 (0.30, 2.40)	SP+CHG	NA	NA	NA	**0.61 (0.41, 0.89)**
1.78 (0.40, 7.82)	1.25 (0.41, 3.83)	1.31 (0.59, 2.88)	1.44 (0.56, 3.68)	1.70 (0.72, 4.01)	SP+DCL	NA	NA	**0.47 (0.29, 0.74)**
4.15 (0.79, 21.79)	2.92 (0.76, 11.15)	3.06 (1.04, 9.02)	3.36 (1.02, 11.12)	3.98 (1.29, 12.32)	2.34 (0.83, 6.60)	SP+ASP	NA	1.00 (0.65, 1.56)
1.99 (0.64, 6.19)	1.40 (0.39, 5.04)	1.47 (0.71, 3.04)	1.61 (0.95, 2.73)	1.91 (0.66, 5.51)	1.12 (0.43, 2.91)	0.48 (0.14, 1.61)	SP+CP	NA
0.27 (0.07, 1.10)	0.39 (0.14, 1.05)	**0.37 (0.20, 0.68)**	**0.34 (0.15, 0.74)**	**0.28 (0.14, 0.56)**	**0.49 (0.29, 0.81)**	1.13 (0.46, 2.79)	0.54 (0.24, 1.22)	SP

Fig. 5 Effectiveness values for the comparison of interventions for MDROs colonization. The results of the network meta-analysis are in the lower left section and the results of the pairwise meta-analysis are in the upper right section. Comparison groups corresponding to effect values are read from left to right (intervention group on the left, control group on the right). Bolded type indicates statistically significant results. Effect values in the grid are rate ratio (RR) and 95% confidence intervals (CI). Abbreviations: SP=standard precautions. CP=contact precautions. HH=hand hygiene. ENV=environmental cleaning. ASP=antimicrobial stewardship program. DCL=decolonization. CHG=chlorhexidine gluconate baths. NA=not available

Table 1 Summary of results from network meta-analysis of prevention of MDROs acquisition in different settings, RR (95% CI)

Intervention	Standard analysis (RCT & non-RCT)	SUCRA (%)	Mean rank	ICU	SUCRA (%)	Mean rank	Whole hospital	SUCRA (%)	Mean rank
SP+CP+CHG+ASP	0.35 (0.12,1.04)	90.3	2	**0.46 (0.21,0.98)**	**89.3**	**2**	NA	NA	NA
SP+CP+DCL+CHG	1.05 (0.62,1.77)	30.3	10	1.01 (0.64,1.60)	36.1	9	0.62 (0.15,2.53)	62.2	4
SP+DCL+CHG	0.73 (0.37,1.43)	59.4	6	NA	NA	NA	0.73 (0.27,1.93)	55.2	5
SP+CP+CHG	0.86 (0.61,1.23)	47.2	8	0.76 (0.55,1.06)	63.8	5	1.03 (0.44,2.44)	34.8	7
SP+CP+DCL	0.95 (0.56,1.61)	39.1	0	1.12 (0.64,1.96)	29.7	9	0.77 (0.31,1.91)	52.2	5
SP+CP+ASP	**0.58 (0.37,0.92)**	**77.7**	**4**	0.76 (0.50,1.16)	62.3	6	**0.35 (0.14,0.92)**	**87.5**	**2**
CP+CHG	**0.38 (0.18,0.79)**	**91.5**	**2**	**0.36 (0.20,0.64)**	**96.7**	**1**	NA	NA	NA
SP+CHG	0.72 (0.47,1.11)	62.9	6	0.68 (0.45,1.03)	71.4	4	0.69 (0.28,1.69)	58.7	5
SP+ASP	0.72 (0.51,1.02)	63.7	6	**0.67 (0.47,0.95)**	**73.3**	**4**	0.89 (0.40,1.98)	44.7	6
SP+CP	1.46 (1.06,2.00)	7.7	13	1.31 (0.94,1.83)	14.0	11	1.69 (0.92,3.11)	7.2	9
NO	1.73 (0.40,7.41)	18.5	12	2.03 (0.58,7.10)	10.5	12	NA	NA	NA
HH	0.96 (0.48,1.94)	40.2	9	0.98 (0.58,1.66)	39.2	8	NA	NA	NA
CP	0.97 (0.53,1.78)	38.8	9	1.17 (0.69,1.98)	27.0	10	0.61 (0.13,2.77)	62.1	4
SP	reference	32.8	10	reference	36.6	9	reference	35.4	7
Overall inconsistency	10.02			5.14			2.78		
Chi-square (p value)	0.1873			0.3996			0.7331		
Number of studies	78			55			23		

Notes The effect values in the table are the combined effect values for the direct and indirect comparisons. Bolded type indicates statistically significant results. A p-value greater than 0.05 represents overall consistency

Abbreviations: MDROs=multidrug-resistant organisms. SP=standard precautions. CP=contact precautions. HH=hand hygiene. ASP=antimicrobial stewardship program. DCL=decolonization. CHG=chlorhexidine gluconate baths. ENV=environmental cleaning. NO=no intervention. NA=not available. RR=relative risk. CI=confidence interval. SUCRA=surface under the cumulative ranking. ICU=intensive care unit

Table 2 Summary of results from network meta-analysis of prevention of MDROs infection in different settings, RR (95% CI)

Intervention	Standard analysis (RCT & non-RCT)	SUCRA (%)	Mean rank	ICU	SUCRA (%)	Mean rank	Whole hospital	SUCRA (%)	Mean rank
SP+CP+CHG+DCL	1.21 (0.48,3.07)	19.3	12	1.21 (0.27,5.53)	30.0	7	NA	NA	NA
SP+ASP+DCL	1.66 (0.65,4.20)	9.2	14	1.48 (0.38,5.80)	22.6	8	NA	NA	NA
SP+CHG+DCL	0.50 (0.21,1.18)	63.6	6	0.50 (0.12,2.20)	64.2	4	NA	NA	NA
SP+CP+ENV	**0.04 (0.02,0.08)**	**99.9**	**1**	**0.09 (0.01,0.99)**	**94.2**	**2**	**0.04 (0.02,0.06)**	**99.9**	**1**
SP+CP+CHG	0.65 (0.39,1.09)	49.1	8	NA	NA	NA	**0.66 (0.54,0.81)**	**38.1**	**7**
SP+CP+ASP	**0.47 (0.30,0.71)**	**69.0**	**5**	0.67 (0.17,2.66)	54.1	5	**0.32 (0.26,0.38)**	**79.2**	**4**
SP+CP+HH	**0.35 (0.18,0.66)**	**80.1**	**4**	NA	NA	NA	**0.37 (0.28,0.48)**	**69.7**	**4**
SP+ENV	0.61 (0.32,1.16)	53.3	8	NA	NA	NA	**0.61 (0.45,0.82)**	**43.4**	**6**
SP+DCL	0.45 (0.11,1.90)	63.9	6	0.45 (0.07,2.93)	65.1	4	NA	NA	NA
SP+CHG	0.64 (0.37,1.10)	50.6	8	0.70 (0.27,1.84)	53.1	5	0.49 (0.23,1.04)	53.1	5
SP+ASP	0.77 (0.54,1.11)	38.2	10	0.67 (0.36,1.28)	56.0	5	0.80 (0.49,1.29)	23.3	8
SP+HH	0.28 (0.05,1.47)	77.4	4	NA	NA	NA	0.28 (0.06,1.33)	70.5	4
SP+CP	0.74 (0.47,1.18)	39.7	9	NA	NA	NA	**0.79 (0.65,0.96)**	**19.7**	**8**
NO	1.42 (0.42,4.85)	16.6	13	1.42(0.17,11.54)	27.5	8	NA	NA	NA
SP	reference	20.2	12	reference	32.8	7	reference	3.1	10
Overall inconsistency	1.09			1.63			5.26		
Chi-square (p value)	0.5787			0.2014			0.0721		
Number of studies	35			20			15		

Notes: The effect values in the table are the combined effect values for the direct and indirect comparisons. Bolded type indicates statistically significant results. A p-value greater than 0.05 represents overall consistency

Abbreviations: MDROs=multidrug-resistant organisms. SP=standard precautions. CP=contact precautions. HH=hand hygiene. ASP=antimicrobial stewardship program. DCL=decolonization. CHG=chlorhexidine gluconate baths. ENV=environmental cleaning. NO=no intervention. NA=not available. RR=relative risk. CI=confidence interval. SUCRA=surface under the cumulative ranking. ICU=intensive care unit

Table 3 Summary of results from network meta-analysis of prevention of MDROs colonization in different settings, RR (95% CI)

Intervention	Standard analysis (RCT & non-RCT)	SUCRA (%)	Mean rank	ICU	SUCRA (%)	Mean rank	Whole hospital	SUCRA (%)	Mean rank
SP+CP+ENV+CHG	0.27 (0.07,1.10)	76.3	3	NA	NA	NA	**0.15 (0.06,0.38)**	**95.8**	**1**
SP+CP+DCL+CHG	0.39 (0.14,1.05)	58.8	4	NA	NA	NA	**0.39 (0.21,0.73)**	**44.8**	**4**
SP+CP+DCL	**0.37 (0.20,0.68)**	**63.7**	**4**	NA	NA	NA	**0.28 (0.24,0.32)**	**71.0**	**3**
SP+CP+CHG	**0.34 (0.15,0.74)**	**70.8**	**3**	0.53 (0.27,1.04)	64.8	3	**0.31 (0.18,0.56)**	**57.5**	**4**
SP+CHG	**0.28 (0.14,0.56)**	**78.1**	**3**	**0.28 (0.19,0.43)**	**96.7**	**1**	NA	NA	NA
SP+DCL	**0.49 (0.29,0.81)**	**46.8**	**5**	**0.40 (0.28,0.58)**	**77.0**	**2**	0.76 (0.37,1.56)	15.1	6
SP+ASP	1.13 (0.46,2.79)	9.1	8	1.13 (0.72,1.80)	20.3	5	NA	NA	NA
SP+CP	0.54 (0.24,1.22)	37.0	6	1.51 (0.67,3.43)	9.5	6	**0.30 (0.20,0.45)**	**61.8**	**3**
SP	reference	9.4	8	reference	31.7	4	reference	4.1	7
Overall inconsistency	1.97			no source of inconsistency			2.65		
Chi-square (p value)	0.1606						0.1037		
Number of studies	16			9			7		

Notes: The effect values in the table are the combined effect values for the direct and indirect comparisons. Bolded type indicates statistically significant results. A p-value greater than 0.05 represents overall consistency

Abbreviations: MDROs = multidrug-resistant organisms. SP = standard precautions. CP = contact precautions. HH = hand hygiene. ASP = antimicrobial stewardship program. DCL = decolonization. CHG = chlorhexidine gluconate baths. ENV = environmental cleaning. NA = not available. RR = relative risk. CI = confidence interval. SUCRA = surface under the cumulative ranking. ICU = intensive care unit

Sensitivity analysis and publication bias

Sensitivity analyses that excluded studies with a high risk of bias and those focused on specialty wards indicated that the most effective interventions for reducing MDROs acquisition, infections and colonization, as well as the SUCRA ranks of these interventions, remained unchanged. For the acquired MDROs outcome, the combinations of SP+CP+CHG+ASP and SP+CP+ASP were not statistically significant after excluding studies with a high risk of bias. However, CP+CHG remained the most effective intervention (Table S13.1-S13.3). Therefore, the results of this study are robust. The corrected comparative funnel plots for the various outcome metrics were generated, revealing that the plots exhibited approximately symmetrical shapes, indicating a low level of publication bias (Fig. S14.1-S14.3).

Discussion

Our research has found that the optimal interventions to reduce the acquisition, infection, and colonization of MDROs vary within the hospital setting. These interventions must be tailored according to the specific intervention implemented and the type of resistant strain involved.

Our study found that the combined strategies of CP+CHG and SP+CP+ASP significantly reduced the acquisition of MDROs. However, in subgroup analyses, the combination of SP+CP+ASP was the most effective strategy for reducing the acquisition of MRSA, as well as the acquisition of MDROs throughout the hospital setting. DCL and CHG were among the more commonly used components of the combined measures aimed at reducing MRSA acquisition or infection. Adding CHG or DCL measures to SP or SP+CP can effectively reduce the colonization of MDROs. However, the combination of SP+CP+ENV+CHG is the most effective strategy for preventing MDROs colonization in the entire hospital setting. It is important to note that while there are numerous interventions available for controlling MDROs infections, the SP+CP+ENV combination consistently proves to be the most effective. In our study, most of the effective combinations of interventions were based on SP or SP+CP as the base intervention to which other interventions were added thereby producing better results in the prevention and control of MDROs. CP, as an additional intervention, is not universally implemented across all healthcare settings [14]. However, a 2022 recommendation regarding the prevention of MRSA transmission and infection in acute care hospitals identifies CP as an essential practice for preventing healthcare-associated MRSA infections and mandates its implementation in all acute care facilities [15]. The study conducted by Diekema DJ et al. [16] concluded that the application of CP to all patients with MRSA colonization or infection is not supported by the available evidence and may lead to negative consequences. In addition, the U.S. Department of Veterans Affairs (VA) healthcare system has effectively controlled the spread of MRSA with a combination of interventions [17], with CP being one of these interventions. This study demonstrated through subsequent analysis that hand hygiene reinforcement is the primary driver of the multi-component combination intervention. Therefore, there is no clear and definitive conclusion regarding the effectiveness of CP interventions. However, it is more common to employ a combination of strategies, including CP, to control the spread of MDROs in the ICU setting [18, 19]. Because the ICU environment

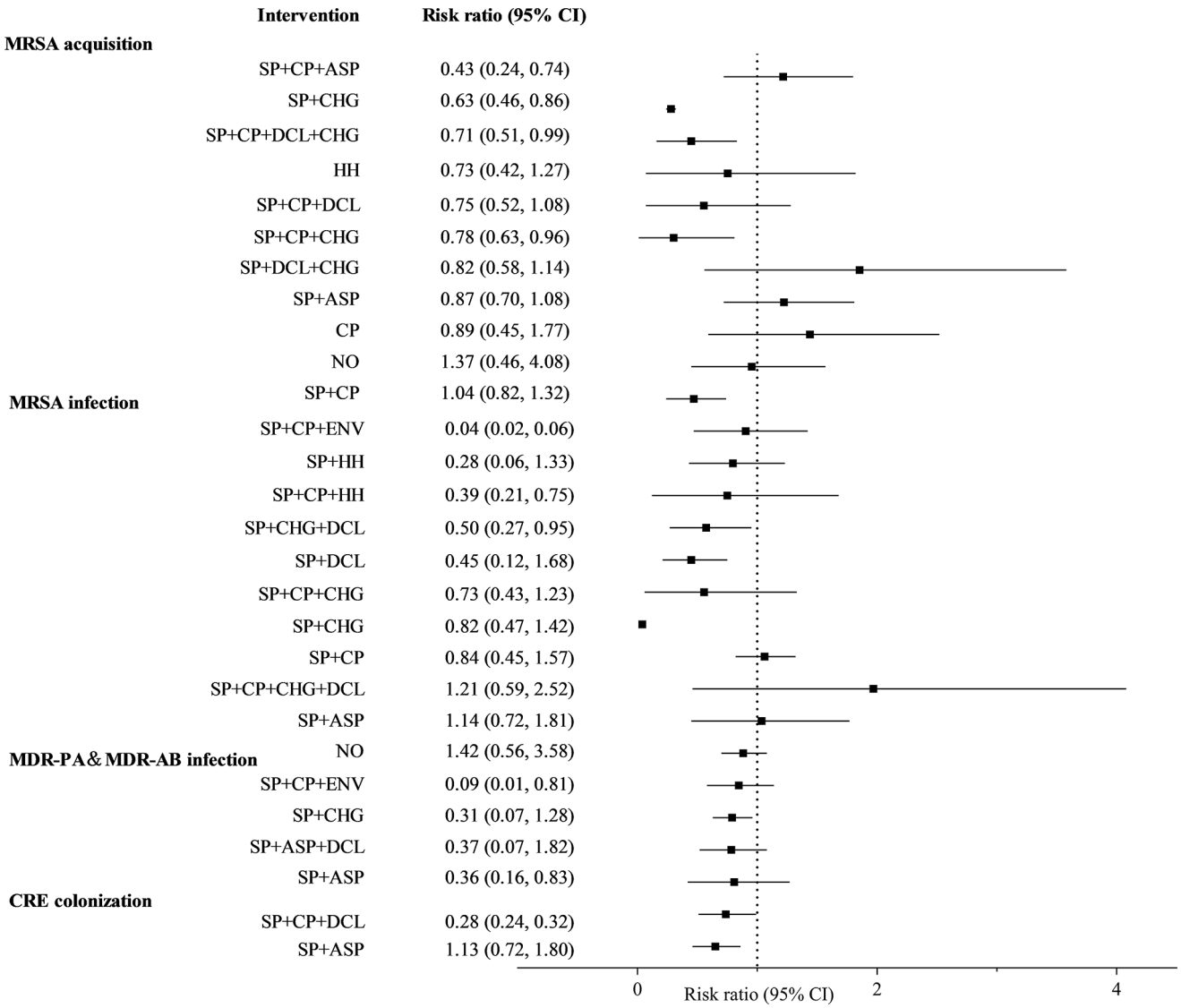

Fig. 6 Results of network meta-analysis for different drug-resistant strains of bacteria. Intervention strategies are ranked according to their surface under the curve cumulative ranking and compared with standard precaution. Effect sizes are presented as risk ratio (RR) with 95% confidence intervals (CI). A combined effect value of less than 1 was favorable for the intervention group measure. Abbreviations: Methicillin-resistant Staphylococcus aureus (MRSA). Multidrug-resistant Acinetobacter baumannii (MDR-AB) and Multidrug-resistant Pseudomonas aeruginosa (MDR-PA). Carbapenem-resistant Enterobacteriaceae (CRE). SP = standard precautions. CP = contact precautions. HH = hand hygiene. ENV = environmental cleaning. ASP = antimicrobial stewardship program. DCL = decolonization. CHG = chlorhexidine gluconate baths. NO = no intervention

is characterized by a higher concentration of critically ill patients, who are often immunocompromised and more susceptible to frequent pathogen exposure, the implementation of control measures is more feasible, and patient compliance tends to be higher [20, 21]. In our study, among all the effective measures to prevent and control the acquisition and infection of MDROs in the ICU setting, CP were included as part of the combined strategies. Further research is necessary to evaluate the effectiveness of CP within these combination measures.

Contaminated surfaces have long been recognized as reservoirs of pathogens that can be transmitted to patients either directly or indirectly through the hands of healthcare workers [22, 23]. Drug-resistant bacteria, such as MRSA, VRE, and MDR-AB, are capable of surviving in dry and rapidly changing environments due to their high resilience, making these environments excellent vectors for transmission. A study conducted by Paul Andrew Watson et al. [24] showed that enhanced hospital-wide disinfection, combined with the targeted isolation of infected patients, led to a 93% reduction in the rate of MRSA infections. A previous

systematic review highlighted various aspects of the positive impact of enhanced environmental cleaning and disinfection on infections or colonization by MRSA, VRE, and Gram-negative drug-resistant bacteria [25]. This is similar to our findings, where the addition of ENV to SP+CP effectively reduced the occurrence of MDROs infections in our meta-analysis.

As a highly drug-resistant and therapeutically complex pathogen, MRSA possesses a significant ability to survive in the environment, which can lead to widespread transmission or even outbreaks through frequent contact. Therefore, it is essential to prevent MRSA infections at an early stage [26, 27]. DCL and CHG can effectively eliminate pathogens at an early stage and minimize their spread, thereby reducing invasive harm to the body. Studies have shown that CHG can effectively reduce the incidence of MDROs, particularly MRSA. However, the effectiveness of CHG is still depends on patient compliance [28, 29]. A four-year ecological study examining the relationship between DCL and antibiotic resistance showed that consistent use of DCL measures was significantly associated with a reduction in antibiotic resistance [30]. In our study, the combination strategy of adding DCL or CHG to SP or SP+CP demonstrated a positive effect on the acquisition and infection of MRSA.

Our study incorporated IPC commonly used in hospital settings, as well as prevalent drug-resistant strains. In comparison to previous meta-analyses, we addressed a broader spectrum of topics that can inform the development of infection prevention and control measures across various healthcare settings. However, this study has several limitations. First, the interventions were primarily evaluated in bundles to assess their overall effects, which presents limitations when evaluating the impact of implementing a specific intervention in isolation. Second, the original studies included in this meta-analysis exhibited a significant risk of bias. The study subjects were not randomly assigned to groups, and there were notable differences in population characteristics. Interventions cannot be blinded, and participants were aware that the intervention they received might differ from the established protocol, which could influence their adherence to the intervention. Most of the original studies did not employ analytical methods to account for bias. Third, the heterogeneity among the studies was relatively high, and this significant heterogeneity may be caused by different intervention strains, different scope of intervention or different duration of intervention. Finally, the absence of raw data to assess adherence to interventions can impact the results of the study.

Conclusions

In conclusion, our network meta-analysis suggests that effective interventions for the acquisition, infection, and colonization of MDROs differ. Additionally, the effectiveness of combination interventions varied across different settings and resistant strains. DCL and CHG are the most common intervention components for the prevention and control of MRSA acquisition and infection. In addition, contact precautions served as the foundational intervention in the combination of measures implemented in our study. Healthcare organizations can select appropriate interventions based on their unique resistance profiles to optimize precision and resource efficiency.

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Author contributions PL obtains funding and manages the project. PL and YG contributed to the study design. ZL, JD, PZ and CC retrieved and screened the literature. PL and YG established the database, while XM and TP extracted the data. DP and MC conducted quality control. YG and YZ performed the statistical analysis, and YG wrote the manuscript. All authors critically reviewed, revised the manuscript, and approved the final submitted version. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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