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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-051983
Article Type:	Original research
Date Submitted by the Author:	04-Apr-2021
Complete List of Authors:	Okeah, Bernard; Bangor University Morrison, Valerie; Bangor University, School of Psychology Huws, Jaci; Bangor University, School of Health Sciences
Keywords:	PUBLIC HEALTH, Infection control < INFECTIOUS DISEASES, MICROBIOLOGY, PREVENTIVE MEDICINE, EPIDEMIOLOGY

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Antimicrobial stewardship and infection prevention interventions targeting healthcare associated *Clostridioides difficile* and carbapenem-resistant *Klebsiella pneumoniae* infections: A scoping review.

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(Word count: 5027 words)

Antimicrobial resistance and mitigation strategies in healthcare settings

Abstract

Objectives: This study mapped out antimicrobial stewardship and infection prevention interventions targeting healthcare associated *Clostridioides difficile* and carbapenem-resistant *Klebsiella pneumoniae* (CRKP) infections, their key outcomes, and assessed the application of behavioural theory in such interventions.

Design: This scoping review was conducted in accordance with PRISMA Extension for Scoping Reviews (PRISMA-ScR) guidelines with a focus on acute healthcare settings in both low-to-middle income and high-income countries.

Data sources: The databases searched include MEDLINE, PubMed, Web of Science, and CINAHL between 22/04/2020 and 06/05/2020 and updated on 30/09/2020.

Eligibility: The review included peer reviewed articles published in English language between 2010 and 2019. Studies that focussed on infection prevention and/ or antimicrobial stewardship interventions primarily targeting *C. difficile* or carbapenem-resistant *Klebsiella pneumoniae* were included. Studies that assessed effectiveness of diagnostic devices or treatment options were excluded from this review.

Data extraction and synthesis: An abstraction sheet calibrated for this study was used to extract data on the main study characteristics including the population, intervention, and outcomes of interest (antimicrobial use, compliance with IP interventions, and risk for *C. difficile* and CRKP). A narrative synthesis of the results is provided.

Results: The review included 34 studies. The interventions targeting *Clostridioides difficile* and *Klebsiella pneumoniae* include **E**ducation, **S**urveillance/**S**creening, **C**onsultations, **A**udits, **P**olicies and **P**rotocols, **E**nvironmental measures, **B**undles, **I**solation, as well as **N**otifications or alerts (ESCAPE-BIN). The identified outcomes include antimicrobial use, resistance rates, risk reduction, adherence to contact precautions, hospital stay, and time savings. The included studies appeared to lack details on the application and/ or outcomes of behaviour change approaches in AMR and IP interventions.

Conclusion: This scoping review identified the AMR and IP interventions targeting *Clostridioides difficile* and CRKP in healthcare settings and described their key outcomes. There was no sufficient evidence to determine the extent to which current evidence on behaviour change has been applied in the targeted AMR and IP interventions.

Key words: Antimicrobial, antibiotics, resistance, Clostridioides difficile, carbapenem-resistant Klebsiella pneumoniae, healthcare associated infections, infection prevention.

Ethics statement: Permission to conduct this review was granted by Bangor University's Research and Ethics Committee since prior ethical approval was not required.

Strengths and limitations

- This review considered the specific AMS and IP interventions in line with the core elements of AMS as outlined by the CDC.
- The review only considered studies that primarily focussed on AMS and/ or IP interventions targeting *C. difficile* and/ or CRKP.
- The screening and selection of studies as well as data extraction were completed by two reviewers.
- The COM-B ("capability", "opportunity", "motivation", and "behaviour") model elements were used to assess the application of behaviour change approaches in AMS and IP interventions.

Introduction

Over the past centuries, infectious diseases have claimed millions of lives presenting a real threat to human existence [1]. The discovery of antimicrobial agents during the 19th and 20th century reduced the morbidity and mortality associated with infections [2] following observations of Alexander Fleming on the effect of *Penicillium* on bacteria cultures that birthed the era of anti-infective agents [3]. In 1947, Waksman, coined the term "antibiotic" in reference to a chemical agent capable of destroying or inhibiting the growth of microorganisms [4]. Subsequently, clinicians began to recognise and employ antibiotics as an effective strategy for treating and eradicating pathogenic microorganisms. As the use of antibiotics gained popularity worldwide with noted successes including the treatment of gram positive cocci with penicillin [3], [5], a new threat namely antimicrobial resistance, emerged due to the over-reliance on these life-saving therapeutic agents [6]. More than 50% of antimicrobials used are either inappropriate or unnecessary and within the last two decades alone, the use of antimicrobial agents has risen by 65% significantly contributing to antimicrobial resistance (AMR) [7]. Coupled with the rapid human-to-human transmission of pathogens [8], microorganisms continue to evolve adaptively rendering antibiotics ineffective [9]–[11] and causing more potent infections as they acquire resistance. AMR represents a public health emergency with 10 million fatalities globally projected by 2050 [12] coupled with increasing costs for treating multi-drug resistant organisms (MDROs) [13].

Today, infectious diseases remain top on the leading causes of death globally [14] with a worrying increase of deaths attributable to MDROs. A modelling study reported 33,000 deaths associated with MDROs in Europe in 2015, representing a significant rise since 2007 [15]. Healthcare settings appear to have a higher risk of human-to-human transmission of MDROs. According to the European Center for Disease Prevention and Control (ECDC), the EU records an estimated 3.2 million healthcare associated infections (HAIs) and an associated 37,000 deaths annually [16]. This translates to 2.5 million disability adjusted life years (DALYs), 16 million additional hospitalization days, and an annual economic burden of 7 billion euros [17], [18]. This burden is largely attributed to MDROs [19] of which ESKAPE (***E**nterococcus faecium, **S**taphylococcus aureus, **K**lebsiella pneumoniae, **A**cinetobacter baumannii, **P**seudomonas aeruginosa, and **E**nterobacter spp)* pathogens play a significant role [20]–[23]. In recent years, scientists have suggested the inclusion of *Clostridioides (Clostridium) difficile* as a member of the ESKAPE pathogens and subsequently amending the acronym to **ESCAPE** pathogens [24]. Significant efforts have been made to reduce the burden of healthcare associated infections, but the problem persists. To aid the understanding of potential gaps in evidence, this scoping review mapped literature on interventions targeting *Clostridioides difficile* and carbapenem-resistant *Klebsiella pneumoniae* (CRKP) which are amongst the commonest in healthcare settings and on the WHO's pathogen priority list for research and development of new antibiotics.

Rationale

A preliminary exploration of literature retrieved three scoping reviews on antimicrobial misuse and interventions to address AMR. The first scoping review [25] was limited to dentistry settings; the second [26] examined literature on knowledge, attitudes, and practices amongst community pharmacists and the third focussed on supply related factors for reducing prescription of antibiotics in low-to-middle-income countries [27]. In this scoping review, the focus is on healthcare associated *Clostridioides difficile* and CRKP infections. *Clostridioides difficile* is the single most leading cause of nosocomial diarrhea globally primarily linked with the use of antibiotics that disrupt the stability of gut microbiota allowing the pathogenic bacteria to flourish [28]–[30]. On the other hand, *Klebsiella pneumoniae* also ranks amongst the top three leading causes of neonatal sepsis in resource

limited settings [31], [32] with some strains known to produce extended-spectrum B-lactamases (ESBL) associated with multi-drug resistance to carbapenems and colistin [33]. More often, cultures obtained from patient environments, stools, water, and blood have been shown to contain *Klebsiella pneumoniae* [33] and *Clostridioides difficile.* Studies show that approximately 25% of patients in England, Australia, and the United States of America get colonized by CRKP during their hospitalization period [33]–[35]. Patient-to-patient transmission of CRKP accounts for an estimated 52% of the cases identified in healthcare settings [36]. There appears to be evidence-based infection prevention (IP) and antimicrobial stewardship (AMS) interventions aimed at curbing the healthcare associated transmission of *C. difficile* and CRKP. However, the prevalence of infections caused by these organisms remains high. The interventions broadly aim at changing the behaviours of healthcare workers with regards to antimicrobial prescribing and/ or compliance with infection prevention measures. As recently acknowledged by the World Health Organisation [37], it has become increasingly clear that application of evidence-based interventions is not a guarantee for success emphasizing the need to focus more on the underlying psychosocial mechanisms that influence people's behaviours [38], [39]. Today, it remains unclear whether there is sufficient application of current evidence on behaviour change in AMS and IP interventions for improved effectiveness and sustainability, hence, this scoping review.

Research objectives

1. To map out infection prevention (IP) and antimicrobial stewardship (AMS) interventions targeting healthcare associated *C. difficile* and CRKP.
2. To describe the key outcomes for IP and AMS interventions targeting healthcare associated *C. difficile* and CRKP.
3. To assess the extent to which behavioural theory has been applied in IP and AMS interventions targeting healthcare associated *C. difficile* and CRKP infections.

Methods

This study sought to explore a widely researched topic focussed on infection prevention and antimicrobial stewardship interventions in healthcare settings, hence, the justification of the scoping review approach. Arksey and O'Malley proposed a five-stage framework for undertaking scoping reviews [40]. This staged approach is considered rigorous and enhances the transparency of the findings as sufficient detailing of the procedures employed at each stage allow for replication. The use of explicit approaches improves the reliability of the study and highlights the robustness of the employed methods [41].

Research protocol

The protocol for this scoping review is available on Open Science Framework (OSF) registries via https://osf.io/nk7wf. This scoping review was undertaken and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis Extension for Scoping Reviews (PRISMA-ScR) guidelines [42]. This guidelines integrate the five-stages proposed by Arksey and O'Malley with regard to the conduct of scoping reviews [40].

Eligibility criteria

The review included peer-reviewed quantitative and/ experimental studies that focused on either infection prevention and/ or antimicrobial stewardship interventions with primary outcomes on healthcare associated *C. difficile* and CRKP. Studies involving human participants published in English over the last ten years were included in this scoping review. Studies on infection prevention and/ or antimicrobial stewardship that did not primarily target *C. difficile* or CRKP were excluded. This was to allow for broad comparison between the

interventions which tend to be multi-faceted in nature with some variations depending on the targeted organisms. Studies that explored new diagnostic devices or therapeutic interventions in relation to the two organisms were also excluded. Table 1 below summarizes the eligibility criteria that was used to screen the retrieved articles.

Table 1: Eligibility criteria

	Proposed criteria	**Refined criteria**
Population/ Setting	Healthcare facilities	Healthcare facilities
Intervention/ Exposure	AMS interventions for *C. diff* or *Klebsiella pneumoniae*	Infection prevention and antimicrobial stewardship interventions primarily targeting *C. difficile* and/ or *Klebsiella pneumoniae*
Comparison	No intervention	No intervention
Outcome	Control of *C. diff* and/ or *Klebsiella pneumoniae*	Changes in use of antimicrobial agents associated with *C. difficile* or CRKP. Compliance with IPC interventions Risk of *C. difficile* and *K. pneumoniae*
Study designs	All study designs	Observational studies, quasi-experimental studies, randomised controlled trials (RCTs)

Information sources

The search for literature was conducted across electronic databases accessible through the Bangor University library search engine, bibliographies, key journals, and websites for relevant organisations. The specific databases searched included MEDLINE via EBSCO*host*, PubMed Open Access via NCBI, Web of Science Core Collection, and CINAHL Plus via EBSCO*host* (see search strategy in supplementary file 1). The search for sources was undertaken with the assistance of the Bangor University librarian between 22/04/2020 and 06/05/2020. A final update for the databases searched was run on 30/09/2020. To ensure that the search was comprehensive and inclusive, and to reduce the effect of publication bias, a search of additional sources including unpublished and grey literature, general searches on Google Scholar as well as PhD theses and dissertations was conducted.

Study selection

Two reviewers (BO and EL) independently applied the inclusion and exclusion criteria on the retrieved articles for inclusion in this review and resolved any disagreements through discussions. 20% of the extracted data was checked for completeness and accuracy.

Data charting

The researchers developed a form for abstracting data that captured the main study characteristics as well as the specific metrics relevant to the objectives of this scoping review. The form was subjected to preliminary calibration to ensure its accuracy, consistency, and reliability. The data items extracted (see supplementary file 2) included the reference, the study type, the study objectives, population or setting, country, the intervention, intervention duration, healthcare workers involved, outcome measures or findings, and the conclusions of the study. A second reviewer (EL) audited the data extracted by the first reviewer for accuracy and completeness.

Results collation, summary, and report compilation

The extracted data was organised into themes and a narrative synthesis provided to describe the key findings of this scoping review. The subsequent sections provide a narrative

synthesis of the existing literature on IP and AMS interventions targeting *C. difficile* and CRKP as well as the identified gaps in line with the study objectives.

Patient and public involvement

There were no patients involved in the conduct of this scoping review.

Results

Figure 1: PRISMA flow diagram

Selection of studies

The Prisma diagram in Figure 1 (see figure 1) summarises the study screening and selection process. The search for literature across the retrieved 808 records with an additional six titles identified through bibliographic searches. Following de-duplication, 613 titles were screened, and 493 records did not meet the inclusion criteria. The abstracts of the remaining 120 records were further screened leading to the exclusion of 44 articles. Full text reading was done for 76 articles leading to the exclusion of 42 articles and inclusion of 34 articles.

Characteristics of selected studies

16 studies (see Table 2) focussed on *Clostridioides difficile* [43], [44], [53]–[58], [45]–[52] and 18 studies (see Table 3) focussed on CRKP [59], [60], [69]–[76], [61]–[68]. The studies varied in their designs with majority being quasi-experiments (31 articles). The other study designs included two cohort studies and one secondary analysis of a randomized controlled trial. 27 of the studies were undertaken prospectively whereas 7 studies followed a retrospective approach. 32.4% (11) of the studies were conducted in the United States of America [46], [49], [72], [77], [50]–[53], [55], [57], [58], [67] whereas two studies each are based in Canada [43], [45] and Greece [66], [68]. Four of the retrieved studies are from Italy [44], [48], [65], [73] while Israel [56], [61], [64] and China [60], [70], [71] had three studies each. Lastly, the selected articles included one study each from Japan [54], United Kingdom [47], South Africa, Denmark [62], Brazil [63], France [69], South Korea [74], Hungary [75], and the Netherlands [76]. There were variations in the study populations with three studies on *Klebsiella pneumoniae* involving neonates in the neonatal intensive care unit [71], [72], [75] whereas 31 studies involved adult subjects admitted for care within the hospital settings. All the studies on *Clostridioides difficile* involved adult populations further affirming advanced age as a risk factor for CDIs while three interventions targeting CRKP involved neonatal populations [71], [72], [75].

Synthesis of results

Interventions

Broadly, the interventions entailed components of antimicrobial stewardship (AMS) and/ or infection prevention (IP) measures targeting *C. difficile* and CRKP. Tables 2 and 3 below provide an outline of the specific AMS or IP components included across the included studies. The duration of interventions varied across the studies from three weeks up to six years [74]. The interventions involved various cadres of professionals namely infectious disease (ID) experts [44], [45], [55], [56], [70], consultants [48], [61], [70], [72], [76], nurses [44], [56], [71], [72], [75], [76], [58], [59], [61], [64], [65], [68]–[70], doctors [47], [54]–[56], [68], physicians [43], [44], [69], [70], [72], [74], [76], [46], [48], [49], [53], [55], [58], [59],

[64], pharmacists [43], [46]–[48], [53], [55]–[57], epidemiologists [56], [59], [67], [72], laboratory personnel [64], microbiologists [55], [64], [69], [72], and support staff (cleaners, caregivers, housekeepers, paramedics, porters, environmental officers) [56], [58], [61], [65], [72], [75], [76]. Additional cadres involved include managers [47], [72], infection control staff [49], [54], [58], [59], [61], [64], [65], [71], [72], unspecified clinicians/ medical personnel [49], [50], [69], [73]–[75], [51], [52], [54], [63], [65]–[68], quality improvement (QI) staff [55], patients [61], public health (PH) staff [64], and patient visitors [76]. Figure 2 summarizes the proportions of health professionals included across study interventions.

The interventions tended to be multi-faceted involving the implementation of at least two strategies to achieve the intended outcomes as highlighted in Tables 2 and 3 below. The strategies employed in interventions targeting *Clostridioides difficile* included surveillance through screening of stool samples or environmental cultures [47], [49], [54], alerts and notifications on detection of new cases or patients with previous history [49], [54], [57], isolation precautions [49], [54], [56]–[58], environmental disinfection [52], [56], [58], audits and feedback [43], [45], [46], [48], [53]–[55], antimicrobial policies and/ protocols [44], [47], [53], [57], care bundles [58], staff education [44], [45], [47], [53], [56], and specialised biocidal linen [50], [51]. Table 2 (see the online supplementary file 1) outlines how these strategies were combined across the included studies.

Table 2: IP and AMS interventions targeting Clostridioides difficile.

	References															
Interventions	[43]	[44]	[45]	[46]	[47]	[48]	[49]	[50]	[51]	[52]	[53]	[54]	[55]	[56]	[57]	[58]
Surveillance/ Screening					✓		✓					✓				
Alerts and notifications							✓					✓			✓	
Isolation precautions							✓					✓		✓	✓	✓
Environmental disinfection										✓				✓		✓
Audits and feedback	✓		✓	✓		✓					✓	✓	✓			
Consultations		✓	✓													
Antimicrobial policies and/ protocols		✓			✓						✓				✓	
Care bundles																✓
Staff education		✓	✓		✓						✓			✓		
Biocidal (Cu_2O) linen								✓	✓							
Intervention duration (months)	24	18	18	12	16	18		8	27	27	16	12	13	24		22

The commonest strategy targeting *Clostridioides difficile* reported across seven studies involved the use of audits and feedback [43], [45], [46], [48], [53]–[55]. This entailed reviewing the prescribed antibiotics by an antimicrobial pharmacist [43], [45], [46], [48], [53], [55] or the infection control team [54] and feedbacking to the prescriber. In some instances, the audits were undertaken offsite using electronic records systems [45], [46] and teleconferences. Audits were also combined with staff education sessions organised on identified gaps aimed at optimising the use of antimicrobials [45], [53]. Some interventions combined the audits with formulary restrictions and treatment protocols occasionally requiring approval prior to issuing a prescription [53]. Another intervention combined audits

with screening patients and notifying physicians on detection of *C. difficile*, promptly isolating infected patients, and monitoring appropriate use of antibiotics with prompt feedback to the responsible prescribers [54]. Additional interventions with a component of staff education included bedside infectious diseases consultation [44], restricting the use of broad spectrum antibiotics [44], [47], [56], and contact precautions [56]. Bedside consultations involved a part-time infectious diseases expert reviewing antibiotic prescriptions three times a week and discussing these with attending physicians [44]. This was coupled with revising antimicrobial treatment protocols and educating staff on reducing the appropriate use of antimicrobials [44]. Lastly, an intervention undertaken in a geriatric hospital involved educating all healthcare workers on isolation precautions and environmental disinfection as well as restricting the use of broad spectrum antibiotics [56].

A multi-site collaborative intervention involving an infection prevention bundle also promoted adherence to isolation precautions and an environmental cleaning protocol [58]. The isolation precautions included nursing patients in a single room, hand washing at recommended times, and the use of appropriate personal protective equipment namely gloves, and disposable aprons. Environmental cleaning entailed the use of appropriate decontamination agents to clean the patient environment and reduce the presence of *Clostridioides difficile.* A single centre study combined isolation precautions with a computer generated real time notification system for toxigenic *C. difficile* results and a treatment protocol using vancomycin only or vancomycin with metronidazole [57]. The final study on isolation precautions also incorporated an automated system that tracked *C. difficile* results and triggered alerts on the patient's electronic records as well as automatically ordering for the appropriate isolation precautions thus aiding the healthcare personnel's actions [49]. Three standalone interventions aimed at reducing the bioavailability of *Clostridioides difficile* [50]–[52] in the hospital environment. One multisite randomised controlled trial employed four disinfection strategies for environmental cleaning following the discharge of *C. difficile* patients [52]. These strategies included standard disinfection with an ammonium solution or 10% hypochlorite (bleach), standard disinfection with ultraviolet (UV) light or bleach with UV light, bleach only, or UV light with bleach [52]. Lastly, two quasi-experiments involved replacing hospital linen with biocidal coper oxide impregnated bedsheets, pillow cases, washcloths, and towels [50], [51].

Interventions targeting carbapenem-resistant *Klebsiella pneumoniae* (CRKP) included surveillance and/ or active screening though cultures [59], [60], [72], [73], [75], [76], [64]–[71], alerts and notifications upon detection of CRKP [59], [61], [62], [64], [66], [67], isolation precautions [59], [61], [72], [73], [75], [64]–[71], environmental decontamination [61], [65], [67], [68], [70]–[72], antimicrobial audits and feedback [62], [64], [68], [72], specialist consultations [65], antimicrobial policies and/ or protocols [59], [62], [63], [75], care bundles [70], and staff and/ or patient education [61], [62], [68], [72], [73]. The commonest strategy targeting CRKP appears to be surveillance or active screening through cultures to detect the presence of CRKP. One surveillance intervention involved the use of a flagging system for suspected patients at the emergency department, cohorting active cases, sampling cultures from hands of healthcare personnel and the environment, and a policy restricting the use of carbapenems [59]. Another multisite intervention combined routine screening of patients with mandatory isolation of confirmed cases with dedicated staff looking after the patients and mandatory notification of all carbapenem resistant cases to public health authorities [64]. Similarly, a surveillance intervention in a 250-bed general hospital required adherence to isolation precautions and compulsory notification of public health authorities on identified cases [66].

Table 3: IP and AMS interventions targeting CRKP.

	References																	
Interventions	[59]	[60]	[61]	[62]	[63]	[64]	[65]	[66]	[67]	[68]	[69]	[70]	[71]	[72]	[73]	[74]	[75]	[76]
Surveillance/ Screening	✓	✓				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓
Alerts and notifications	✓		✓	✓		✓		✓	✓									
Isolation precautions	✓		✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Environmental disinfection			✓				✓		✓	✓		✓	✓	✓				
Audits and feedback				✓		✓				✓				✓		✓		
Consultations							✓											
Antimicrobial policies and protocols	✓			✓	✓												✓	
Care bundles												✓						
Staff education and/ patient education			✓	✓						✓				✓		✓		
Intervention duration (months)	36	14	48	36	24	14	2	36	6	17	4	24	8	< 1	2	72	3	6

An outbreak containment intervention in an ICU setting employed active screening of patients, disinfection of the environment and respiratory equipment, and isolation precautions. One standalone intervention investigated the effectiveness of active screening on detection of CRKP cases in an ICU setting [60] while another study tracked sporadic hospital outbreaks using whole genome sequencing [76]. An observational study used rectal swabs for the active surveillance of CRKP in a cancer centre and a tertiary hospital [67]. Subsequently, the confirmed cases were promptly isolated requiring healthcare personnel's adherence to contact precautions and environmental cleaning protocols [67]. Other surveillance interventions similarly effected isolation precautions for confirmed cases [69] combined with either environmental cleaning protocols, staff education, adherence audits, or a bathing protocol [68], [69], [71]–[73], [75]. An intervention based in an Israeli medical centre rolled out isolation guidelines in combination with staff education, and environmental cleaning protocols supported with a computerized system for flagging CRKP cases [61]. A multi-disciplinary intervention in a 510-bed Danish university hospital employed Kotter's eight stages of change by delivering staff training and notification systems to enhance isolation precautions, and appropriate use of antimicrobial agents [62]. An antimicrobial stewardship intervention in a Brazilian tertiary care hospital examined the effectiveness of a restrictive antimicrobial policy on the use of carbapenems [63]. Lastly, a south-Korean based study in a 900-bed tertiary university hospital examined the effectiveness of enhanced contact isolation precautions on CRKP incidence. This was delivered through staff education, auditing prescriptions and discontinuing inappropriate antibiotics within 72 hours, and strict adherence to contact precautions including hand hygiene, single use gowns, and gloves.

Outcomes reported from IP and AMS interventions targeting *C. difficile* and CRKP.

The key outcomes reported across the studies included consumption of antimicrobial agents [43]–[45], [47], [48], [53], [54] and/ or associated costs [43], [44], [63], [45]–[48], [53], [54], [59], [62], incidence of *Clostridioides difficile* [43], [44], [54]–[56], [58], [45]–[48], [50]–[53] or incidence and/ resistance rates of carbapenem-resistant *Klebsiella pneumoniae* [59], [60], [75], [61]–[65], [68], [70], [74] as well as risk of other HCAIs [45], [52], [54], [58], [61], [68], [70], outbreak containment [66], [67], [69], [71]–[73], [76], adherence to infection prevention precautions [45], [51], [58], [65]–[67], [71], [74], [75],

time savings [49], [57], hospital stay [75], and associated mortality rates [44]. Table 4 and Table 5 below summarise the reported outcomes.

Interventions targeting C. difficile.

Antimicrobial use

Seven studies reported variations in the consumption of antimicrobial agents following the stewardship interventions [43], [45], [46], [48], [53]–[55]. The changes in antimicrobial use were reported in daily defined doses per 1000 patient days (DDD/1000PDs). Reduction in the use of antimicrobials ranged between 6.58 DDDs/1000 PDs and 310 DDDs/1000 PDs. The least (11%) reduction in antimicrobial use was reported from an intervention that involved audits for prescribed antibiotics and providing feedback to the prescribers [43]. The largest (79%) reduction in antimicrobials use was reported following an intervention involving restrictive antimicrobial policies and staff education [47]. A 54% reduction in antimicrobial costs was reported from an intervention involving half-hour monthly staff education sessions and audits of prescribed antibiotics using a structured electronic checklist [45]**.** 679 patients from two internal medicine units in a tertiary care hospital were observed over 18 months in the study [45]. One study reported a 52% improvement in antimicrobial streamlining following weekly reviews of prescribed antibiotics combined with remote consultations with an infectious diseases pharmacist through teleconferencing [55]. The latter study was conducted in a 141-bed community hospital over 13 months [55]. None of the *C. difficile* targeting interventions reported on the resistance rates for specific antimicrobial agents following their implementation.

Table 4: Summary of outcomes for interventions targeting Clostridioides difficile.

Key outcomes	References															
	[43]	[44]	[45]	[46]	[47]	[48]	[49]	[50]	[51]	[52]	[53]	[54]	[55]	[56]	[57]	[58]
Antimicrobials use (DDD/1000PDs)	↓310	↓200		↓6.58	↓124	↓141					↓34	↓10.7				
Antimicrobials use (% reduction)	11	47	46		72.5-95	22					12	37				
Antibiotics cost (↓%)			↓54			↓24							↓51			
Antimicrobials streamlining (%/week)													↑52			
Resistance rates																
CD risk/100,000 or/10000PDs (post-intervention)	⇔	12		14	55	60			2.8	170	2.8	11	16	⇔		85
CD absolute risk (%)	⇔	↓67	↓46	↓83	↓77	↓31		↓51	↑87	↓5	↓71	↓36	↓71	⇔		↓37
Risk of HCAIs (AR)		↓25			17-25					⇔		↓				↓
% reduction in time for start of treatment															64	
Time savings (hrs/1000 admissions)							↓43									
Hospital stay																
Adherence to infection prevention precautions (%)									↓6							↑95
Mortality		⇔														

DDD: Daily defined doses; PD: Patient days; CD: Clostridioides difficile; HCAIs: Healthcare associated infections; AR: Absolute risk, ↓: Significant reduction ↑: Significant increase; ⇔: No significant changes (Remained the same); ●: Outbreak was contained.

Risk of CDIs, other HCAIs, and associated mortality

Fourteen studies reported on the impact of the interventions on the risk of *Clostridioides difficile* infections (CDIs) or other healthcare associated infections [43], [44], [54]–[56], [58], [45]–[48], [50]–[53]. The highest overall reduction of 83% in absolute risk of CDIs was reported from a 12-months antimicrobial audits and feedback intervention involving physicians and pharmacists in a 212-bed Massachusetts hospital [46]**.** On the other hand, a 24-months multisite intervention amongst leukemia patients involving antimicrobial audits and feedbacks [43] reported no significant change on the risk of CDIs and associated mortality. Similarly, a second 24-months cross-sectional study involving geriatric patients from two Israeli hospitals that entailed staff education, environmental disinfection, and isolation precautions had no impact on the risk of CDIs [56]. Regarding the effect of CDI interventions on other HCAIs, an antimicrobial stewardship intervention in a 150-bed spinal injury hospital involving bedside infectious diseases consultation, staff education, and antimicrobial policies reported a 25% absolute risk reduction for other HCAIs [44] but no differences on mortality between the experimental and control groups [44]. A multisite RCT investigating the effectiveness of four environmental disinfection strategies reported no effect on the risk of other HCAIs [52]. A twelve-months intervention assessing the impact of intensified IPC precautions on MDROs in a 409-bed Japanese tertiary hospital reported a reduction in the risk of other HCAIs but it's not clear whether this change was significant [54]. Two studies involving the use of biocidal linen impregnated with copper oxide reported contradictory findings which could be partly due to the differences in study settings and how the interventions were delivered. The first study involved six hospitals in both urban and rural settings with a total of 1019 beds implemented over eight months (568,397 patient days) and reported a 51% reduction in the risk of CDIs [50]. The second study was conducted in one long-term care hospital over 27 months (29,342 patient days) reported an 87% increase in the risk of CDIs [51]. In the latter study, the researchers acknowledged that study participants were never blinded possibly leading to the deterioration of contact precautions specifically hand hygiene that reduced by 6% [51].

Adherence to isolation precautions

The highest (95%) improvement in adherence to isolation precautions was reported by a 22-months multisite (35 hospitals) intervention involving the use of an infection prevention bundle with isolation precautions and an environmental cleaning protocol [58]. On the other hand, an intervention involving the use of biocidal linen impregnated with copper oxide reported a 6% reduction in adherence to isolation precautions [51] as discussed above.

Time savings

Two studies reported outcomes related to time savings [49], [57]. The first intervention involved treatment protocols for *C. difficile*, real-time computerized notifications of toxigenic *C. difficile results*, and isolation precautions. This was undertaken in a 433-bed adults medical center and recorded a 64% reduction in time prior to the initiation of appropriate antibiotics treatment [57]. The second study involving active surveillance, an alert system, and isolation precautions in a 410-bed hospital treating trauma, burns, and cancer patients reported a 43% reduction in care hours per 1000 admissions [49]**.** There were no studies on *C. difficile* that reported on the effect of interventions on the length of hospital stay.

Carbapenem-resistant *Klebsiella pneumoniae*

Antimicrobials use.

Three studies reported on antimicrobial use with regards to CRKP interventions [59], [70], [71]. One study involving a flagging system for confirmed cases, isolation precautions, and a carbapenems restriction policy in a 1000-bed tertiary university hospital simply indicated there was a reduction in the use of meropenem [59]. The second study employed Kotter's stages of change in a multi-disciplinary intervention involving staff education, notifications on prescription of restricted antibiotics and antimicrobial protocols in a 510-bed Danish hospital recorded a 75% reduction in antibiotics consumption [62]. The last study involving restrictive antimicrobial policies reported a 21% (12.9 DDDs/1000 PDs) reduction in antibiotics use [63]. Two interventions involving active surveillance through screening [60] and staff education combined with isolation precautions [74] reported a reduction of the resistance rates for *K. pneumoniae*. The first intervention was conducted over 14 months in an ICU setting in China [60] while the second intervention was undertaken in a 900-bed tertiary hospital in South Korea [74]. A 24-months intervention in a tertiary hospital (200 beds) involving restriction of group two carbapenems recorded no changes in the resistance rates for *K. pneumoniae* [63].

Risk of Klebsiella pneumoniae, other HCAIs, and associated mortality.

The largest risk reduction (97%) for CRKP was reported from a 36-months hospital wide intervention that involved physicians, epidemiologists, nurses, and the infection control team [59]. The lowest reported reduction in the absolute risk of CRKP was from a 17-months multi-faceted intervention that entailed active surveillance, isolation precautions, audits and feedback, environmental cleaning, and staff education [68]. Seven outbreak investigations did not have outcomes on the relative risk CRKP [66], [67], [69], [71]–[73], [76]. An intervention involving staff education, isolation, environmental cleaning, and computerized flagging of cases reported a 55% reduction in other HCAIs [61] while another intervention involving screening, isolation, environmental disinfection, and care bundles reported an 84% reduction in other HCAIs over a 48 months period [70]. On the other hand, one study reported a 59% rise in the risk of other HCAIs following an intervention that involved screening, isolation, environmental decontamination, audits, and education over a 17 months duration [68]. The intervention involved 601 patients retrospectively and 250 patients prospectively in the solid organ transplant (SOT) department. The increase in the incidence of other carbapenem resistant organisms was attributed to the intrahospital transfer of carriers to the SOT department and the subsequent transfer of post-surgical patients to the ICU where they were allegedly colonized by the bacteria [68]. There are no studies that reported on mortality associated with CRKP.

Table 5: Summary of outcomes for interventions targeting CRKP.

Key outcomes	References																	
	[59]	[60]	[61]	[62]	[63]	[64]	[65]	[66]	[67]	[68]	[69]	[70]	[71]	[72]	[73]	[74]	[75]	[76]
Antimicrobial use (DDD/1000PDs)	↓				13													
Antimicrobials use (% reduction)				↓75	↓21													
Antibiotics cost (↓%)																		
Antimicrobials streamlining (%/week)																		
Resistance rates		↓			⇔				●							↓		
CRKP risk/100,000 or/10000PDs	18		0.5	23%		↓	56		↓	↓	●	28				0.9	↓	
CRKP absolute risk (%)	↓97		↓92	↓17	12	12	●	●	10	●		●	●	●	46	↓	●	
Risk of HCAIs (AR)			↓55						↑59		↓84							
% reduction in time for start of treatment																		
Time savings (hours/1000 admissions)																		
Hospital stay (%PDs)																↓15		
Adherence to IP precautions (%)							↑	↑	↑				↑			↑35	↑29	
Mortality																		

DDD: Daily defined doses; PD: Patient days; IP: Infection prevention; CRKP: Carbapenem-resistant Klebsiella pneumoniae Ca; HCAIs: Healthcare associated infections; AR: Absolute risk, ↓: Significant reduction ↑: Significant increase; ⇔: No significant changes (Remained the same); ●: Outbreak was contained.

Hospital stay and adherence to contact precautions.

A three-months intervention involving 355 patients in a 17-bed neonatal intensive care unit in Hungary reported a 15% reduction in the hospitalization duration with an associated 29% increase in adherence to contact precautions [75]. Another six years intervention involving staff education reported a 35% improvement in adherence to contact precautions [74]. Lastly, four additional studies also reported an improvement in adherence to contact precautions [65]–[67], [71].

Discussion

Summary of evidence

This scoping review mapped studies on infection prevention (IP) and antimicrobial stewardship (AMS) interventions targeting healthcare associated *C. difficile* and CRKP published between 2010 and 2019. Interventions on antimicrobial stewardship included restrictive antimicrobial policies and treatment protocols, specialists' consultations, notifications and alert systems, as well as audits and feedback (also referred to as academic detailing). Interventions on infection prevention precautions aimed at curbing the healthcare associated transmission of *C. difficile* and CRKP included surveillance through active screening and cultures, isolation precautions, environmental measures (disinfection and biocidal linen), use of care bundles, and education of staff and or patients. Interventions targeting *C. difficile* appeared to focus more on AMS while interventions targeting CRKP appeared to focus more on screening, isolation precautions, or environmental disinfection as core strategies. *Clostridioides difficile* and *Klebsiella pneumoniae* belong to the wider group of ESKAPE pathogens that significantly contribute to the burden of healthcare associated infections. The findings above also show that interventions targeting either *C. difficile* and CRKP have a significant impact on the health care associated risk of other ESKAPE pathogens. The interventions could also be applicable to interventions targeting other members of the ESKAPE pathogens in healthcare settings.

This scoping review proposes the acronym ESCAPE-BIN (**E**ducation, **S**urveillance/**S**creening, **C**onsultations, **A**udits, **P**olicies and **P**rotocols, **E**nvironmental measures, **B**undles of care, **I**solation, and **N**otifications or alerts) to denote the common AMS and IP interventions targeting *Clostridioides difficile* and CRKP in healthcare settings. The proposed acronym provides a useful categorisation of the specific actions applicable to antimicrobial stewardship programmes as broadly outlined in the core elements for AMS by the Centres for Disease Control and Prevention (CDC) [78]. This acronym could potentially improve the understanding of the core elements by AMS teams as it highlights the specific interventions that address the requirements of the core elements. These include educating clinicians on appropriate use of antibiotics, specialist consultations to provide required expertise in antimicrobial prescribing, as well as audits, feedback and surveillance to track and report on appropriate use of antimicrobials as outlined in the core elements [37], [78]. Furthermore, the acronym provides a quick reference for AMS teams that could be useful in identifying gaps in AMS programmes or mapping intervention priorities.

This study also set out to describe the key outcomes for IP and AMS interventions targeting healthcare associated *C. difficile* and CRKP. The identified outcomes included antimicrobial use, resistance rates of the targeted pathogens, risk reduction, adherence to infection prevention precautions, hospital stay, and time savings. Majority (56%) of the interventions targeting *Clostridioides difficile* appeared to focus more on the use of antimicrobial agents as a key outcome. This is consistent with available evidence on the inappropriate use of antimicrobial agents as a key risk factor for CDIs. Recent studies have

shown that reducing the prescription of antimicrobials can potentially reduce the incidence of CDIs in both healthcare and community settings [79], [80]. Comparatively, only 16% of the interventions targeting CRKP reported an impact on the use of antimicrobial agents as summarised in the findings above.

This scoping review also sought to assess whether AMS and IP interventions targeting *C. difficile* and *K. pneumoniae* incorporated existing evidence on behaviour change. A systematic review on behaviour change frameworks identified three key components namely capability, opportunity, and motivation (COM-B) as being critical for interventions targeting behaviour change [81]. Capability refers to one's capacity/ ability to engage in a behaviour while motivation is the brain process that energises or directs a person's behaviour. Lastly, opportunity refers to factors extrinsic to an individual that make a desired behaviour possible [81]. Broadly, the interventions assessed in this scoping review focussed on antimicrobial prescription behaviours and infection prevention behaviours. However, it was not possible to ascertain whether a specific behaviour change framework was applied across the included studies except for one intervention that applied Kotter's 8-steps model for organisational change [62] and recorded the second largest (75%) sustained reduction in antimicrobials use over a three years period. Although Kotter's model provides detailed guidance on organisational change, it's been criticised for being too top-down with more focus on the management staff as opposed to junior employees [82]. Due to the limited information provided about the interventions, this review could not establish whether the interventions considered all the critical elements necessary for successful behaviour change namely capability, opportunity, and motivation. Comparatively, interventions targeting CRKP generally appeared to impact more on the risk of other HCAIs when compared with interventions targeting *Clostridioides difficile*. This could be because CRKP interventions appeared to broadly target infection prevention behaviours of healthcare personnel which cut across most pathogens while *Clostridioides difficile* interventions broadly targeted prescription behaviours which tend to be specific to the targeted organism.

Generally, the application of current behaviour change evidence appears to be either limited or not reported across IP and AMS interventions targeting *C. difficile* and CRKP in healthcare settings, hence, the need for further exploration. In addition, there was limited evidence from the included studies on how the interventions influenced compliance with either IP or AMS interventions targeting *C. difficile* and CRKP. This scoping review also established that physicians tend to be involved more in IP and AMS interventions targeting *C. difficile* and CRKP in comparison to other cadres of healthcare professionals. Almost half of the interventions in the present study involved physicians which was slightly higher than nurses (44%) whereas support staff including care workers participated in nearly one third of the interventions. In healthcare settings, physicians are amongst the least proportionate healthcare workers and their contact with patients may be less frequent compared to nurses and carers looking after patients round the clock. Consequently, it is also worth exploring whether proportionate variations in the cadres involved in IP and AMS interventions could have an influence on the key outcomes.

Limitations

There are some limitations to this scoping review. First, this review included studies with primary outcomes on *C. difficile* and CRKP, thus excluding other interventions that might have applied behaviour change evidence without necessarily focussing on a specific pathogen. Secondly, the study population and settings of included articles were very diverse, and no adjustments were undertaken to account for these differences. Thirdly, the duration of the specific IP and AMS interventions was not considered in this review.

Conclusions

Antimicrobial resistance represents a global threat requiring urgent measures to protect lives. Reducing the burden of AMR entails a host of multi-level approaches on infection prevention and antimicrobial stewardship. This review mapped out IP and AMS interventions targeting *Clostridioides difficile* and carbapenem-resistant *Klebsiella pneumoniae* (CRKP). These interventions include **E**ducation, **S**urveillance/**S**creening, **C**onsultations, **A**udits, **P**olicies/**P**rotocols, **E**nvironmental disinfection, **B**undles, **I**solation, and **N**otifications or alerts (**ESCAPE-BIN**). The review also described the key outcomes for these interventions including antimicrobial use, cost reductions, resistance rates, and risk of infection, time savings, hospital stay, as well as adherence to contact / infection prevention precautions and protocols. Lastly, the review established evidence gaps on the application of current evidence on behaviour change interventions and adherence to IP and AMS interventions.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Authors' contributions

BO: conceived the idea, designed the study protocol and was the first reviewer; Both JH and VM reviewed the study protocol, methods, and the final report. VM: reviewed the study protocol, methods, and reviewed the final report. All the three authors discussed the findings of this study and contributed to the final report.

Competing interests

None

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request through brk18vjr@bangor.ac.uk

Figure legend

Figure 1: PRISMA flow diagram summarising the study screening and selection process.

Figure 2: Proportion of staff involvement in infection prevention interventions targeting Clostridioides difficile and Klebsiella pneumoniae in healthcare settings per staff cadre.

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Prisma diagram

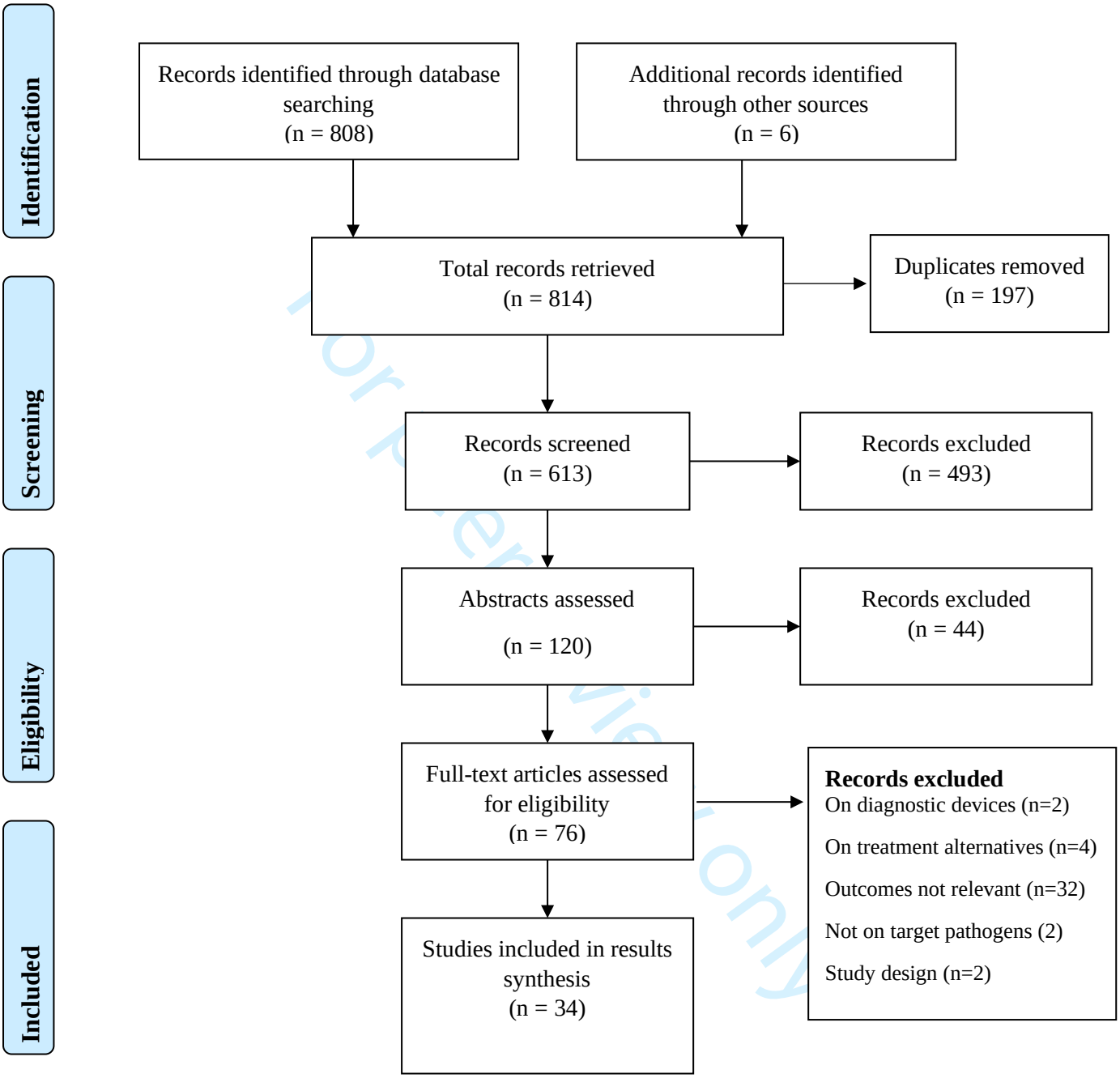

Figure 1: PRISMA flow diagram summarising the study screening and selection process

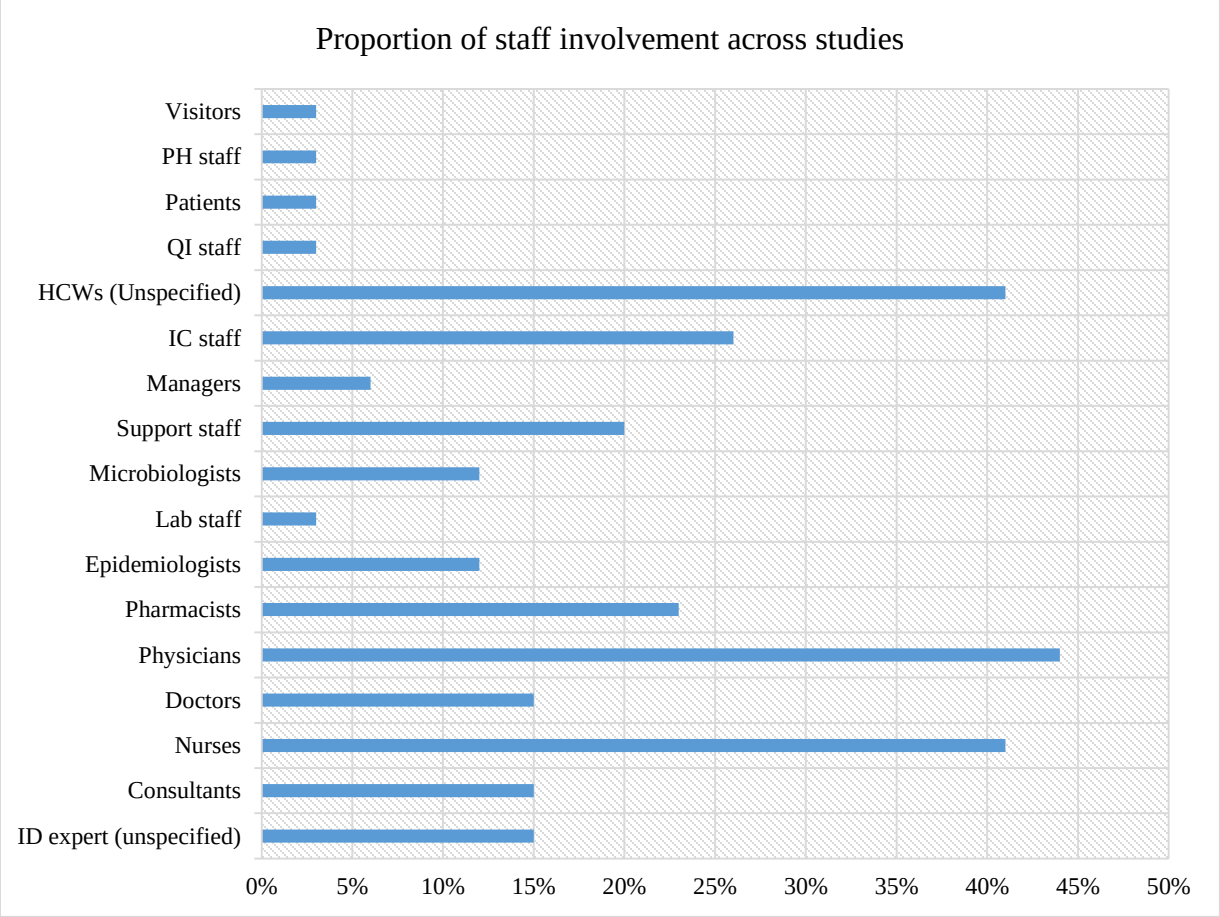

Figure 2: Proportion of staff involvement in infection prevention interventions targeting Clostridioides difficile and Klebsiella pneumoniae in healthcare settings per staff cadre.

Appendix 1: Search strategy

a. MEDLINE search strategy

Search ID	Search Terms	Results
S1	(MM "Clostridium difficile")	7,452
S2	(MM "Klebsiella pneumoniae")	8,828
S3	S1 OR S2	16,277
S4	(MM "Drug Resistance, Microbial+")	68,909
S5	(MM "Antimicrobial Stewardship")	982
S6	S4 OR S5	69,747
S7	S3 AND S6	1,649
S8	(MM "Cross Infection+")	42,792
S9	S7 AND S8	192
S10	S7 AND S8	187

b. CINAHL Plus

Search ID	Search Terms	Results
S1	(MM "Clostridium Difficile")	2,307
S2	"klebsiella pneumonia*"	2,719
S3	S1 OR S2	5,023
S4	(MM "Drug Resistance, Microbial+")	15,817
S5	(MM "Antimicrobial Stewardship")	427
S6	S4 OR S5	16,176
S7	S3 AND S6	719
S8	(MM "Cross Infection+")	27,268
S9	S7 AND S8	166
S10	S7 AND S8	160
S11	S7 AND S8	127

c. Web of Science Core Collection

Search ID	Search terms	Results
# 1	TS= "clostridium difficile" OR TS= "clostridioides difficile"	12,612
# 2	TS= "klebsiella pneumonia*"	17,207
# 3	#2 OR #1	29,679
# 4	TS= "drug resistance"	50,192
# 5	TS= "antimicrobial stewardship"	3,586
# 6	#5 OR #4	53,661
# 7	#6 AND #3	1,415

# 8	TS= "cross infection" OR TS= nosocomial	17,523
# 9	#8 AND #7	193
# 10	#8 AND #7	193
# 11	#8 AND #7	193

d. PubMed

Search ("Cross Infection"[Majr]) AND ((((("Klebsiella pneumoniae"[Mesh]) OR "Clostridium difficile"[Mesh])) AND ((("Drug Resistance"[Mesh] OR "Drug Resistance, Multiple, Bacterial"[Mesh] OR "Drug Resistance, Bacterial"[Mesh] OR "Drug Resistance, Microbial"[Mesh])) OR "Antimicrobial Stewardship"[Majr])) Filters: published in the last 10 years; Humans.

EXTRACTED DATA ON STUDIES AND INTERVENTIONS TARGETING CLOSTRIDIUM DIFFICILE AND KLEBIELLA PNEUMONIAE IN HEALTHCARE SETTINGS

STUDIES AND INTERVENTIONS TARGETING CLOSTRIDIUM DIFFICILE IN HEALTHCARE SETTINGS

Reference	Study type	Aims/ objectives	Population/ Setting	Intervention	Outcome/ key findings	Conclusions	Useful notes
34	Retrospective observational time-series.	To examine the effectiveness of an antimicrobial stewardship programme on utilization and cost of antimicrobials in leukemia patients in Canada	Leukemia patients. Canada Multi-site	Academic detailing (aka Audit + Feedback) Duration: 24 months Involved: ID physician, AMR pharmacist	Utilization of antimicrobials reduced from 278DDD/100 PD to 247 DDD/100 PD CDI remained stable	AMS reduces antimicrobial use but has no effect on mortality	ISS persons have neutropenia, mostly treated with broad spectrum antibiotics hence high risk for CDI
35	Quasi-experimental	To assess the impact of an ASP on antimicrobials use, CDIs, and AMR patterns	Rehabilitation hospital 150 beds Spinal injuries patients Bologna, Italy	Bedside ID consultation Revision of antibiotics prophylaxis protocols Staff education Duration: 18 months Involved: ID consultant, physicians, and nurses.	Abx consumption reduced from 42 to 22 DDD/ 100 PDs (Carbapenems from 13 to 0.4 DDD/100PDs, Fluoroquinolones from 11.8 to 0.99 DDD/ 100 PDs) CDIs reduced from 3.6 to 1.2 cases per 10000 PDs Prevalence of KP reduced from 42% to 17% No effect on mortality or length of stay.		
36	Quasi-experimental	To optimize the use of antibiotics through trainee-led time outs	Montreal University tertiary care hospital (417 beds) Internal medicine. 2 units, 46 beds 679 inpatients Canada	Twice-weekly time-out audits using a structured electronic checklist and monthly feedback AMS monthly education: 30 minutes to all rotating staff Duration: 18 months Involved: Consultants (ID, critical care, and general medicine)	A 46% reduction of antibiotics costs from $149 743CAD to $69 424 78% of the cost reduction linked with reduced use of carbapenems 80% adherence to the audit CDI reduced from 24.2 to 19.6 per 10,000 PDs	An antibiotic self-stewardship bundle to implement the CDC's suggested time-outs seems to have reduced overall costs and targeted antibiotic use.	About 50% use of abx is not necessary or inappropriate
37	Quasi-experimental	To implement an AMS program in a long-term care	212 bed-New England Sinai Hospital in	CDIs Offsite electronic medical record audit.	An overall decrease in antimicrobials use.	AMS using remote EMR audit is associated with a	

		hospital using telemedicine Provide antimicrobial oversight To improve the quality of care by standardizing antimicrobial prescribing practices	Stoughton Massachusetts Oversight undertaken by staff from Tufts Medical Center	Duration: 12 months Involved: ID physicians and pharmacists	Overall usage of anti abx reduced by 6.58DDD/1,000 PDs A reduction in the incidence of HAIs and CDIs (from 1.4 to 0.57/1000PDs)	reduction in antimicrobials use.	
38	Quasi-experimental	To reduce the number of healthcare associated CDI cases	450-bed district general hospital Hairmyres Hospital (Glasgow, UK)	A restrictive policy on the use of ceftriaxone and ciprofloxacin Educational campaign Duration: 16 months Involved: Doctors, pharmacists and managers.	Overall reduction of targeted antimicrobials (ceftriaxone: 95% and ciprofloxacin: 72.5%) (Ceftriaxone from 46.213 to 2.129 DDD/1000PDs Ciprofloxacin from 109.804 to 30.205 DDDs/1000PDs) 77% reduction in hospital acquisition of CDIs Sustained reduction of CDIs up to 0.259 cases/ 1000 patient beds 3 years post-intervention	Restricting the two antibiotics significantly reduced healthcare associated CDIs	
39	Prospective, controlled interrupted time series	To evaluate the impact of audit and feedback on the use of broad-spectrum antimicrobials in critical care patients	Single site 150-bed tertiary hospital Intensive care unit (3). Italy	Review of all patients on day 3 and 10 after admission with suggestions for optimizing antimicrobial use given to responsible physicians. Then placing a computer-generated progress note on the patient chart, then feedback completed on same day Critical care team Targeted antimicrobials: ceftriaxone, ceftazidime, piperacillin-tazobactam, meropenem, ertapenem, levofloxacin, ciprofloxacin, and vancomycin Duration: 18 months Involved: Consultants, pharmacists, and ID physicians	Use of broad-spectrum antimicrobials reduced from 644 to 503 therapy days per 1,000 PDs Nosocomial CDIs incidence reduced from 11 to 6	Prospective audit and feedback appear to be an effective and safe means for reducing the use of broad-spectrum antimicrobials	Approximately half of antibiotics use in hospitals is inappropriate or not necessary
40	Quasi experimental	Assessing the impact of automated tracking and ordering	University of California, Irvine Medical center	An automated system for identifying, tracking CDIs and other MDROs that involved monitoring microbiology results, triggering chart-based alerts,	Time savings estimated at 43 hours per 1000 admissions	Automated systems integrated within the EHRs have potential for	No report on CDI outcomes

		precautions on MDROs	410 beds Serves trauma, burns and cancer patients.	ordering for appropriate contact precautions on admission as well as inactivation of the precautions. The alert was in form of a visual header banner on the HER. Duration: Involved: Physician, infection prevention team, and clinicians.	Timely initiation of contact precautions	protecting patients by ensuring precautions are ordered in a timely manner. The system also contributes to time savings for IPC teams.	
41	Quasi-experimental	To assess the effect of biocidal copper oxide impregnated linen on HCAIs CDIs	Multi-site (six hospitals). Sentara Albermarle Healthcare hospitals 1019 beds NC, USA	Replacement of linen with copper oxide impregnated linen Duration: 8 months	A reduction in C. diff associated HCAIs by 41.1-61.2% per 10,000 PDs during the intervention period	The use of the biocidal impregnated copper-oxide linen significantly reduced C. diff associated HCAIs as well as other MDROs	Copper has some biocidal activity against some drug resistant bacteria. Its use in hospital environments potentially reduces the bioburden of HCA pathogens
42	Quasi-experimental	To examine the effect of copper impregnated linens on MDROs and CDIs	Long-term acute care hospital (LTACH). 40-beds Charlottesville, Virginia	Copper-impregnated linens including bedsheets, pillowcases, towels, and washcloths Duration: 27 months	Copper linens were associated with a much higher rate of CDIs. (1.5 to 2.8 cases per 1000PDs) There was a reduction in the compliance with hand hygiene practices (-5.6%)	There was no beneficial effect of the copper impregnated linens	No blinding of staff members
43	Secondary analysis of a multicenter cluster RCT (BETR Disinfection)	To assess the effectiveness of disinfection strategies on C. diff incidence in hospital settings BETR (Benefits of enhanced terminal room) disinfection study	Multisite: 9 hospitals in southeastern USA	Four disinfection strategies post-discharge of MDRO or C. diff patients: Standard disinfection with quaternary ammonium solution or 10% hypochlorite (bleach) for C. diff cases. Standard disinfection + UV light or bleach + UV light for C. diff cases. Bleach strategy with 10% hypochlorite Bleach + UV light Duration: 27 months	No significant differences in the hospital-wide risk of the target organisms between standard disinfection and the other three enhanced disinfection strategies. The use of UV light as part of the disinfection strategy significantly reduced the risk of C. diff (from 18.1 to 17.2/1000PDs)	Enhanced terminal room disinfection using UV light contributed to a reduction in the risk of C. diff and VRE. Enhanced terminal room disinfection overcomes the challenges of standard disinfection and potentially reduces acquisition of C. diff and other MDROs.	Contaminated healthcare environments act as sources of infectious pathogens hence the importance of enhanced terminal room disinfection.

44	Quasi-experimental. Retrospective pre- and post-intervention	To assess the impact of an ASP intervention on HA-CDI	The Western Pennsylvania Hospital (WPH). 317-bed community teaching hospital. Approximately 6800 admissions yearly.	Education. Restriction of target antimicrobials requiring prior approval. Audit + feedback. Annual guidelines for antimicrobials use. Duration: 16 months Involved: ID physician and ID pharmacist	Significant reduction in HA-CDIs from 0.84 to 0.28 cases per 1000PDs (P=0.035). A cumulative reduction in the use of clindamycin, ceftriaxone, carbapenems, fluoroquinolones, linezolid, tigecycline (from 295.1 to 261.3 DDD/1000PDs)	Implementing an ASP program significantly reduced the incidence of HA-CDI as well as abx use	Antibiotics associated with higher rates of CDI include fluoroquinolones, clindamycin, and ceftriaxone
45	Pre- and post-intervention	To assess the impact of intensive IPC activities on MRSA, drug resistant P. aeruginosa (DRP), and C. diff acquisition.	Tsukuba Medical Center Hospital (TMCH) Japan. 409 beds. Tertiary emergency medical center.	Screening + notification of new and previous MDROs. Daily review of new patients' medical records/ microbiological results. Contact precautions or standard precautions. Monitoring inappropriate use of carbapenems and promptly instructing responsible doctors. Duration: 12 months Involved: Infection control team, doctors, and ward staff	Reduction of carbapenems' use from 28.5 to 17.8 DDD/1000PDs. Improved uptake of contact precautions. A reduction in the incidence of CDI (from 0.47 to 0.11 cases/1000PDs). Incidence of MRSA and DRP also reduced significantly	Proactive intensive ICT measures have the potential for reducing the hospital transmission of MDROs.	
46	POS	To assess the impact of a technology-mediated pharmacy-directed ASP in a rural hospital	St. Mary Medical center. 141 beds. Community hospital. Washington	Weekly antimicrobial review teleconferences involving an ID pharmacist Duration: 13 months Involved: ID consultant, physicians, doctors, QI staff, pharmacists, and microbiologists.	Pharmacy-initiated AMS interventions increased from 2.1 to 6.8 interventions per week. Antimicrobial streamlining improved from 44% to 96%. There was enhanced interdisciplinary collaboration. A 51% reduction in the cost of targeted antimicrobials.		

					HA-CDIs reduced from 5.5 to 1.6 cases per 10,000PDs		
47	ROS cross-sectional study	To assess the effect of intensive staff education on CDAD amongst hospitalized geriatrics	390-bed geriatric hospital 217 geriatric patients observed. Israel	Staff education on isolation precautions, handwashing, transporting patients within the hospital, and cleaning. Duration: 24 months Involved: ID specialist, epidemiologic nurse, clinical pharmacist, doctors, nurses, paramedics, cleaners, and porters.	There were no significant differences in the incidence of CDAD pre- and post-intervention.	Intensive staff education did not reduce the nosocomial CDAD rates but remains an important strategy	Toxin positive C. diff is the leading cause of diarrhea amongst geriatrics.
48	Retrospective cohort study	To assess the impact of real-time notification upon detecting toxigenic C. diff	Single center. 433 bed tertiary care medical center. Lexington, Kentucky. Adult patients aged more than 18 years	Computer generated real-time notification of toxigenic C. diff results + Initiation of appropriate antimicrobial therapy (Vancomycin or Vancomycin + metronidazole). Contact precautions. Involved: Pharmacist led ASP team	The time for initiating appropriate treatment reduced from 5.75 to 2.05 hours. The ASP intervention shortened the time from diagnosis to recording the appropriate antimicrobial in the EMHRs	The real-time notification intervention reduced the time for entering and initiating the appropriate antimicrobial treatment as well as contact precautions.	
49	POS	To assess the impact of a multifaceted collaborative intervention on CDIs	Multisite 35 hospitals Hospitalized patients, 18+ years. US, NY	C. diff collaborative intervention: IP bundle: Contact precautions, signage, PPE, hand hygiene, isolation precautions Environmental cleaning protocol Duration: 22 months Involved: Internal disciplinary team (Infection preventionist, physicians, nurses, support staff, and QI staff.)	95% mean compliance with IP bundles 96% mean compliance with environmental cleaning protocol. Reduction in HA-CDIs from about 13.5 to 8.5 per 10,000	The C. diff collaborative potentially impacts on hospital practices. The intervention influences the other HCAIs	
STUDIES AND INTERVENTIONS TARGETING KLEBSIELLA PNEUMONIAE IN HEALTHCARE SETTINGS							
Reference	**Study type**	**Aims/ objectives**	**Population/ Setting**	**Intervention**	**Outcome/ key findings**	**Conclusions**	**Useful notes**
50	ROS + POS Quasi-experimental Medical records	To devise a local strategy for eradication of a hospital-wide outbreak caused by carbapenem-resistant Klebsiella pneumoniae (CRKP)	CRKP patients 1000 bed tertiary care university hospital	ED flagging system Isolation precautions Eradicating clusters Environmental and personnel hand cultures Carbapenem restriction policy Duration: 36 months.	CRKP infections reduced from 5.26 to 0.18 per 10,000 patient days No nosocomial CRKP infections diagnosed Meropenem use reduced		

				Involved: Physicians, epidemiologists, nurses, infection control staff			
51	Quasi-experimental?	To examine the effect of active screening on the resistance rates of MDRBs in ICUs	ICU. China	Active screening. Duration: 14 months	Improved detection of MDRBs (KP)	Active screening reduces the resistance rates of pathogenic bacteria and useful in detecting MDRB	
52	Quasi-experimental	To reduce the prevalence of CRKP (KPC-3)	Medical center Israel	Guidelines for isolation precautions, environmental cleaning, staff education, and computerized notification/ flagging Duration: 48 months. Involved: Consultants, nurses, IP staff, housekeeping staff, patients, and caregivers.	A decrease in the CRKP incidence rate sustained over 30 months from 6.6 to 0.5/10,000PDs Reduction in cross-infections from 6% to 2.7% Surveillance of asymptomatic carriers improved from 20% to 89%	A multidisciplinary IPC programme is effective in controlling the prevalence of CRKP	
53	Quasi-experimental	To optimize the use of antimicrobials	510-bed Danish university hospital Copenhagen University Hospital. Denmark	Multi-disciplinary change project Kotter's stages of change Multi-level intervention: 1. Professional: Education, clinician leaflets, new drug container, yellow sticker for bed post, signboard for doors, hotline, notification on prescription of restricted antimicrobials 2. Social: Presentations for the quality board, prevalence studies, feedback, newsletter and website. 3. Patient: Information leaflets for isolation precautions 4. Organizational: Revising antimicrobial guidelines, cefuroxime restriction. Duration: 36 months. Involved: Physicians, nurses, pharmacy staff, and patients.	Overall antimicrobials consumption remained unaffected. Immediate and sustained reduction in cefuroxime use (74.5%) An increase in the use of ertapenem, piperacillin/ tazobactam, and b-lactamase sensitive penicillin. Reduction in ESBL-KP diagnostic samples Reduced incidence of ESBL-KP infections from 39.5 to 22.5% Reduced need for isolation precautions	Changing antimicrobial consumption and reducing the incidence of ESBL-KP is possible through a multi-faceted intervention that does not require ongoing antibiotic stewardship	Restricting cephalosporins may reduce ESBL infection rates Carbapenems (B-lactamase inhibitors) are recommended as first-lines for serious ESBL producing bacteria
54	Quasi-experimental	To evaluate the impact of an AMS program restricting	Hospital das Clinicas	Antimicrobial restriction	A reduction of group 2 carbapenems use from 61.1 DDD to 48.7 DDD/1,000 patient days	There was a significant reduction in the use	

		carbapenems (imipenem and meropenem)	Institute of Orthopedics and Traumatology 200 beds tertiary care hospital. Brazil	Ertapenem was made mandatory for treatment of ESBL-Enterobacteriaceae Restricting group 2 carbapenems for gram negative bacteria. Duration: 24 months.	Susceptibility of K. pneumoniae and P. aeruginosa to trimethoprim-sulfamethoxazole	of carbapenems following preferential use of ertapenem.	
55	Prospective Observational study	To contain an outbreak of carbapenem resistant KP	27 Acute care hospitals. 14,000 beds. Israel	Screening Mandatory reporting of every CRE patient to PH authorities Mandatory isolation of hospitalized new and previous carriers (single rooms isolation) Dedicated staff Oversight taskforce that supervised adherence to isolation protocols, provided technical support, and feedback to management. Duration: 14 months. Involved: Nurses, IP staff, microbiologists, laboratory staff, physicians, and Public health staff	Increase in the incidence of KP was halted with a subsequent reduction of 11.7 cases per 100,000	An intervention coordinated centrally showed better outcomes for containment of a KP outbreak as compared to local measures. Strategic planning and national oversight are crucial in addressing AMR	**Outbreak control**
56	Outbreak investigation	To curb the spread of KPC-3 producing KP	Italy 12-bed ICU hospital Cannizaro hospital, Catania	Screening Environmental cleaning Respiratory equipment disinfection Hand hygiene Single room isolation Weekly meetings between IPTs and ICU staff. Duration: 2 months. Involved: Nurses, ICU staff, IP staff, and cleaning staff.	Outbreak containment within 4 months Improved adherence to contact precautions		**Outbreak control** Ten recognized KPC types (KPC-2 to KPC 11). KPC-2 are the commonest

57	POS	To curb CRKP and Acinetobacter baumannii	Serres General Hospital 250-bed hospital Greece	Prokroustes action plan: Surveillance and compulsory notification + IPC measures: Isolation precautions Duration: 36 months	Containment of CR associated with KP and PA three years post-intervention. An increase in KP resistant to Colistin, Tigecycline, and gentamycin	There exist challenges for addressing MDROs in regions with established carbapenem resistance.	
58	Observational	To identify and control CRKP originating from endoscopic equipment	206-beds cancer center + 988 beds tertiary hospital. Florida, USA.	Active surveillance using rectal swabs Source isolation Contact precautions Environmental cleaning Hand hygiene PPE: Gowns + gloves MDRO flags on EMRs and charts Duration: 6 months. Involved: Epidemiologists and health personnel	7 CRKP cases identified resistant to imipenem		Transmission of carbapenem resistant genes across microbial spp within the same environment contributes to resistance. KP outbreaks have also been associated with contaminated sinks, IV saline solutions, bath soap, and ultrasonography gel
59	Quasi-experimental	To assess the impact of intensified IC measures on colonization and infections associated with CRKP, P. aeruginosa, and Actionbater baumannii	Hippokration General Hospital. Solid organ transplant department. Thessaloniki, Greece	Active surveillance, contact precautions, hand hygiene, education, environmental cleaning, monitoring adherence, audit and feedback. Duration: 17 months. Involved: Nurses, doctors, non-surgical staff.	Reduction in incidence of colonization from 19 to 9%. Improved adherence to contact precautions. An increase in the monthly incidence of CR bacteria from 2.8 to 6.9/ 1000 PDs	In CR gram -ve bacteria endemic regions, SOT patients have disproportionately higher infections rates of the organisms. Implementation of enhanced IC measures significantly reduces the colonization	
60	POS	To control an outbreak of imipenem resistant K. pneumoniae (IR-KP)	Abdominal surgery care center. 15-bed liver ICU. France	Screening all patients + Contact isolation + hand hygiene using alcohol-based hand sanitizer. Enhanced measures: Isolating carriers, dedicated staff, restricting ward admissions, and strict control of patient transfers.	Rapid containment of the outbreak		

				Duration: 4 months. Involved: Nurses, medical staff, physicians, and microbiologists.			
61	Quasi-experimental	To establish if IPC interventions can reduce CRKP infection in ICU	ICU China 629 patients enrolled.	Screening of cultures, de-escalation interventions, contact precautions, isolation precautions, sterilization and disinfection, and bundles (for IV catheter infections, VAP, CAUTIs, and skin or soft tissue infections). Duration: 24 months Involved: Consultants, physicians, nurses, ID specialists	CRKP incidence reduced from 10.08 to a low of 2.84 cases per 1000 PDs. ICU acquired CRKP bloodstream infections decreased from 2.54 to 0.41 cases per 1000PDs	Comprehensive IPC interventions significantly reduced ICU related CRKP infections	
62	Quasi-experimental	To assess the effect of IPC on a CRKP outbreak	NICU. 20-beds. 8 patients. China	Active surveillance using rectal swabs. IPC measures: hand hygiene, auditing compliance, environmental cleaning, and isolating patients. Duration: 8 months Involved: Nurses and IP professionals	Outbreak containment after isolation and IPC measures.	Physical isolation is important in preventing the spread of MDROs. ASP is useful in reducing the spread of MDROs	
63	Cohort. POS	Assessing the effectiveness of multidisciplinary interventions on the transmission of ESBL-KP	Parkland Memorial Hospital. NICU. 61 infants. Dallas, USA	Re-educating staff. Auditing hand hygiene and environmental sanitation. Contact precautions. Isolating Staff & infants. Reducing overcrowding. Screening NICU cultures frequently. Duration: 3 weeks. Involved: Neonatologists, ID physicians, nurses, managers, epidemiologists, respiratory therapists, microbiologists, IP staff, and environmental officers.	Outbreak contained within three weeks	Multidisciplinary intervention using standard IPC measures halted the transmission of ESBL-KP in the NICU.	
64	POS	To halt the spread of CRKP	Cà Granda Ospeda- le	Active surveillance.	Outbreak containment		

			Maggiore Hospital. ICU. Milan, Italy	Isolation. Hand hygiene. Duration: 2 months. Involved: Healthcare workers.			
65	ROS & POS	To assess the effect of enhanced contact precautions on CRE/ CRKP incidence and resistance rates	Tertiary care university hospital. 900 beds. South Korea	Staff education Contact precautions without active surveillance. Cohort isolation. Hand hygiene. Duration: ?6 years Involved: physicians and medical personnel	An initial increase of the CRE cases (from 1.62 to 9.81/100,000PDs) after which the rates fell back to (0.882/ 100,000PDs0 below baseline levels. A reduction in the resistance rates to imipenem and meropenem following enhanced contact precautions. Hand hygiene adherence improved from 35.2% to 70%	Enhanced infection control measures without active surveillance appear to be effective against the spread of CRE in low prevalence settings	
66	ROS & POS	To stop the spread of ESBL-producing nosocomial bacteria in NICU	17-bed NICU. 355 patients observed. University of Szeged Pediatrics Department. Hungary	Introduction of the INSURE protocol. Antimicrobial regimens review. Microbiological screening. Bathing protocol. Hand hygiene. Continuous monitoring of cases. Duration: 3 months. Involved: Nurses, clinicians, cleaning staff, all staff.	A significant reduction in the proportion of CRKP colonization or infections. Average number of PDs reduced from 343.72 to 292.44 PDs/ month. Hand hygiene compliance improved from 26.02 to 33.6 HH procedures per patient per hospital day.	A successful roll back of the CRE infections and colonization was achieved through an interdisciplinary approach.	ESBL-producing bacteria includes E. coli, Enterobacteriaceae, and KP
67	Quasi-experimental	To track an outbreak of ESBL-KP using WGS	The University Medical Center Groningen (UMCG). 1300 bed tertiary care center. Netherlands	Screening patients and the environment using WGS. Duration: 6 months. Involved: Nurses, physicians, respiratory therapists, housekeepers, and visitors.	There was no association between the sporadic case of KP and those that had been diagnosed prior to 2013	Tailor-made makers for identifying genomic signatures have potential for improving the efficiency of IPC measures	

BMJ Open

Antimicrobial stewardship and infection prevention interventions targeting healthcare associated Clostridioides difficile and carbapenem-resistant Klebsiella pneumoniae infections: A scoping review.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-051983.R1
Article Type:	Original research
Date Submitted by the Author:	18-Jul-2021
Complete List of Authors:	Okeah, Bernard; Bangor University Morrison, Valerie; Bangor University, School of Psychology Huws, Jaci; Bangor University, School of Health Sciences
Primary Subject Heading:	Public health
Secondary Subject Heading:	Infectious diseases, Public health, Epidemiology
Keywords:	PUBLIC HEALTH, Infection control < INFECTIOUS DISEASES, MICROBIOLOGY, PREVENTIVE MEDICINE, EPIDEMIOLOGY

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Antimicrobial stewardship and infection prevention interventions targeting healthcare associated *Clostridioides difficile* and carbapenem-resistant *Klebsiella pneumoniae* infections: A scoping review.

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(Word count: 6093 words)

Antimicrobial stewardship and infection prevention interventions in healthcare settings

Abstract

Objectives: This study assessed antimicrobial stewardship (AMS) and infection prevention (IP) interventions targeting healthcare associated *Clostridioides difficile* and carbapenem-resistant *Klebsiella pneumoniae* (CRKP) infections, their key outcomes, and the application of behaviour change principles in these interventions.

Design: This scoping review was conducted in accordance with PRISMA Extension for Scoping Reviews (PRISMA-ScR) guidelines while focusing on acute healthcare settings in both low-to-middle income and high-income countries.

Data sources: The databases searched were MEDLINE, PubMed, Web of Science, and CINAHL between 22/04/2020 and 30/09/2020.

Eligibility: The review included peer reviewed articles published in English language between 2010 and 2019. Studies that focussed on infection prevention and/ or antimicrobial stewardship interventions primarily targeting *C. difficile* or carbapenem-resistant *K. pneumoniae* (CRKP) were included. Studies that assessed effectiveness of diagnostic devices or treatment options were excluded from this review.

Data extraction and synthesis: An abstraction sheet calibrated for this study was used to extract data on the main study characteristics including the population, intervention, and outcomes of interest (antimicrobial use, compliance with IP interventions, and risk for *C. difficile* and CRKP). A narrative synthesis of the results is provided.

Results: The review included 34 studies. Analysis indicates that interventions targeting *C. difficile* and CRKP include **E**ducation, **S**urveillance/**S**creening, **C**onsultations, **A**udits, **P**olicies and **P**rotocols, **E**nvironmental measures, **B**undles, **I**solation, as well as **N**otifications or alerts (represented using the ESCAPE-BIN acronym). The identified outcomes include antimicrobial use, resistance rates, risk reduction, adherence to contact precautions, hospital stay, and time savings. AMS and IP interventions tend to be more adhoc with limited application of behaviour change principles.

Conclusion: This scoping review identified the AMS and IP interventions targeting *C. difficile* and CRKP in healthcare settings and described their key outcomes. The application of behaviour change principles in AMS and IP interventions appears to be limited.

Key words: Antimicrobial, antibiotics, resistance, stewardship, Clostridioides difficile, carbapenem-resistant Klebsiella pneumoniae, healthcare associated infections, infection prevention.

Ethics statement: This study does not involve human participants. Permission to conduct this review was granted by Bangor University's Research and Ethics Committee.

Strengths and limitations

- This review considered the specific AMS and IP interventions in line with the core elements of AMS as outlined by the CDC.
- The review only considered studies that primarily focussed on AMS and/ or IP interventions targeting *C. difficile* and/ or CRKP.
- The screening and selection of studies as well as data extraction were completed by two reviewers.
- The COM-B ("capability", "opportunity", "motivation", and "behaviour") model elements were used to assess the application of behaviour change principles in AMS and IP interventions.

Introduction

Infectious diseases have remained a leading cause of morbidity and mortality over the past centuries [1]. The discovery of antimicrobial agents during the 19th and 20th century [2] following observations by Alexander Fleming on the effect of *Penicillium* on bacteria cultures birthed the era of anti-infective agents [3] and was a major breakthrough in the fight against infectious diseases. In 1947, Waksman, coined the term "antibiotic" in reference to a chemical agent capable of destroying or inhibiting the growth of microorganisms [4]. Subsequently, clinicians began to recognise and rely on antibiotics as an effective strategy for treating and eradicating pathogenic microorganisms. As the use of antibiotics gained popularity worldwide with noted successes including the treatment of gram positive cocci with penicillin [3], [5], a new threat namely antimicrobial resistance (AMR), emerged due to the over-reliance on these life-saving therapeutic agents [6]. More than 50% of antimicrobials used are either inappropriate or unnecessary and within the last two decades alone, the use of antimicrobial agents has risen by 65% significantly contributing to AMR [7]. Coupled with the rapid human-to-human transmission of pathogens [8], microorganisms continue to evolve adaptively rendering antibiotics ineffective [9]–[11] and causing more potent infections as they acquire resistance. AMR represents a public health emergency with 10 million fatalities globally projected by 2050 [12] coupled with increasing costs for treating multi-drug resistant organisms (MDROs) [13].

Today, the mortality burden of infectious diseases remains high globally [14] with a worrying increase of deaths attributable to MDROs. A modelling study reported 33,000 deaths associated with MDROs in Europe in the year 2015, representing a significant rise since the year 2007 [15]. Healthcare settings appear to have a higher risk of human-to-human transmission of MDROs. According to the European Center for Disease Prevention and Control (ECDC), the EU records an estimated 3.2 million healthcare associated infections (HAIs) and an associated 37,000 deaths annually [16]. This translates to 2.5 million disability adjusted life years (DALYs), 16 million additional hospitalization days, and an annual economic burden of 7 billion euros [17], [18]. This burden is largely attributed to MDROs [19] of which ESKAPE (***E**nterococcus faecium, **S**taphylococcus aureus, **K**lebsiella pneumoniae, **A**cinetobacter baumannii, **P**seudomonas aeruginosa, and **E**nterobacter spp)* pathogens play a significant role [20]–[23]. In recent years, scientists have suggested the inclusion of *Clostridioides (Clostridium) difficile* as a member of the ESKAPE pathogens and subsequently amending the acronym to **ESCAPE** pathogens [24]. Significant efforts have been made to reduce the burden of healthcare associated infections, but the problem persists. To aid the understanding of potential gaps in evidence, this scoping review explored the literature on interventions targeting *C. difficile* and carbapenem-resistant CRKP which are amongst the most common infections in healthcare settings and on the WHO's pathogen priority list for research and development of new antibiotics.

Rationale

A preliminary exploration of literature retrieved three scoping reviews on antimicrobial misuse and AMS interventions. The first scoping review [25] was limited to dentistry settings; the second [26] examined literature on knowledge, attitudes, and practices amongst community pharmacists and the third focussed on supply related factors for reducing prescription of antibiotics in low-to-middle-income countries [27]. In this scoping review, the focus is on healthcare associated *C. difficile* and CRKP infections. *C. difficile* is the single most leading cause of nosocomial diarrhea globally primarily linked with the use of antibiotics that disrupt the stability of gut microbiota allowing the pathogenic bacteria to flourish [28]–[30]. *K. pneumoniae* ranks amongst the top three leading causes of neonatal sepsis in resource limited settings [31], [32] with some strains known to produce extended-

spectrum B-lactamases (ESBL) associated with multi-drug resistance to carbapenems and colistin [33]. More often, cultures obtained from patient environments, stools, water, and blood, have been shown to contain *CRKP* [33] and *C. difficile.* Studies show that approximately 25% of patients in England, Australia, and the United States of America are colonized by CRKP during their hospitalization period [33]–[35]. Patient-to-patient transmission of CRKP accounts for an estimated 52% of the cases identified in healthcare settings [36]. There appears to be evidence-based infection prevention (IP) and antimicrobial stewardship (AMS) interventions aimed at curbing the healthcare associated transmission of *C. difficile* and CRKP. However, the prevalence of infections caused by these organisms remains high. The interventions broadly aim at changing the behaviours of healthcare workers with regards to antimicrobial prescribing and/ or compliance with infection prevention measures. As recently acknowledged by the World Health Organisation [37], it has become increasingly clear that application of evidence-based interventions is not a guarantee for success emphasizing the need to focus more on the underlying psychosocial mechanisms that influence people's behaviours [38], [39]. It therefore remains unclear whether there is sufficient application of current evidence on behaviour change in AMS and IP interventions for improved effectiveness and sustainability, hence, this scoping review.

Research objectives

1. To assess infection prevention (IP) and antimicrobial stewardship (AMS) interventions targeting healthcare associated *C. difficile* and CRKP.
2. To describe the key outcomes for IP and AMS interventions targeting healthcare associated *C. difficile* and CRKP.
3. To assess the application of behaviour chane principles in IP and AMS interventions targeting healthcare associated *C. difficile* and CRKP infections.

Methods

Research protocol

The protocol for this scoping review is available on Open Science Framework (OSF) registries via https://osf.io/nk7wf. This scoping review was undertaken and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis Extension for Scoping Reviews (PRISMA-ScR) guidelines [40]. These guidelines integrate the five-stages proposed by Arksey and O'Malley with regard to the conduct of scoping reviews [41].

Eligibility criteria

Table 1 below summarizes the eligibility criteria that was used to screen the retrieved articles. The review included peer-reviewed studies involving human participants published in English over the previous ten years Studies on infection prevention and/ or antimicrobial stewardship that did not primarily target *C. difficile* or CRKP were excluded as were studies that explored new diagnostic devices or therapeutic interventions in relation to the two organisms.

Table 1: Eligibility criteria

	Proposed criteria	**Refined criteria**
Population/ Setting	Healthcare facilities	Healthcare facilities
Intervention/ Exposure	AMS interventions for *C. diff* or *CRKP*	Infection prevention and antimicrobial stewardship interventions primarily targeting *C. difficile* and/ or CRKP
Comparison	No intervention	No intervention
Outcome	Control of *C. diff* and/ or *CRKP*	Changes in use of antimicrobial agents associated with *C. difficile* or CRKP. Compliance with IPC interventions Risk of *C. difficile* and CRKP
Study designs	All study designs	Observational studies, quasi-experimental studies, randomised controlled trials (RCTs)

Information sources

The search for literature was conducted across electronic databases accessible through the Bangor University library search engine, bibliographies, key journals, and websites for relevant organisations. The specific databases searched were MEDLINE via EBSCO*host*, PubMed Open Access via NCBI, Web of Science Core Collection, and CINAHL Plus via EBSCO*host* (see search strategy in supplementary file 1). The search for sources was undertaken with the assistance of the Bangor University librarian between 22/04/2020 and 30/09/2020. To ensure that the search was comprehensive and inclusive, a search of additional sources including unpublished and grey literature, general searches on Google Scholar as well as PhD theses and dissertations was conducted.

Study selection

Two reviewers (BO and EL) independently applied the inclusion and exclusion criteria on the retrieved articles for inclusion in this review and resolved any disagreements through discussions.

Data charting

The data items extracted (see supplementary file 2) included the reference, the study type, the study objectives, population or setting, country, the intervention, intervention duration, healthcare workers involved, outcome measures or findings, and the conclusions of the study. Twenty percent of the extracted data was checked for completeness and accuracy by the two reviewers who exchanged their extracted data for checking. See supplementary file 2 for presentation of the extracted study characteristics.

Results collation, summary, and report compilation

The extracted data was organised into themes and a narrative synthesis was conducted. The subsequent sections provide a narrative synthesis of the existing literature on IP and AMS interventions targeting *C. difficile* and CRKP as well as the identified gaps in line with the study objectives.

Patient and public involvement

There were no patients involved in the conduct of this scoping review.

Results

Selection of studies

The Prisma diagram in Figure 1 (see figure 1) summarises the study screening and selection process. Thirty-four studies were ultimately included in the current review.

Figure 1: PRISMA flow diagram

Characteristics of selected studies

Sixteen studies (see Table 2) focussed on *C. difficile*[42]–[57] and 18 studies (see Table 3) focussed on CRKP [58]–[75]. The studies varied in their designs with the majority (n=31) being quasi-experiments. Other study designs included cohort studies (n=2) and one secondary analysis of a randomized controlled trial. Twenty-seven studies were undertaken prospectively, whereas 7 studies followed a retrospective approach. 32.4% (n=11) of the studies were conducted in the United States of America [45], [48], [49]–[52], [54], [56], [57], [66], [71], whereas two studies each are based in Canada [42], [44] and Greece [65], [67]. Four of the retrieved studies were conducted in Italy [43], [47], [64], [72] while Israel [55], [60], [63] and China [59], [69], [70] had three studies each. Lastly, the selected articles included one study each from Japan [53], United Kingdom [46], South Africa, Denmark [61], Brazil [62], France [68], South Korea [73], Hungary [74], and the Netherlands [75]. There were variations in the study populations with three studies on *K. pneumoniae* involving neonates in the neonatal intensive care unit [70], [71], [74] whereas 31 studies involved adults admitted for care within the hospital settings. All the studies on *C. difficile* involved adult populations [70], [71], [74].

Synthesis of results

Interventions

Broadly, the interventions entailed components of antimicrobial stewardship (AMS) and/ or infection prevention (IP) measures targeting *C. difficile* and CRKP. Tables 2 and 3 below provide an outline of the specific AMS or IP components included across the included studies. The duration of interventions varied across the studies from three weeks up to six years [73]. The interventions involved various cadres of professionals namely infectious disease experts, consultants, nurses, doctors, physicians, pharmacists, epidemiologists, laboratory personnel, microbiologists, and support staff (cleaners, caregivers, housekeepers, paramedics, porters, environmental officers). Additional cadres involved include managers, infection control staff, unspecified clinicians/ medical personnel, quality improvement (QI) staff, patients, public health staff, and patient visitors. Figure 2 summarizes the proportions while supplementary file 2 highlights the specific cadres of health professionals included across study interventions.

The interventions tended to be multi-faceted involving the implementation of at least two strategies to achieve the intended outcomes as highlighted in Tables 2 and 3. The strategies employed in interventions targeting *C. difficile* and how they were combined across studies are also summarised in table 2.

Antimicrobial stewardship and infection prevention interventions in healthcare settings

Table 2: IP and AMS interventions targeting C. difficile.

	References															
Interventions	[42]	[43]	[44]	[45]	[46]	[47]	[48]	[49]	[50]	[51]	[52]	[53]	[54]	[55]	[56]	[57]
Surveillance/ Screening	-	-	-	-	✓	-	✓	-	-	-	-	✓	-	-	-	-
Alerts and notifications	-	-	-	-	-	-	✓	-	-	-	-	✓	-	-	✓	-
Isolation precautions	-	-	-	-	-	-	✓	-	-	-	-	✓	-	✓	✓	✓
Environmental disinfection	-	-	-	-	-	-	-	-	-	✓	-	-	-	✓	-	✓
Audits and feedback	✓	-	✓	✓	-	✓	-	-	-	-	✓	✓	✓	-	-	-
Consultations	-	✓	✓	-	-	-	-	-	-	-	-	-	-	-	-	-
Antimicrobial policies and/ protocols	-	✓	-	-	✓	-	-	-	-	-	✓	-	-	-	✓	-
Care bundles	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	✓
Staff education	-	✓	✓	-	✓	-	-	-	-	-	✓	-	-	✓	-	-
Biocidal (Cu_2O) linen	-	-	-	-	-	-	-	✓	✓	-	-	-	-	-	-	-
Intervention duration (months)	24	18	18	12	16	18	-	8	27	27	16	12	13	24	-	22
Behaviour change elements addressed																
Capability	✓	✓	✓	✓	✓	✓	✓	-	-	-	✓	✓	✓	✓	✓	✓
Opportunity	-	✓	✓	-	-	✓	-	-	-	-	-	-	-	-	-	-
Motivation	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

The most common strategy targeting *C. difficile* reported across seven studies involved the use of audits and feedback [42], [44], [45], [47], [52]–[54]. This entailed reviewing the prescribed antibiotics by an antimicrobial pharmacist [42], [44], [45], [47], [52], [54] or the infection control team [53] and feedbacking to the prescriber. In some instances, the audits were undertaken offsite using electronic records systems [44], [45] and teleconferences. Audits were also combined with staff education sessions organised on identified gaps aimed at optimising the use of antimicrobials [44], [52]. Some interventions combined the audits with formulary restrictions and treatment protocols occasionally requiring approval prior to issuing a prescription [52]. Another intervention combined audits with screening patients and notifying physicians on detection of *C. difficile*, promptly isolating infected patients, and monitoring appropriate use of antibiotics with prompt feedback to the responsible prescribers [53]. Additional interventions with a component of staff education included bedside infectious diseases consultation [43], restricting the use of broad spectrum antibiotics [43], [46], [55], and contact precautions [55]. Bedside consultations involved a part-time infectious diseases expert reviewing antibiotic prescriptions three times a week and discussing these with attending physicians [43]. This was coupled with revising antimicrobial treatment protocols and educating staff on reducing the appropriate use of antimicrobials [43]. Lastly, an intervention undertaken in a hospital caring for older adults involved educating all healthcare workers on isolation precautions and environmental disinfection as well as restricting the use of broad spectrum antibiotics [55].

A multi-site collaborative intervention involving an infection prevention bundle also promoted adherence to isolation precautions and an environmental cleaning protocol [57]. The isolation precautions included nursing patients in a single room, hand washing at recommended times, and the use of appropriate personal protective equipment namely

gloves, and disposable aprons. Environmental cleaning entailed the use of appropriate decontamination agents to clean the patient environment and reduce the presence of *C. difficile.* A single centre study [56] combined isolation precautions with a computer generated real time notification system for toxigenic *C. difficile* results and a treatment protocol using vancomycin only or vancomycin with metronidazole. The final study on isolation precautions [48] also incorporated an automated system that tracked *C. difficile* results and triggered alerts on the patient's electronic records as well as automatically ordering for the appropriate isolation precautions thus aiding the healthcare personnel's actions. Three standalone interventions [49]–[51] aimed at reducing the bioavailability of *C. difficile* in the hospital environment. One multisite randomised controlled trial employed four disinfection strategies for environmental cleaning following the discharge of *C. difficile* patients [51]. These strategies included standard disinfection with an ammonium solution or 10% hypochlorite (bleach), standard disinfection with ultraviolet (UV) light or bleach with UV light, bleach only, or UV light with bleach [51]. Lastly, two quasi-experiments involved replacing hospital linen with biocidal coper oxide impregnated bedsheets, pillow cases, washcloths, and towels [49], [50].

Interventions targeting carbapenem-resistant *K. pneumoniae* (CRKP) included surveillance and/ or active screening through the use cultures[58], [60], [63]–[66], [68]–[71], [72], [74]–[76], alerts and notifications upon detection of CRKP [58], [60], [61], [63], [65], [66], isolation precautions [58], [60], [63]–[66], [68]–[72], [74], [76], environmental decontamination [60], [64], [66], [67], [69]–[71], antimicrobial audits and feedback [61], [63], [67], [71], specialist consultations [64], antimicrobial policies and/ or protocols [58], [61], [62], [74], care bundles [69], and staff and/ or patient education [60], [61], [67], [71], [72]. The commonest strategy targeting CRKP appears to be surveillance or active screening through cultures to detect the presence of CRKP. One surveillance intervention [58] involved the use of a flagging system for suspected patients at the emergency department, cohorting active cases, sampling cultures from hands of healthcare personnel and the environment, and a policy restricting the use of carbapenems. Another multisite intervention [63] combined routine screening of patients with mandatory isolation of confirmed cases with dedicated staff looking after the patients and mandatory notification of all carbapenem resistant cases to public health authorities. Similarly, a surveillance intervention [65] in a 250-bed general hospital required adherence to isolation precautions and compulsory notification of public health authorities on identified cases.

Antimicrobial stewardship and infection prevention interventions in healthcare settings

Table 3: IP and AMS interventions targeting CRKP.

	References																	
Interventions	[58]	[59]	[60]	[61]	[62]	[63]	[64]	[65]	[66]	[67]	[68]	[69]	[70]	[71]	[72]	[73]	[74]	[75]
Surveillance/ Screening	✓	✓	-	-	-	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	-	✓	✓
Alerts and notifications	✓	-	✓	✓	-	✓	-	✓	✓	-	-	-	-	-	-	-	-	-
Isolation precautions	✓	-	✓	-	-	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	-
Environmental disinfection	-	-	✓	-	-	-	✓	-	✓	✓	-	✓	✓	✓	-	-	-	-
Audits and feedback	-	-	-	✓	-	✓	-	-	-	✓	-	-	-	✓	-	✓	-	-
Consultations	-	-	-	-	-	-	✓	-	-	-	-	-	-	-	-	-	-	-
Antimicrobial policies and protocols	✓	-	-	✓	✓	-	-	-	-	-	-	-	-	-	-	-	✓	-
Care bundles	-	-	-	-	-	-	-	-	-	-	-	✓	-	-	-	-	-	-
Staff education and/ patient education	-	-	✓	✓	-	-	-	-	-	✓	-	-	-	✓	-	✓	-	-
Intervention duration (months)	36	14	48	36	24	14	2	36	6	17	4	24	8	<1	2	72	3	6
Behaviour change elements addressed																		
Capability	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Opportunity	-	-	-	✓	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Motivation	-	-	-	✓	✓	-	-	✓	-	-	-	-	-	-	-	-	-	-

An outbreak containment intervention [58] in a tertiary hospital employed active screening of patients, disinfection of the environment and respiratory equipment, and isolation precautions. One standalone intervention investigated the effectiveness of active screening on detection of CRKP cases in an ICU setting [59] while another study tracked sporadic hospital outbreaks using whole genome sequencing [75]. An observational study used rectal swabs for the active surveillance of CRKP in a cancer centre and a tertiary hospital [66]. Subsequently, the confirmed cases were promptly isolated requiring healthcare personnel's adherence to contact precautions and environmental cleaning protocols [66]. Other surveillance interventions similarly effected isolation precautions for confirmed cases [68] combined with either environmental cleaning protocols, staff education, adherence audits, or a bathing protocol [67], [68], [70]–[72], [74]. An intervention based in an Israeli medical centre rolled out isolation guidelines in combination with staff education, and environmental cleaning protocols supported with a computerized system for flagging CRKP cases [60]. A multi-disciplinary intervention in a 510-bed Danish university hospital employed Kotter's eight stages of change [61] by delivering staff training and notification systems to enhance isolation precautions, and appropriate use of antimicrobial agents. An antimicrobial stewardship intervention in a Brazilian tertiary care hospital examined the effectiveness of a restrictive antimicrobial policy on the use of carbapenems [62]. Lastly, a south-Korean based study in a 900-bed tertiary university hospital examined the effectiveness of enhanced contact isolation precautions on CRKP incidence. This was delivered through staff education, auditing prescriptions, and discontinuing inappropriate antibiotics within 72 hours, and strict adherence to contact precautions including hand hygiene, single use gowns, and gloves.

Outcomes reported from IP and AMS interventions targeting *C. difficile* and CRKP.

The key outcomes reported across the studies included consumption of antimicrobial agents [42]–[44], [46], [47], [52], [53] and/ or associated costs [42], [43], [44]–[47], [52], [53], [58], [61], [62], incidence of *C. difficile* [42], [43], [44]–[47], [49]–[52], [53]–[55], [57], or incidence and/ resistance rates of carbapenem-resistant *K. pneumoniae* [58]–[64], [67],

[69], [73], [74], as well as risk of other HCAIs [44], [51], [53], [57], [60], [67], [69], outbreak containment [65], [66], [68], [70]–[72], [75], adherence to infection prevention precautions [44], [50], [57], [64]–[66], [70], [73], [74], time savings [48], [56], hospital stay [74], and associated mortality rates [43]. Table 4 and Table 5 below summarise the reported outcomes.

Interventions targeting C. difficile.

Antimicrobial use

Seven studies reported variations in the consumption of antimicrobial agents following the stewardship interventions [42], [44], [45], [47], [52]–[54]. The changes in antimicrobial use were reported in daily defined doses per 1000 patient days (DDD/1000PDs). Reduction in the use of antimicrobials ranged between 6.58 DDDs/1000 PDs and 310 DDDs/1000 PDs. The least (11%) reduction in antimicrobial use was reported from an intervention that involved audits for prescribed antibiotics and providing feedback to the prescribers [42]. The largest (79%) reduction in antimicrobials use was reported following an intervention involving restrictive antimicrobial policies and staff education [46]. A 54% reduction in antimicrobial costs was reported from an intervention involving half-hour monthly staff education sessions on antimicrobial stewardship and audits of prescribed antibiotics using a structured electronic checklist [44]**.** 679 patients from two internal medicine units in a tertiary care hospital were observed over eighteen months in the study [44]. One study reported a 52% improvement in antimicrobial streamlining following weekly reviews of prescribed antibiotics combined with remote consultations with an infectious diseases pharmacist through teleconferencing [54]. The latter study was conducted in a 141-bed community hospital over 13 months [54]. None of the *C. difficile* targeting interventions reported on the resistance rates for specific antimicrobial agents following their implementation.

Table 4: Summary of outcomes for interventions targeting C. difficile.

Key outcomes	References															
	[42]	[43]	[44]	[45]	[46]	[47]	[48]	[49]	[50]	[51]	[52]	[53]	[54]	[55]	[56]	[57]
Antimicrobials use (DDD/1000PDs)	↓310	↓200		↓6.58	↓124	↓141					↓34	↓10.7				
Antimicrobials use (% reduction)	11	47	46		72.5-95	22					12	37				
Antibiotics cost (↓%)			↓54			↓24							↓51			
Antimicrobials streamlining (%/week)													↑52			
Resistance rates																
CD risk/100,000 or/10000PDs (post-intervention)	⇔	12		14	55	60			2.8	170	2.8	11	16	⇔		85
CD absolute risk (%)	⇔	↓67	↓46	↓83	↓77	↓31		↓51	↑87	↓5	↓71	↓36	↓71	⇔		↓37
Risk of HCAIs (AR)		↓25			17-25					⇔		↓				↓
% reduction in time for start of treatment															64	
Time savings (hrs/1000 admissions)							↓43									
Hospital stay																
Adherence to infection prevention precautions (%)									↓6							↑95
Mortality		⇔														

DDD: Daily defined doses; PD: Patient days; CD: C. difficile; HCAIs: Healthcare associated infections; AR: Absolute risk, ↓: Significant reduction ↑: Significant increase; ⇔: No significant changes (Remained the same); ●: Outbreak was contained.

Risk of CDIs, other HCAIs, and associated mortality

Fourteen studies reported on the impact of the interventions on the risk of *C. difficile* infections (CDIs) or other healthcare associated infections [42], [43], [44]–[47], [49]–[52], [53]–[55], [57]. The highest overall reduction of 83% in absolute risk of CDIs was reported from a 12-months antimicrobial audits and feedback intervention involving physicians and pharmacists in a 212-bed Massachusetts hospital [45]**.** On the other hand, a 24-month multisite intervention amongst leukemia patients involving antimicrobial audits and feedbacks [42] reported no significant change on the risk of CDIs and associated mortality. Similarly, a second 24-month cross-sectional study involving older adults from two Israeli hospitals that entailed staff education, environmental disinfection, and isolation precautions had no impact on the risk of CDIs [55]. Regarding the effect of CDI interventions on other HCAIs, an antimicrobial stewardship intervention in a 150-bed spinal injury hospital involving bedside infectious diseases consultation, staff education, and antimicrobial policies reported a 25% absolute risk reduction for other HCAIs [43] but no differences on mortality between the experimental and control groups [43]. A multisite RCT investigating the effectiveness of four environmental disinfection strategies reported no effect on the risk of other HCAIs [51]. A twelve-months intervention assessing the impact of intensified IPC precautions on MDROs in a 409-bed Japanese tertiary hospital reported a reduction in the risk of other HCAIs but it's not clear whether this change was significant [53]. Two studies involving the use of biocidal linen impregnated with copper oxide reported contradictory findings which could be partly due to the differences in study settings and how the interventions were delivered. The first study involved six hospitals in both urban and rural settings with a total of 1019 beds implemented over eight months (568,397 patient days) and reported a 51% reduction in the risk of CDIs [49]. The second study was conducted in one long-term care hospital over 27 months (29,342 patient days) reported an 87% increase in the risk of CDIs [50]. In the latter study, the researchers acknowledged that study participants were never blinded possibly leading to the deterioration of contact precautions specifically hand hygiene that reduced by 6% [50].

Adherence to isolation precautions

The highest (95%) improvement in adherence to isolation precautions was reported by a 22-months multisite (35 hospitals) intervention [57] involving the use of an infection prevention bundle with isolation precautions and an environmental cleaning protocol [57]. On the other hand, an intervention involving the use of biocidal linen impregnated with copper oxide reported a 6% reduction in adherence to isolation precautions [50] as discussed above.

Time savings

Two studies reported outcomes related to time savings [48], [56]. The first intervention involved treatment protocols for *C. difficile*, real-time computerized notifications of toxigenic *C. difficile results*, and isolation precautions. This was undertaken in a 433-bed adults medical center and recorded a 64% reduction in time prior to the initiation of appropriate antibiotics treatment [56]. The second study involving active surveillance, an alert system, and isolation precautions in a 410-bed hospital treating trauma, burns, and cancer patients reported a 43% reduction in care hours per 1000 admissions [48]**.** There were no studies on *C. difficile* that reported on the effect of interventions on the length of hospital stay.

Carbapenem-resistant *K. pneumoniae*

Antimicrobials use.

Three studies [58], [69], [70] reported on antimicrobial use as a key outcome of CRKP interventions. One study involving a flagging system for confirmed cases, isolation precautions, and a carbapenems restriction policy in a 1000-bed tertiary university hospital reported a reduction in the use of meropenem [58]. The second study employed Kotter's stages of change [61] in a multi-disciplinary intervention involving staff education on isolation precautions and appropriate prescribing, notifications on prescription of restricted antibiotics and antimicrobial protocols in a 510-bed Danish hospital recorded a 75% reduction in antibiotics consumption [61]. The last study involving restrictive antimicrobial policies reported a 21% (12.9 DDDs/1000 PDs) reduction in antibiotics use [62]. Two interventions involving active surveillance through screening [59] and staff education combined with isolation precautions [73] reported a reduction of the resistance rates for *K. pneumoniae*. The first intervention was conducted over 14 months in an ICU setting in China [59] while the second intervention was undertaken in a 900-bed tertiary hospital in South Korea [73]. A 24-months intervention in a tertiary hospital (200 beds) involving restriction of group two carbapenems recorded no changes in the resistance rates for *K. pneumoniae* [62].

Risk of CRKP, other HCAIs, and associated mortality.

The largest risk reduction (97%) for CRKP was reported from a 36-months hospital wide intervention that involved physicians, epidemiologists, nurses, and the infection control team [58]. The lowest reported reduction in the absolute risk of CRKP was from a 17-months multi-faceted intervention that entailed active surveillance, isolation precautions, audits and feedback, environmental cleaning, and staff education [67]. Seven outbreak investigations did not have outcomes on the relative risk CRKP [65], [66], [68], [70]–[72], [75]. An intervention involving staff education, isolation, environmental cleaning, and computerized flagging of cases reported a 55% reduction in other HCAIs [60] while another intervention involving screening, isolation, environmental disinfection, and care bundles reported an 84% reduction in other HCAIs over a 48 months period [69]. On the other hand, one study reported a 59% rise in the risk of other HCAIs following an intervention that involved screening, isolation, environmental decontamination, audits, and education over a 17 months duration [67]. The intervention involved 601 patients retrospectively and 250 patients prospectively in the solid organ transplant (SOT) department. The increase in the incidence of other carbapenem resistant organisms was attributed to the intrahospital transfer of carriers to the SOT department and the subsequent transfer of post-surgical patients to the ICU where they were allegedly colonized by the bacteria [67]. There are no studies that reported on mortality associated with CRKP.

Table 5: Summary of outcomes for interventions targeting CRKP.

Key outcomes	References																	
	[58]	[59]	[60]	[61]	[62]	[63]	[64]	[65]	[66]	[67]	[68]	[69]	[70]	[71]	[72]	[73]	[74]	[75]
Antimicrobial use (DDD/1000PDs)	↓				13													
Antimicrobials use (% reduction)				↓75	↓21													
Antibiotics cost (↓%)																		
Antimicrobials streamlining (%/week)																		
Resistance rates		↓			⇔				●							↓		
CRKP risk/100,000 or/10000PDs	18		0.5	23%		↓	56		↓	↓	●	28				0.9	↓	
CRKP absolute risk (%)	↓97		↓92	↓17	12	12	●	●	10	●		●	●	●	46	↓	●	
Risk of HCAIs (AR)			↓55						↑59		↓84							
% reduction in time for start of treatment																		
Time savings (hours/1000 admissions)																		
Hospital stay (%PDs)																↓15		
Adherence to IP precautions (%)							↑	↑	↑				↑			↑35	↑29	
Mortality																		

DDD: Daily defined doses; PD: Patient days; IP: Infection prevention; CRKP: Carbapenem-resistant Klebsiella pneumoniae Ca; HCAIs: Healthcare associated infections; AR: Absolute risk, ↓: Significant reduction ↑: Significant increase; ⇔: No significant changes (Remained the same); ●: Outbreak was contained.

Hospital stay and adherence to contact precautions.

A three-month intervention involving 355 patients in a 17-bed neonatal intensive care unit in Hungary reported a 15% reduction in the hospitalization duration with an associated 29% increase in adherence to contact precautions [74]. Another six years intervention involving staff education reported a 35% improvement in adherence to contact precautions [73]. Lastly, four additional studies also reported an improvement in adherence to contact precautions [64]–[66], [70].

Application of behaviour change theory

There was only one study that explicitly stated the application of a behaviour change theory (Kotter's stages of change theory) [61], while the remaining 33 studies did not indicate whether they applied behaviour change principles or strategies in their interventions. However, 62.5% of the *C. difficile* interventions had a component that targeted modifying antibiotics prescription behaviours, and 31.3% of the interventions targeted improving compliance with infection prevention bundles, screening, isolation, hand hygiene, and environmental cleaning protocols (as summarized in table 2). However, 18.8% of the interventions lacked a behavioural component as they focused on either replacing patient linen with biocidal copper oxide or tested the effectiveness of cleaning strategies on reducing the burden of *C. difficile* in hospital settings. On the other hand, 22.2% of CRKP interventions had a component targeting antibiotics prescription behaviours whereas 94.4% of the interventions focused on improving compliance with infection prevention bundles, screening, isolation, hand hygiene, and environmental cleaning protocols (as summarised in table 3).

A mapping of the interventions using the COM-B (capability, opportunity, motivation, and behaviour) elements [77] revealed that 81.3% of the studies on *C. difficile* focused on improving the competence/ capacity of healthcare workers to adopt the desired behaviour, and, 18.8% of the studies focused on creating opportunities for healthcare workers to express the desired behaviour [43], [44], [47]. None of the interventions targeting *C. difficile* had a component aimed at motivating healthcare workers to adopt desired behaviours as recommended in the COM-B framework. However, all the interventions targeting CRKP had a component aimed at improving the competence of healthcare workers regarding the desired behaviour, 5.6% of the interventions had a component focusing on opportunities for behaviour change, and 16.7% of the studies addressed the motivation element for behaviour change [61], [62], [65].

The strategies used to enhance the capability component of behaviour change included: staff education on appropriate prescribing and/ or infection prevention precautions, trainee led audits and providing feedback [44]-[47], [54], [63], [65], [69], [70],; use of checklists, protocols and guidelines for antibiotics prescription, screening, isolation, hand hygiene, environmental cleaning, [44], [48], [52], [58], [63]-[67], [69], [71]-[74]; and the use of alerts, notifications, information leaflets, signposts, and stickers on the targeted behaviours [47], [58], [69], [70]. The strategies used to address the opportunity element of behaviour change included audits undertaken by trainee prescribers [50], opportunities to issue new prescriptions following review of the prescribed antibiotics during the patients' hospitalisation period [53], and bedside consultations with microbiologists, pharmacists, and infectious diseases consultants [44].

Discussion

Summary of evidence

This scoping review mapped studies on infection prevention (IP) and antimicrobial stewardship (AMS) interventions targeting healthcare associated *C. difficile* and CRKP published between 2010 and 2019. Interventions on antimicrobial stewardship included restrictive antimicrobial policies and treatment protocols, specialists' consultations, notifications, and alert systems, as well as audits and feedback (also referred to as academic detailing). Interventions on infection prevention precautions aimed at curbing the healthcare associated transmission of *C. difficile* and CRKP included surveillance through active screening and cultures, isolation precautions, environmental measures (disinfection and biocidal linen), use of care bundles, and education of staff and or patients. Interventions targeting *C. difficile* appeared to focus more on AMS while interventions targeting CRKP appeared to focus more on screening, isolation precautions, or environmental disinfection as core strategies. *C. difficile* and *CRKP* belong to the wider group of ESKAPE pathogens that significantly contribute to the burden of healthcare associated infections. The findings above also show that interventions targeting either *C. difficile* or CRKP have a significant impact on the health care associated risk of other ESKAPE pathogens. The interventions could also be applicable to interventions targeting other members of the ESKAPE pathogens in healthcare settings.

Based on the findings of this scoping review, we propose that the acronym ESCAPE-BIN (**E**ducation, **S**urveillance/**S**creening, **C**onsultations, **A**udits, **P**olicies and **P**rotocols, **E**nvironmental measures, **B**undles of care, **I**solation, and **N**otifications or alerts) is used to denote the common AMS and IP interventions targeting *C. difficile* and CRKP in healthcare settings. The proposed acronym provides a useful categorisation of the specific actions applicable to antimicrobial stewardship programmes as broadly outlined in the core elements for AMS by the Centres for Disease Control and Prevention (CDC) [78]. This acronym could potentially improve the understanding of the core elements by AMS teams as it highlights the specific interventions that address the requirements of the core elements. These include educating clinicians on appropriate use of antibiotics, specialist consultations to provide required expertise in antimicrobial prescribing, as well as audits, feedback and surveillance to track and report on appropriate use of antimicrobials as outlined in the core elements [37], [78]. Furthermore, the acronym provides a quick reference for AMS teams that could be useful in identifying gaps in AMS programmes or mapping intervention priorities.

This study also set out to describe the key outcomes for IP and AMS interventions targeting healthcare associated *C. difficile* and CRKP. The identified outcomes included antimicrobial use, resistance rates of the targeted pathogens, risk reduction, adherence to infection prevention precautions, hospital stay, and time savings. The majority (56%) of the interventions targeting *C. difficile* appeared to focus more on the use of antimicrobial agents as a key outcome. This is consistent with available evidence on the inappropriate use of antimicrobial agents as a key risk factor for CDIs. Recent studies have shown that reducing the prescription of antimicrobials can potentially reduce the incidence of CDIs in both healthcare and community settings [79], [80]. Comparatively, only 16% of the interventions targeting CRKP reported an impact on the use of antimicrobial agents as summarised in the findings above.

This scoping review also sought to assess whether AMS and IP interventions targeting *C. difficile* and *K. pneumoniae* incorporated existing evidence on behaviour change. A systematic review on behaviour change frameworks identified three key components namely

capability, opportunity, and motivation (COM-B) as being critical for interventions targeting behaviour change [77]. Capability refers to one's capacity/ ability (perceived or actual) to engage in a behaviour while motivation comprises the cognitive and emotional processes that energise or directs a person's behaviour. Lastly, opportunity refers to factors extrinsic to an individual that make a desired behaviour possible, such as time, equipment, space [77]. Broadly, the interventions assessed in this scoping review focussed on antimicrobial prescription behaviours and infection prevention behaviours from a 'capability' or 'opportunity' perspective. However, it was not possible to ascertain whether a specific behaviour change framework was applied across the included studies except for one intervention that applied Kotter's 8-steps model for organisational change [61] and recorded the second largest (75%) sustained reduction in antimicrobials use over a three years period. Although Kotter's model provides detailed guidance on organisational change, it's been criticised for being too top-down with more focus on the management staff as opposed to junior employees [81]. Due to the limited information provided about the interventions, this review could not establish whether the interventions considered all the critical elements necessary for successful behaviour change namely capability, opportunity, and motivation. Comparatively, interventions targeting CRKP generally appeared to impact more on the risk of other HCAIs when compared with interventions targeting *C. difficile*. This could be because CRKP interventions appeared to broadly target infection prevention behaviours of healthcare personnel which cut across most pathogens while *C. difficile* interventions broadly targeted prescription behaviours which tend to be specific to the targeted organism.

Generally, IP and AMS interventions targeting *C. difficile* and CRKP in healthcare settings tend not to be based on behaviour change principles but are rather more adhoc and building interventions around BCT and its principles could potentially lead to greater success. There was limited evidence from the included studies on how the interventions influenced compliance with either IP or AMS interventions targeting *C. difficile* and CRKP. This scoping review also established that physicians tend to be involved more in IP and AMS interventions targeting *C. difficile* and CRKP in comparison to other cadres of healthcare professionals. Almost half of the interventions in the present study involved physicians which was slightly higher than nurses (44%) whereas support staff including care workers participated in nearly one third of the interventions. In healthcare settings, physicians are amongst the least proportionate healthcare workers and their contact with patients may be less frequent compared to nurses and carers looking after patients round the clock. Consequently, it is also worth exploring whether proportionate variations in the cadres involved in IP and AMS interventions could have an influence on the key outcomes.

Limitations

There are some limitations to this scoping review. First, this review included studies with primary outcomes on *C. difficile* and CRKP, thus excluding other interventions that might have applied behaviour change evidence without necessarily focussing on a specific pathogen. In addition, inter-rater reliability between reviewers for the included studies was not conducted for this scoping review. Second, the study population and settings of included articles were very diverse, and no adjustments were undertaken to account for these differences. Third, the duration of the specific IP and AMS interventions was not considered in this review and no risk of bias assessment was conducted for the included studies.

Conclusions

Antimicrobial resistance represents a global threat requiring urgent measures to protect lives. Reducing the burden of AMR entails a host of multi-level approaches on infection prevention and antimicrobial stewardship. This review mapped out IP and AMS

interventions targeting *C. difficile* and carbapenem-resistant *K. pneumoniae* (CRKP). These interventions include **E**ducation, **S**urveillance/**S**creening, **C**onsultations, **A**udits, **P**olicies/**P**rotocols, **E**nvironmental disinfection, **B**undles, **I**solation, and **N**otifications or alerts (**ESCAPE-BIN**). The review also described the key outcomes for these interventions including antimicrobial use, cost reductions, resistance rates, and risk of infection, time savings, hospital stay, as well as adherence to contact / infection prevention precautions and protocols. Lastly, the review established evidence gaps on the application of current evidence on behaviour change interventions and adherence to IP and AMS interventions.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Authors' contributions

BO: conceived the idea, designed the study protocol and was the first reviewer; both JH and VM reviewed the study protocol, methods, and the final report. All the three authors discussed the findings of this study and contributed to the final report.

Acknowledgements

EL independently checked 20% of the extracted data for accuracy.

Competing interests

None

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request through brk18vjr@bangor.ac.uk or bernardokeah@gmail.com

Figure legend

Figure 1: PRISMA flow diagram summarising the study screening and selection process.

Figure 2: Proportion of staff involvement in infection prevention interventions targeting C. difficile and K. pneumoniae in healthcare settings per staff cadre.

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Prisma diagram

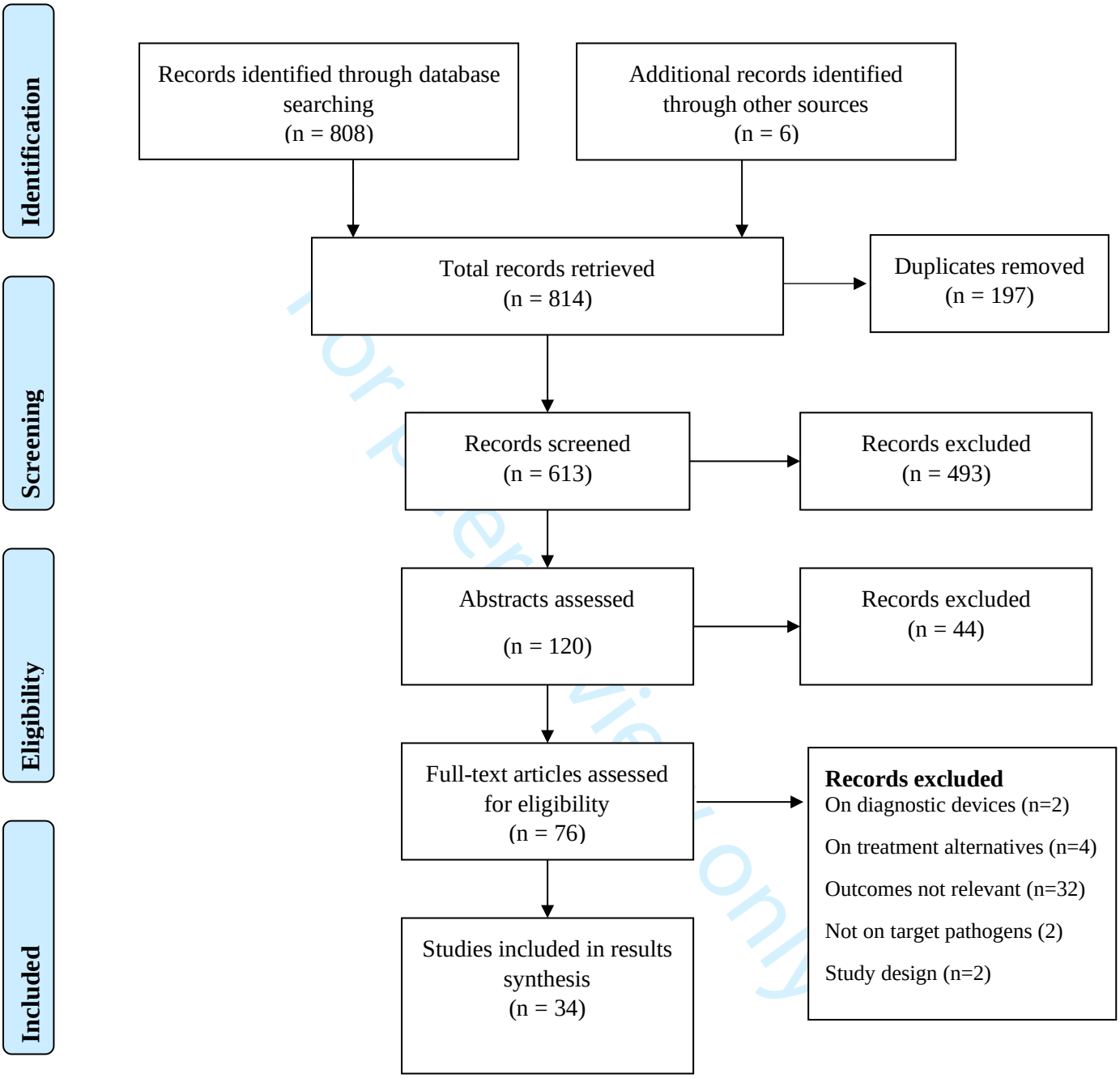

Figure 1: PRISMA flow diagram summarising the study screening and selection process

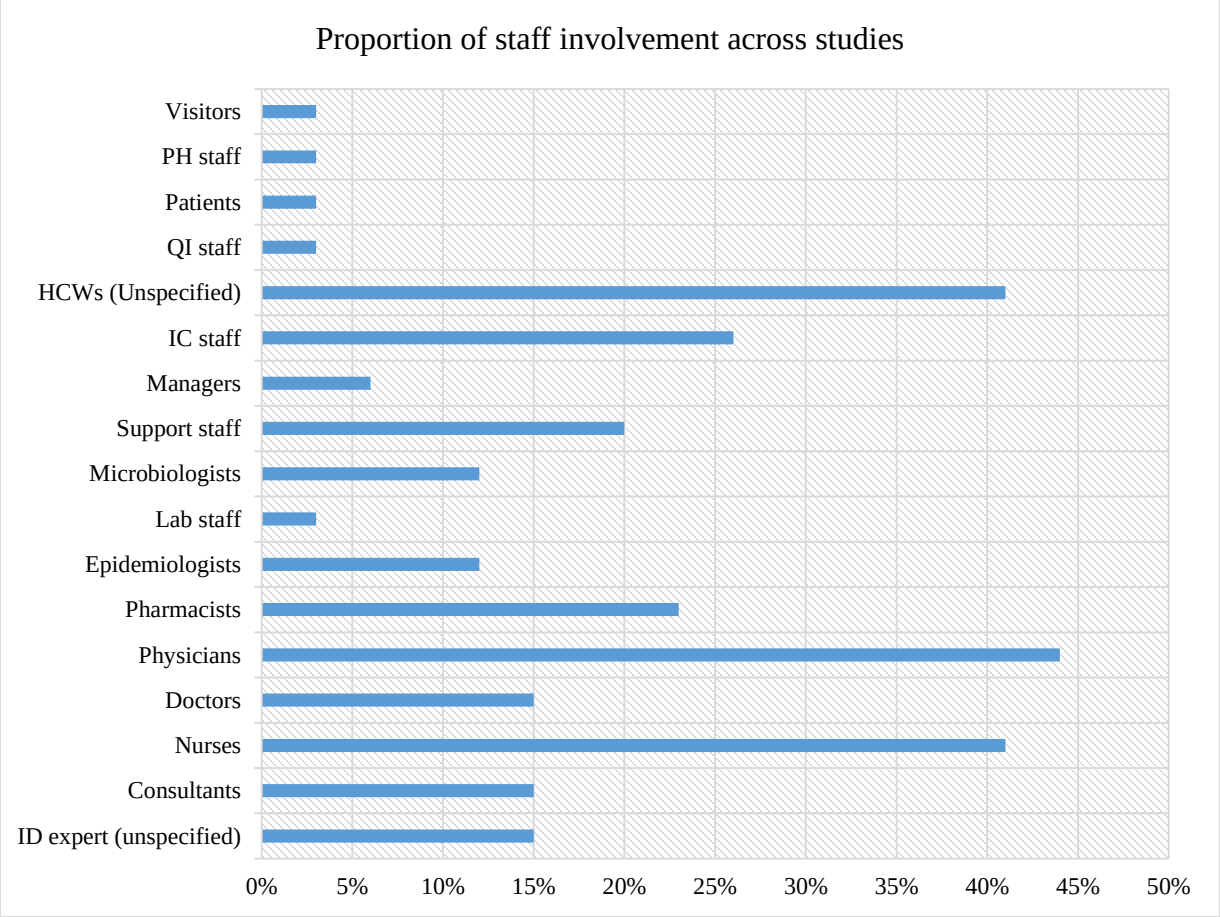

Figure 2: Proportion of staff involvement in infection prevention interventions targeting Clostridioides difficile and Klebsiella pneumoniae in healthcare settings per staff cadre.

Appendix 1: Search strategy

a. MEDLINE search strategy

Search ID	Search Terms	Results
S1	(MM "Clostridium difficile")	7,452
S2	(MM "Klebsiella pneumoniae")	8,828
S3	S1 OR S2	16,277
S4	(MM "Drug Resistance, Microbial+")	68,909
S5	(MM "Antimicrobial Stewardship")	982
S6	S4 OR S5	69,747
S7	S3 AND S6	1,649
S8	(MM "Cross Infection+")	42,792
S9	S7 AND S8	192
S10	S7 AND S8	187

b. CINAHL Plus

Search ID	Search Terms	Results
S1	(MM "Clostridium Difficile")	2,307
S2	"klebsiella pneumonia*"	2,719
S3	S1 OR S2	5,023
S4	(MM "Drug Resistance, Microbial+")	15,817
S5	(MM "Antimicrobial Stewardship")	427
S6	S4 OR S5	16,176
S7	S3 AND S6	719
S8	(MM "Cross Infection+")	27,268
S9	S7 AND S8	166
S10	S7 AND S8	160
S11	S7 AND S8	127

c. Web of Science Core Collection

Search ID	Search terms	Results
# 1	TS= "clostridium difficile" OR TS= "clostridioides difficile"	12,612
# 2	TS= "klebsiella pneumonia*"	17,207
# 3	#2 OR #1	29,679
# 4	TS= "drug resistance"	50,192
# 5	TS= "antimicrobial stewardship"	3,586
# 6	#5 OR #4	53,661
# 7	#6 AND #3	1,415

# 8	TS= "cross infection" OR TS= nosocomial	17,523
# 9	#8 AND #7	193
# 10	#8 AND #7	193
# 11	#8 AND #7	193

d. PubMed

Search ("Cross Infection"[Majr]) AND ((((("Klebsiella pneumoniae"[Mesh]) OR "Clostridium difficile"[Mesh])) AND ((("Drug Resistance"[Mesh] OR "Drug Resistance, Multiple, Bacterial"[Mesh] OR "Drug Resistance, Bacterial"[Mesh] OR "Drug Resistance, Microbial"[Mesh])) OR "Antimicrobial Stewardship"[Majr])) Filters: published in the last 10 years; Humans.

Appendix 2: Data Extraction

Data charting

The researchers developed a form for abstracting data that captured the main study characteristics as well as the specific metrics relevant to the objectives of this scoping review. The form was subjected to preliminary calibration to ensure its accuracy, consistency, and reliability. The data items extracted (see below) included the reference, the study type, the study objectives, population or setting, country, the intervention, intervention duration, healthcare workers involved, outcome measures or findings, and the conclusions of the study. A second reviewer (EL) audited the data extracted by the first reviewer for accuracy and completeness.

STUDIES ON INTERVENTIONS TARGETING CLOSTRIDIUM DIFFICILE IN HEALTHCARE SETTINGS							
Reference	**Study type**	**Aims/ objectives**	**Population/ Setting**	**Intervention**	**Outcome/ key findings**	**Conclusions**	**Useful notes**
[42]	Retrospective observational time-series.	To examine the effectiveness of an antimicrobial stewardship programme on utilization and cost of antimicrobials in leukemia patients in Canada	Leukemia patients. Canada Multi-site	Academic detailing (audits and feedback)	Utilization of antimicrobials reduced from 278DDD/100 PD to 247 DDD/100 PD CDI remained stable	AMS reduces antimicrobial use but has no effect on mortality	ISS persons have neutropenia, mostly treated with broad spectrum antibiotics hence high risk for CDI
[43]	Quasi-experimental	To assess the impact of an ASP on antimicrobials use, CDIs, and AMR patterns	Rehabilitation hospital 150 beds Spinal injuries patients	Bedside ID consultation Revision of antibiotics prophylaxis protocols Staff education	Abx consumption reduced from 42 to 22 DDD/ 100 PDs (Carbapenems from 13 to 0.4 DDD/100PDs, Fluoroquinolones from 11.8 to 0.99 DDD/ 100 PDs) CDIs reduced from 3.6 to 1.2 cases per 10000 PDs Prevalence of KP reduced from 42% to 17% No effect on mortality or length of stay.		
[82]	Quasi-experimental	To optimize the use of antibiotics through trainee-led time outs	679 inpatients Montreal University tertiary care	Twice-weekly time-out audits using a structured electronic checklist and monthly feedback. AMS monthly education: 30 minutes to all rotating staff	A 46% reduction of antibiotics costs from $149 743CAD to $69 424 78% of the cost reduction linked with reduced use of carbapenems	An antibiotic self-stewardship bundle to implement the CDC's suggested time-outs seems to have reduced	About 50% use of antibiotics is not necessary or inappropriate

			hospital (417 beds) Internal medicine. 2 units, 46 beds	Involved: Consultants (ID, critical care, and general medicine)	80% adherence to the audit CDI reduced from 24.2 to 19.6 per 10,000 PDs	overall costs and targeted antibiotic use.	
[51]	Quasi-experimental	To implement an AMS program in a long-term care hospital using telemedicine Provide antimicrobial oversight To improve the quality of care by standardizing antimicrobial prescribing practices	212 bed-New England Sinai Hospital in Stoughton Massachusetts Oversight undertaken by staff from Tufts Medical Center	CDIs Offsite electronic medical record audit Program involved ID physicians and pharmacists	An overall decrease in antimicrobials use. Overall usage of antibiotics reduced by 6.58DDD/1,000 PDs A reduction in the incidence of HAIs and CDIs (from 1.4 to 0.57/1000PDs)	AMS using remote EMR audit is associated with a reduction in antimicrobials use.	
[52]	Quasi-experimental	To reduce the number of healthcare associated CDI cases	450-bed district general hospital Hairmyres Hospital (Glasgow, UK)	A restrictive policy on the use of ceftriaxone and ciprofloxacin Educational campaign	Overall reduction of targeted antimicrobials (ceftriaxone: 95% and ciprofloxacin: 72.5%) (Ceftriaxone from 46.213 to 2.129 DDD/1000PDs Ciprofloxacin from 109.804 to 30.205 DDDs/1000PDs) 77% reduction in hospital acquisition of CDIs Sustained reduction of CDIs up to 0.259 cases/ 1000 patient-beds 3 years post-intervention	Restricting the two antibiotics significantly reduced healthcare associated CDIs	
[53]	Prospective, controlled interrupted time series	To evaluate the impact of audit and feedback on the use of broad-spectrum antimicrobials in critical care patients	Single site Tertiary hospital Intensive care unit (3)	Review of all patients on day 3 and 10 after admission with suggestions for optimizing antimicrobial use given to responsible physicians. Then placing a computer-generated progress note on the patient chart, then feedback completed on same day Critical care team Targeted antimicrobials: ceftriaxone, ceftazidime, piperacillin-tazobactam,	Use of broad-spectrum antimicrobials reduced from 644 to 503 therapy days per 1,000 PDs Nosocomial CDIs incidence reduced from 11 to 6	Prospective audit and feedback appears to be an effective and safe means for reducing the use of broad-spectrum antimicrobials	Approximately half of antibiotics use in hospitals is inappropriate or not necessary

				meropenem, ertapenem, levofloxacin, ciprofloxacin, and vancomycin Personnel involved: Consultants (Pharmacists, ID physician)			
[54]	Quasi experimental	Assessing the impact of automated tracking and ordering precautions on MDROs	University of California, Irvine Medical center 410 beds Serves trauma, burns and cancer patients.	An automated system for identifying, tracking CDIs and other MDROs that involved monitoring microbiology results, triggering chart-based alerts, ordering for appropriate contact precautions on admission as well as inactivation of the precautions. The alert was in form of a visual header banner on the EHR	Time savings estimated at 43 hours per 1000 admissions Timely initiation of contact precautions	Automated systems integrated within the EHRs have potential for protecting patients by ensuring precautions are ordered in a timely manner. The system also contributes to time savings for IPC teams.	No report on CDI outcomes
[55]	Quasi-experimental	To assess the effect of biocidal copper oxide impregnated linen on HCAIs CDIs	Multi-site (six hospitals). Sentara Albermarle Healthcare hospitals 1019 beds NC, USA	Replacement of linen with copper oxide impregnated linen	A reduction in C. diff associated HCAIs by 41.1-61.2% per 10,000 PDs during the intervention period	The use of the biocidal impregnated copper-oxide linen significantly reduced C. diff associated HCAIs as well as other MDROs	Copper has some biocidal activity against some drug resistant bacteria. Its use in hospital environments potentially reduces the bioburden of HCA pathogens
[56]	Quasi-experimental	To examine the effect of copper impregnated linens on MDROs and CDIs	Long-term acute care hospital (LTACH). 40-beds Charlottesville, Virginia	Copper-impregnated linens including bedsheets, pillowcases, towels, and washcloths	Copper linens were associated with a much higher rate of CDIs. (1.5 to 2.8 cases per 1000PDs) There was a reduction in the compliance with hand hygiene practices (-5.6%)	There was no beneficial effect of the copper impregnated linens	No blinding of staff members
[57]	Secondary analysis of a multicenter cluster RCT (BETR Disinfection)	To assess the effectiveness of disinfection strategies on C. diff incidence in hospital settings BETR (Benefits of enhanced terminal room) disinfection study	Multisite: 9 hospitals in southeastern USA	Four disinfection strategies post-discharge of MDRO or C. diff patients: Standard disinfection with quaternary ammonium solution or 10% hypochlorite (bleach) for C. diff cases. Standard disinfection + UV light or bleach and UV light for C. diff cases. Bleach strategy with 10% hypochlorite	No significant differences in the hospital-wide risk of the target organisms between standard disinfection and the other three enhanced disinfection strategies. The use of UV light as part of the disinfection strategy significantly reduced the risk of C. diff (from 18.1 to 17.2/1000PDs)	Enhanced terminal room disinfection using UV light contributed to a reduction in the risk of C. diff and VRE. Enhanced terminal room disinfection overcomes the challenges of standard	Contaminated healthcare environments act as sources of infectious pathogens hence the importance of enhanced terminal room disinfection.

				Bleach and UV light		disinfection and potentially reduces acquisition of C. diff and other MDROs.	
[44]	Quasi-experimental. Retrospective pre- and post-intervention	To assess the impact of an ASP intervention on HA-CDI	The Western Pennsylvania Hospital (WPH). 317-bed community teaching hospital. Approximately 6800 admissions yearly.	Education. Restriction of target antimicrobials requiring prior approval. Audit and feedback. Annual guidelines for antimicrobials use.	Significant reduction in HA-CDIs from 0.84 to 0.28 cases per 1000PDs (P=0.035). A cumulative reduction in the use of clindamycin, ceftriaxone, carbapenems, fluoroquinolones, linezolid, tigecycline (from 295.1 to 261.3 DDD/1000PDs)	Implementing an ASP program significantly reduced the incidence of HA-CDI as well as antibiotics use	Antibiotics associated with higher rates of CDI include fluoroquinolones, clindamycin, and ceftriaxone
[45]	Pre- and post-intervention	To assess the impact of intensive IPC activities on MRSA, drug resistant P. aeruginosa (DRP), and C. diff acquisition.	Tsukuba Medical Center Hospital (TMCH) Japan. 409 beds. Tertiary emergency medical center.	Screening and notification of new and previous MDROs. Daily review of new patients' medical records/ microbiological results. Contact precautions or standard precautions. Monitoring inappropriate use of carbapenems and promptly instructing responsible doctors.	Reduction of carbapenems' use from 28.5 to 17.8 DDD/1000PDs. Improved uptake of contact precautions. A reduction in the incidence of CDI (from 0.47 to 0.11 cases/1000PDs). Incidence of MRSA and DRP also reduced significantly	Proactive intensive ICT measures have the potential for reducing the hospital transmission of MDROs.	
[46]	POS	To assess the impact of a technology-mediated pharmacy-directed ASP in a rural hospital	St. Mary Medical center. 141 beds. Community hospital. Washington	Weekly antimicrobial review teleconferences involving an ID pharmacist	Pharmacy-initiated AMS interventions increased from 2.1 to 6.8 interventions per week. Antimicrobial streamlining improved from 44% to 96%. There was enhanced interdisciplinary collaboration. A 51% reduction in the cost of targeted antimicrobials.		

					HA-CDIs reduced from 5.5 to 1.6 cases per 10,000PDs		
[47]	ROS cross-sectional study	To assess the effect of intensive staff education on CDAD amongst hospitalized geriatrics	390-bed geriatric hospital 217 geriatric patients observed	Staff education on isolation precautions, handwashing, transporting patients within the hospital, and cleaning.	There were no significant differences in the incidence of CDAD pre- and post-intervention.	Intensive staff education did not reduce the nosocomial CDAD rates but remains an important strategy	Toxin positive C. diff is the leading cause of diarrhea amongst geriatrics.
[83]	Retrospective case series	To assess the risk factors for CDAD and safety of administering FMT via NGT	27 patients with recurrent CDAD Wits Donald Gordon Medical Centre, Johannesburg, South Africa	Feacal microbiota transplant	Resolution of CDAD 4 weeks after FMT. Risk factors for CDAD included age >65 years, exposure to antibiotics	FMT is an effective treatment for CDAD that can be administered via NGT	
[84]	Retrospective cohort study	To assess the impact of real-time notification upon detecting toxigenic C. diff	Single center. 433 bed tertiary care medical center. Lexington, Kentucky. Adult patients aged more than 18 years	Computer generated real-time notification of toxigenic C. diff results and Initiation of appropriate antimicrobial therapy (Vancomycin or Vancomycin and metronidazole). Contact precautions.	The time for initiating appropriate treatment reduced from 5.75 to 2.05 hours. The ASP intervention shortened the time from diagnosis to recording the appropriate antimicrobial in the EMHRs	The real-time notification intervention reduced the time for entering and initiating the appropriate antimicrobial treatment as well as contact precautions.	

STUDIES ON INTERVENTIONS TARGETING CRKP IN HEALTHCARE SETTINGS

Reference	Study type	Aims/ objectives	Population/ Setting	Intervention	Outcome/ key findings	Conclusions	Useful notes
[58]	Retrospective observational Quasi-experimental Medical records	To devise a local strategy for eradication of a hospital-wide outbreak caused by carbapenem-resistant Klebsiella pneumoniae (CRKP)	CRKP patients 1000 bed tertiary care university hospital	ED flagging system Cohorting Eradicating clusters Environmental and personnel hand cultures Carbapenem restriction policy	CRKP infections reduced from 5.26 to 0.18 per 10,000 patient days No nosocomial CRKP infections diagnosed Meropenem use reduced		
[59]	Quasi-experimental?	To examine the effect of active screening on the resistance rates of MDRBs in ICUs	ICU	Active screening	Improved detection of MDRBs (KP)	Active screening reduces the resistance rates of pathogenic bacteria and useful in detecting MDRB	

[68]	Quasi-experimental	To reduce the prevalence of CRKP (KPC-3)	Medical center Israel	Guidelines for isolation, cohorting, environmental cleaning, staff education, and computerized notification/ flagging	A decrease in the CRKP incidence rate sustained over 30 months from 6.6 to 0.5/10,000PDs Reduction in cross-infections from 6% to 2.7% Surveillance of asymptomatic carriers improved from 20% to 89%	A multidisciplinary IPC programme is effective in controlling the prevalence of CRKP	
[85]	Quasi-experimental	To optimize the use of antimicrobials	510-bed Danish university hospital Copenhagen University Hospital-Denmark	Multi-disciplinary change project Kotter's stages of change Multi-level intervention: 1. Professional: Education, clinician leaflets, new drug container, yellow sticker for bed post, signboard for doors, hotline, notification on prescription of restricted antimicrobials 2. Social: Presentations for the quality board, prevalence studies, feedback, newsletter, and website. 3. Patient: Information leaflets for isolation precautions Organizational: Revising antimicrobial guidelines, cefuroxime restriction.	Overall antimicrobials consumption remained unaffected. Immediate and sustained reduction in cefuroxime use (74.5%) An increase in the use of ertapenem, piperacillin/ tazobactam, and b-lactamase sensitive penicillin. Reduction in ESBL-KP diagnostic samples Reduced incidence of ESBL-KP infections from 39.5 to 22.5% Reduced need for isolation precautions	Changing antimicrobial consumption and reducing the incidence of ESBL-KP is possible through a multi-faceted intervention that does not require ongoing antibiotic stewardship	Restricting cephalosporins may reduce ESBL infection rates Carbapenems (B-lactamase inhibitors) are recommended as first-lines for serious ESBL producing bacteria
[70]	Quasi-experimental	To evaluate the impact of an AMS program restricting carbapenems (imipenem and meropenem)	Hospital das Clinicas Institute of Orthopedics and Traumatology 200 beds tertiary care hospital	Ertapenem was made mandatory for treatment of ESBL-Enterobacteriaceae Restricting group 2 carbapenems for gram negative bacteria	A reduction of group 2 carbapenems use from 61.1 DDD to 48.7 DDD/1,000 patient days Susceptibility of K. pneumoniae and P. aeruginosa to trimethoprim-sulfamethoxazole	There was a significant reduction in the use of carbapenems following preferential use of ertapenem.	
[71]	Prospective Observational???	To contain an outbreak of carbapenem resistant KP	27 Acute care hospitals Israel 14,000 beds	Screening Mandatory reporting of every CRE patient to PH authorities Mandatory isolation of hospitalized new and previous carriers (single rooms or cohorting)	Increase in the incidence of KP was halted with a subsequent reduction of 11.7 cases per 100,000	An intervention coordinated centrally showed better outcomes for containment of a KP outbreak as compared to local measures. Strategic planning and	**Outbreak control**

				Dedicated staff Oversight taskforce that supervised adherence to isolation protocols, provided technical support, and feedback to management		national oversight are crucial in addressing AMR	
[72]		To curb the spread of KPC-3 producing KP	Italy 12-bed ICU hospital Cannizaro hospital, Catania	Screening Environmental cleaning Respiratory equipment disinfection Hand hygiene Single room isolation Weekly meetings between IPTs and ICU staff	Outbreak containment within 4 months Improved adherence to contact precautions		**Outbreak control** Ten recognized KPC types (KPC-2 to KPC 11). KPC-2 are the commonest
[73]	POS	To curb CRKP and Acinetobacter baumannii	Greece Serres General Hospital 250-bed hospital	Prokroustes action plan: Surveillance and compulsory notification and IPC measures: Isolation or cohorting, contact precautions, hand hygiene	Containment of CR associated with KP and PA three years post-intervention. An increase in KP resistant to Colistin, Tigecycline, and gentamycin	There exist challenges for addressing MDROs in regions with established carbapenem resistance.	
[74]	Observational	To identify and control CRKP originating from endoscopic equipment	206-beds cancer center + 988 beds tertiary hospital	Active surveillance using rectal swabs Source isolation Contact precautions Environmental cleaning Hand hygiene PPE: Gowns and gloves MDRO flags on EMRs and charts	7 CRKP cases identified resistant to imipenem		Transmission of carbapenem resistant genes across microbial species within the same environment contributes to resistance. KP outbreaks have also been associated with contaminated sinks, IV saline solutions, bath soap, and ultrasonography gel
[86]	Quasi-experimental	To assess the impact of intensified IC measures on colonization and infections associated with CRKP, P.	Solid organ transplant department	Active surveillance + contact precautions + hand hygiene + education + environmental cleaning + monitoring adherence + audit and feedback	Reduction in incidence of colonization from 19 to 9%. Improved adherence to contact precautions.	In CR gram negative bacteria endemic regions, SOT patients have disproportionately higher infections rates of the	

		aeruginosa, and Actionbater baumannii			An increase in the monthly incidence of CR bacteria from 2.8 to 6.9/ 1000 PDs	organisms. Implementation of enhanced IC measures significantly reduces the colonization	
[60]	POS	To control an outbreak of imipenem resistant K. pneumoniae (IR-KP)	France Abdominal surgery care center. 15-bed liver ICU	Screening all patients + Contact isolation + hand hygiene using alcohol-based hand sanitizer. Enhanced measures: Cohorting carriers, dedicated staff, restricting ward admissions, and strict control of patient transfers	Rapid containment of the outbreak		
[61]	Quasi-experimental	To establish if IPC interventions can reduce CRKP infection in ICU	ICU China 629 patients enrolled.	Screening of cultures, de-escalation interventions, contact precautions, isolation/ cohorting, sterilization and disinfection, and bundles (for IV catheter infections, VAP, CAUTIs, and skin or soft tissue infections).	CRKP incidence reduced from 10.08 to a low of 2.84 cases per 1000 PDs. ICU acquired CRKP bloodstream infections decreased from 2.54 to 0.41 cases per 1000PDs	Comprehensive IPC interventions significantly reduced ICU related CRKP infections	
[62]	Quasi-experimental	To assess the effect of IPC on a CRKP outbreak	NICU. 20-beds	Active surveillance using rectal swabs. IPC measures: hand hygiene, auditing compliance, environmental cleaning, and cohorting.	Outbreak containment after cohorting and IPC measures.	Physical isolation is important in preventing the spread of MDROs. ASP is useful in reducing the spread of MDROs	
[63]	Cohort. POS	Assessing the effectiveness of multidisciplinary interventions on the transmission of ESBL-KP	Parkland Memorial Hospital, Dallas. NICU. 61 infants	Re-educating staff. Auditing hand hygiene and environmental sanitation. Contact precautions. Cohorting Staff & infants. Reducing overcrowding. Screening NICU cultures frequently.	Outbreak contained within three weeks	Multidisciplinary intervention using standard IPC measures halted the transmission of ESBL-KP in the NICU.	
[64]	POS	To halt the spread of CRKP	Cà Granda Ospeda- le Maggiore Hospital. ICU.	Active surveillance. Isolation. Hand hygiene	Outbreak containment		

			Milan, Italy				
[65]	POS	To assess the effect of enhanced contact precautions on CRE/ CRKP incidence and resistance rates	Tertiary care university hospital. 900 beds. South Korea	Staff education Contact precautions without active surveillance. Cohort isolation. Hand hygiene	An initial increase of the CRE cases (from 1.62 to 9.81/100,000PDs) after which the rates fell back to (0.882/ 100,000PDs0 below baseline levels. A reduction in the resistance rates to imipenem and meropenem following enhanced contact precautions. Hand hygiene adherence improved from 35.2% to 70%	Enhanced infection control measures without active surveillance appear to be effective against the spread of CRE in low prevalence settings	
[66]	ROS & POS	To stop the spread of ESBL-producing nosocomial bacteria in NICU	17-bed NICU. 355 patients observed. University of Szeged Pediatrics Department. Hungary	Introduction of the INSURE protocol. Antimicrobial regimens review. Microbiological screening. Bathing protocol. Hand hygiene. Continuous monitoring of cases	A significant reduction in the proportion of CRKP colonization or infections. Average number of PDs reduced from 343.72 to 292.44 PDs/ month. Hand hygiene compliance improved from 26.02 to 33.6 HH procedures per patient per hospital day.	A successful roll back of the CRE infections and colonization was achieved through an interdisciplinary approach.	ESBL-producing bacteria includes E. coli, Enterobacter cloacae, and *K. Pneumoniae*
[67]	Quasi-experimental	To track an outbreak of ESBL-KP using WGS	The University Medical Center Groningen (UMCG). 1300 bed tertiary care center. Netherlands	Screening patients and the environment using WGS	There was no association between the sporadic case of KP and those that had been diagnosed prior to 2013	Tailor-made makers for identifying genomic signatures have potential for improving the efficiency of IPC measures	

Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	0
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	2-3
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	3
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	3
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	3-4
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	4
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	4
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	4
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	4
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	N/A
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	5-6

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	5
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	5
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	N/A
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	6, 8, 10, & 13
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	5-14
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	15-16
Limitations	20	Discuss the limitations of the scoping review process.	16
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	16-17
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	17

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.