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Infection prevention, control and antimicrobial stewardship measures in intensive in-patient rehabilitation setting: a systematic review

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Abstract

Introduction

The necessity for targeted strategies to prevent and manage multidrug-resistant organism infections in intensive rehabilitation settings is driven by the heightened vulnerability of patients, exacerbated by the unique organizational and technical aspects of these environments.

This study aimed to establish an interpretative framework of internationally validated interventions to enhance infection prevention in intensive rehabilitation facilities.

Materials and methods

A systematic review, conducted following PRISMA guidelines, categorized interventions into three key domains: Antimicrobial Stewardship, Behavioural Prevention, and Sanitation and Environmental Cleaning.

Results

The 17 articles selected for review provide a comprehensive overview of interventions within the three domains. Antimicrobial Stewardship interventions demonstrated potential in reducing *Clostridioides difficile* colonization through decreased antimicrobial use. Behavioural Prevention interventions were associated with reduced multidrug-resistant organism colonization and infections. Sanitation and Environmental Cleaning interventions, including hand hygiene, correlated with a decreased incidence of *Clostridioides difficile* cases.

Discussion and conclusions

This systematic review underscores the importance of implementing multi-component interventions, encompassing both pharmacological and non-pharmacological approaches, across this critical setting.

Keywords

multidrug-resistant organism infections; intensive rehabilitation; Antimicrobial Stewardship; Behavioural Prevention; Environmental Cleaning

Introduction

Intensive rehabilitation in post-acute-care setting is reserved for patients who have experienced a rapid loss of their functional abilities following an acute event, such

as surgery for femur fracture or stroke within 30 days prior to admission to an intensive rehabilitation unit (IRU). [1,2]

Although IRUs, whether hospital-based or in other healthcare facilities, provide specialized care aimed at functional recovery and mitigation of specific risks (e.g., falls or medication errors), they also represent environments associated with an increased of health-care associated infections (HAIs). Importantly, this risk profile differs substantially from that of acute care settings and has been relatively understudied. The increased infection risk is attributable to several patient-related and system-related factors, including reduced mobility and prolonged bed rest, close proximity to other potentially colonized or infected frail individuals, and frequent use of invasive devices for therapeutic purposes (e.g., the urinary catheters, peripheral venous catheters, rectal probes, percutaneous endoscopy gastrostomy, colostomies, and tracheostomies) [3-5].

Compared with acute care units, intensive rehabilitation settings pose distinct challenges for infection prevention and control (IPC) interventions. Rehabilitation care in such settings is intrinsically multidisciplinary involving physicians, nurses, physical, occupational, and speech therapists, psychologists, and other health care professionals. In addition, a substantial number of individuals who do not have direct contact with patients, such as cleaning staff or other, are present in these environments and may contribute to transmission dynamics. Moreover, patients admitted to IRUs typically have a prolonged length of stay, further increasing cumulative exposure risk [6].

In most cases, access to rehabilitation units occurs directly from medical or surgical acute wards. Patients usually enter the hospital through the Emergency Department, receive acute care and may also transit through intensive care units.

These multiple care transitions substantially increase the risk of colonization by multi drug resistant organisms (MDRO) [7,8].

Patients in rehabilitation settings frequently share equipment, including mobility aids, rehabilitation devices, and robotic instruments. Group therapies are often provided in shared environments [9]. Furthermore, rehabilitation programs often encourage family and caregiver involvement, further increasing the potential for transmission of pathogens. Lastly, nurse-to-patient ratios in rehabilitation units are often lower than in acute settings, placing additional strain on infection prevention efforts [10]. Taken together, these characteristics not only escalate risk but differentiate IRU environment from traditional acute care contexts, highlighting the need for tailored IPC and antimicrobial stewardship (AMS) models.

According to the 2022-2023 European Centre for Disease Prevention and Control (ECDC) Point Prevalence Survey (PPS), 472 of 10,143 rehabilitation patients (4.7%) had at least one HAI (adjusted OR 0.9, 95% CI 0.8 - 1.1) while antimicrobial use was reported in 6.7% of patients (adjusted OR 0.2, 95% CI 0.2 - 0.2) [11].

Infections frequently complicate the course of patients in IRUs, limiting the delivery of rehabilitative interventions and potentially affecting functional recovery trajectories. As previously reported by Doherty and colleagues, patients in post-acute rehabilitation facilities have a higher prevalence of MDRO colonization and infection, compared with almost all other acute inpatient populations [5]. In the same study, institutions were found to screen for a range of MDROs including methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant Enterococci (VRE), extended spectrum beta-lactamase producer (ESBL), and carbapenemase-producing Enterobacteriales (CPE). However, estimated prevalence of MDROs varied widely across European rehabilitation facilities ranging from 9%

to 31% or higher, and no correlation between facility bed capacity and MDRO prevalence was found [5].

Despite awareness of the challenges associated with the prevention and management of MDROs in inpatient rehabilitation, the available evidence remains fragmented and current IPC and AMS recommendations are largely derived from acute care and long-term care settings. Consequently, the uncertain applicability of existing IPC and AMS models to intensive inpatient rehabilitation settings underscores the need to develop context-specific recommendations for this population. A comprehensive synthesis of the current evidence is therefore needed to better characterize preventive and control strategies that may result most appropriate and feasible in IRUs.

The present systematic review aims to synthesize and appraise the available evidence on pharmacological (antimicrobial stewardship–related) and non-pharmacological (infection prevention and control) interventions for the prevention and control of MDROs in intensive inpatient rehabilitation settings, and to develop an interpretive framework to support their context-specific implementation in clinical practice.

Materials and methods

Study design

We conducted a systematic review following the PRISMA guidelines [12]. The population included adult patients (≥ 18 years old) in post-acute care, who were admitted to an inpatient rehabilitation facility. Outcomes of interest included indicators of good control of multi-resistant infections.

Search strategies

An electronic search of MEDLINE, Scopus, Web of Science Core Collection, and Cochrane Library databases was performed in October 2023 looking for relevant studies that could be included in this study. Only studies published in English were included and grey literature was excluded. The search was performed by employing keywords such as “post-acute care”, “inpatient rehabilitation”, “long term care hospital”, “infection prevention”, “antimicrobial resistant” (the full search string is provided in Appendix 1).

Inclusion and exclusion criteria

Data limited to adult patients (≥18 years old) were retrieved.

Studies conducted in post-acute inpatient settings providing structured and intensive rehabilitation were eligible for inclusion, including both inpatient rehabilitation units and long-term acute care hospitals (LTACHs). The rationale for this choice was to capture IPC models and AMS strategies implemented in contexts where intensive inpatient rehabilitation is delivered to clinically complex patients, irrespective of the specific institutional classification. No predefined length-of-stay threshold was applied for study selection; instead, length of stay was reported as described in each individual study. Finally, studies conducted in long-term care settings, including nursing homes and skilled nursing facilities, were excluded because these settings are primarily oriented toward long-term custodial care and do not routinely provide structured, intensive post-acute inpatient rehabilitation.

Randomized clinical trials (RCTs), controlled clinical trials (CCTs), pre-post-intervention observational studies, cross-sectional studies were considered eligible for inclusion.

Letters to the editor, case reports, brief reports, supplements articles and reviews were excluded.

Selection of studies, data extraction and management

The abstracts of all selected papers were evaluated for eligibility independently by three members of the review team. Full copies of articles were obtained for all papers meeting the inclusion criteria. Members of the review team were not permitted to review any paper on which they had been an author at any stage of the appraisal process. Data were independently extracted by two review authors. The data extraction was discussed in case of disagreement and the justification for excluding studies from the analysis was documented.

The following data were extracted: (1) authors, (2) geographical Scope, (3) title, (4) journal , (5) intervention, (6) category of the intervention, (7) hand hygiene y/n, (8) Study objective(s), (9) Study design, (10) Setting, (11) Bed number, (12) patients characteristics, (13) Length of stay (days), (14) Length of follow-up, (15) Sample size, (16) outcome(s) of Interest, (17) MDRO(s) considered, (18) Antimicrobial Considered. When available, all data were extracted with their confidence intervals, Standard Deviation (SD) or Variance.

Primary and secondary outcomes

The primary objective was to classify and systematize the different options of interventions to tackle MDROs, in the post-acute setting. To determine the impact of those measures, we analysed a set of indicators associated with good control of multi-resistant infections and appropriate use of antimicrobials in the target population, based on CDC recommendations [13] which suggest employing the incidence of hospital acquired infections and the data obtained through surveillance to detect transmission of infectious agents. Specifically, the outcomes assessed were infection rates for key MDROs, including Methicillin-resistant *Staphylococcus aureus* (MRSA), Vancomycin-resistant *Enterococci* (VRE) and Carbapenem-resistant

Enterobacteriaceae (CRE). Furthermore, the surveillance focused on Carbapenemase-producing *Klebsiella pneumoniae* (KPC), Carbapenemase-producing Acinetobacter baumannii (CRAB), and *Clostridioides difficile* (CD).

As for Antimicrobial Stewardship Programs (ASP), the outcome measures to be collected were identified according to the Core Elements of Hospital Antibiotic Stewardship Programs [14], published by CDC, that include: Antimicrobial consumption, expressed as days of therapy (DOT) or as defined daily doses (DDDs), C. difficile infections (CD was considered as outcome also in other interventions), Antibiotic Resistance data (i.e., incidence of resistant Hospital Acquired-Infections), and the Financial impact of the interventions, particularly antibiotic costs.

The full set of indicators used is provided in Appendix 3.

Data Synthesis

Interventions reported in the included articles were categorized into three distinct categories: Antimicrobial Stewardship (AMS) interventions, behaviour preventive (BP) interventions and sanitation and environmental cleaning (SEC). To ensure consistency, AMS interventions were defined in alignment with the World Health Organization (WHO) 2021 framework, "Antimicrobial stewardship interventions: a practical guide." [15] This category encompasses a multifaceted range of clinical and administrative strategies designed to optimize antibiotic use, including educational Initiatives, targeted training for clinicians, as well as awareness programs for patients and the general public, clinical protocols, implementation of institution-specific guidelines for managing common infections and the use of cumulative antibiograms to inform local resistance patterns, active oversight, prospective audit and feedback mechanisms, alongside mandatory prior authorization for restricted antimicrobial age and pharmacological optimization,

strategies focused on dose and duration optimization, "antibiotic timeouts" (self-directed reassessments), and the systematic de-labelling of spurious antibiotic allergies to prevent the unnecessary use of broad-spectrum drugs. BP interventions and SEC were identified, based on the CDC's "Core Infection Prevention and Control Practices for Safe Healthcare Delivery in All Settings" [16], which lists the main practices as "Standard Precautions". SEC focuses on the physical environment and basic hygiene infrastructure. Key practices include standardized environmental cleaning, rigorous disinfection protocols, and the promotion of hand hygiene. BP interventions focus on clinical behaviours and patient-specific protocols to limit transmission. This includes the implementation of contact precautions and the execution of colonization screening to identify and isolate asymptomatic carriers.

Data were presented in tables showing the characteristics of the interventions and of each setting; only statistically significant data on the effectiveness of the interventions were reported, according to the principles of narrative synthesis.

The included studies were analysed by evaluating comparable outcomes—such as the reduction in multi-drug-resistant organism infections—using a narrative synthesis approach. Due to the heterogeneity of the data, different facility types and study designs, no pooled or cumulative analyses across were performed.

Risk of bias assessment

The Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool was used to rate the risk of bias for non-randomized included studies [17]. This tool assesses seven domains: risk of bias from confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported results. A proposed judgment about the risk of bias arising from each domain is generated by an

algorithm, based on answers to the signalling questions. Judgment can be “Low”, “Moderate” or “High” risk of bias or can express “Some concerns”. Thus, Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2) is the recommended tool to assess the risk of bias in randomized trials included in Cochrane Reviews [18]. RoB 2 is structured into a fixed set of domains of bias, focusing on different aspects of trial design, conduct, and reporting. Within each domain, a series of questions ('signalling questions') aim to elicit information about features of the trial that are relevant to risk of bias. A proposed judgement about the risk of bias arising from each domain is generated by an algorithm, based on answers to the signalling questions. Judgement can be 'Low' or 'High' risk of bias or can express 'Some concerns'. Low and moderate risk articles were considered in the study as per methodological guidance as performed by other studies [19,20]. For each included study, two reviewers independently assessed the risk of bias using ROBINS-I (for non-randomized studies) or RoB 2 (for randomized trials). Discrepancies were resolved by discussion or by consulting a third reviewer. Detailed domain-level judgments for each study, including the signaling question responses and the overall risk-of-bias classification, are presented in Appendix-2. These assessments informed the narrative synthesis, guiding the interpretative weight given to individual studies.

Results

Study selection

The search strategy retrieved 380 records from 1977 to November 2023. Results were screened by title and abstract and 84 manuscripts underwent full-text review. Finally, only 17 articles [21-37] met full inclusion criteria and were selected for review according to PRISMA methodology (Fig.1).

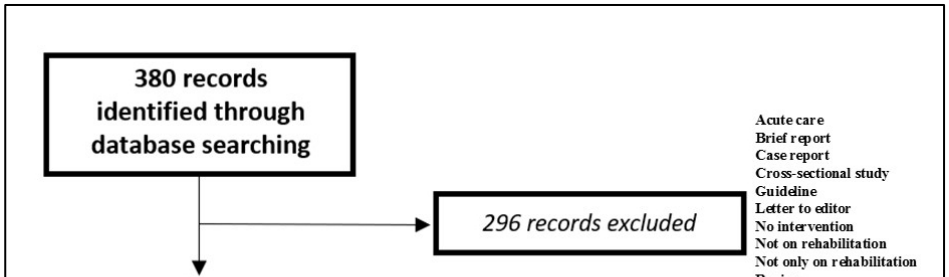

Figure 1. Flow chart of included studies

Characteristics of the studies

A synopsis of the characteristics of each retrieved publication is shown in Table 1. Most of the studies (ten, 58.8%) were performed in the US, including those conducted in long-term acute care hospitals (LTACHs), while two studies were conducted in Italy, two in Canada, and the remaining three in Japan, Singapore and Australia. None of the selected papers reported evidence regarding the implementation of interventions in a limited-resource setting or in Low and Middle-Income Countries (LMICs). The observation period during the implementation of each intervention ranged from 10 days (E. Chipps et al., 2013) to 48 months (A. Widner et al., 2014; K. Beaulac et al., 2016; A. Cheung et al., 2017).

Author, year	Country	Setting	Study design	Category of the Intervention	Intervention period (months)	Reference
K. Shigemura, 2014	Japan	Rehabilitation ward/unit of a hospital	Prospective cohort study	BP	8	[25]
F. Arena, 2018	Italy	Inpatient Rehabilitation Facility	Prospective cohort study	BP	12	[36]
A. Widner, 2014	US	Inpatient Rehabilitation facility	retrospective cohort study	BP	48	[32]
M. Rawlins, 2017	Australia	Rehabilitation ward/unit of a hospital	Pre-post study	AMS	14	[28]
JA Curran, 2022	Canada	Rehabilitation hospital	Retrospective interrupted time series	AMS	12	[23]
S. Tedeschi, 2016	Italy	Rehabilitation hospital	quasi-experimental before-and-after study	AMS	6	[24]
E. Chipps, 2013	US	Rehabilitation hospital	RCT	SEC	10 days	[33]
A. Cheung, 2017	Canada	Rehabilitation hospital	prospective cohort study	AMS	48	[37]
A. Chow, 2018	Singapore	Rehabilitation hospital	controlled before–after study	BP	45	[26]
B. Brakovich, 2013	US	LTACH	prospective cohort study	AMS, BP, SEC	24	[34]

T. Ethington, 2021	US	LTACH	prospective cohort study	SEC	12	[30]
E.A. Hooker, 2015	US	LTACH	Prospective cohort study	SEC	12	[31]
G.R. Madden, 2018	US	LTACH	retrospective cohort study	SEC	27	[29]
M.K. Hayden, 2015	US	LTACH	Pre-post study	BP	19	[22]
J. Benson, 2014	US	LTACH	Retrospective cohort study	AMS	24	[27]
K. Beaulac, 2016	US	LTACH	interrupted time-series analysis	AMS	48	[35]
A. Mushtaq, 2017	US	LTACH	prospective cohort study	AMS	3	[21]

Table 1. Characteristics of the studies

Risk of bias assessment

Based on ROBINS-I, low-to-moderate risk of bias was found in the included studies with no study appearing at high risk of bias (Table 2). Similarly, low-to-moderate risk of bias was found for the included studies according to version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2) (Table 2).

ROBINS-I							
Author	**Bias due to confounding domains relevant to the setting of the study**	**Bias in selection of participants into the study**	**Bias in classification of interventions**	**Bias due to deviations from intended interventions**	**Bias due to missing data**	**Bias in measurement of outcomes**	**Bias in selection of the reported results**
K. Shigemura	Low	Low	Moderate	Low	Moderate	Moderate	Moderate
M. Rawlins	Low	Moderate	Moderate	Low	Low	Moderate	Moderate
A. Cheung	Low	Moderate	Moderate	Low	Moderate	Moderate	Low
M. Mushtaq	Low	Low	Moderate	Low	Low	Moderate	Moderate
B. Brakovich	Low	Moderate	Low	Low	Moderate	Moderate	Moderate
A. Chow	Low	Moderate	Low	Low	Moderate	Low	Moderate
J. Benson	Low	Moderate	Low	Moderate	Moderate	Moderate	Moderate
G.R. Madden	Low	Moderate	Low	Low	Moderate	Moderate	Low
T. Ethington	Low	Low	Low	Moderate	Moderate	Moderate	Low
S. Tedeschi	Low	Moderate	Low	Low	Low	Moderate	Moderate
E.A. Hooker	Low	Low	Moderate	Low	Moderate	Moderate	Low

M.K. Hayden	Low	Low	Low	Moderate	Moderate	Low	Moderate
A. Widner	Low	Moderate	Low	Low	Moderate	Moderate	Moderate
J.A. Curran	Low	Moderate	Low	Low	Moderate	Moderate	Low
K. Beaulac	Low	Low	Moderate	Low	Low	Moderate	Moderate
F. Arena	Low	Low	Moderate	Low	Low	Moderate	Moderate
RoB-2							
Author	**Domain 1**	**Domain 2 (first part)**	**Domain 2 (second part)**	**Domain 3**	**Domain 4**	**Domain 5**	
E. Chipps	Low	Moderate	Moderate	Moderate	Moderate	Low	

Table 2. Methodological quality evaluation of the included non-randomized studies according to ROBINS-I and RoB-2

Population and Setting

Two main types of facilities were identified: Rehabilitation Facilities, which included Rehabilitation Hospitals and Rehabilitation Units or Wards affiliated to a hospital (nine studies, 52.9%) and Long-Term Acute Care Hospitals (LTACH) (eight studies, 47.1%) (Table 3).

The central tendency value of the length of stay (LOS) ranged between 14.67 (S. Tedeschi et al., 2016) and 113.48 (A. Widner et al., 2014) days. Patients were admitted to IRUs after a loss of functional abilities and self-sufficiency due to pathological acute events, with stroke and brain/spinal cord injuries or orthopedic trauma and other musculo-skeletal conditions being more frequently reported as primary diagnoses.

Patients admitted to LTACHs were typically referred from other healthcare facilities (including ICUs) and required complex and intensive nursing and medical care. Their hospitalization lasted between 26 (M. K. Hayden et al., 2015) and 56 days (K. Beaulac et al., 2016). Mechanical ventilation was the most common procedure performed, as it was cited by five of the included studies.

Table 3 summarizes the type and size of rehabilitation settings, as well as the characteristics of the studied populations in terms of primary diagnosis and length of stay, from the included studies.

Rehabilitation Facilities				**Long-term Acute Care Hospitals**			
Author, year	**Bed number**	**Patients Characteristics/Primary diagnosis**	**Lenghth of stay (days)**	**Author, year**	**Bed number**	**Patients Characteristics/ Primary diagnosis**	**Lenghth of stay (days)**
M. Rawlins, 2017	140	Neuro-rehabilitation, acquired brain injury secondary to trauma, stroke or tumor resection, spinal cord injury and amputee rehabilitation.	median: 49/47.5	**M. K. Hayden, 2015**	NR	mechanical ventilation, central venous catheter, urinary bladder catheter	baseline: 28 (16–43) intervention: 26 (17–39)
J.A Curran, 2022	178	Orthopedic conditions, debility, cardiac, major multiple trauma, stroke, medically complex care, amputations, burns, brain/spinal cord dysfunction, neurological/ cardiac/pulmonary conditions.	NR	**K. Beaulac, 2016**	212	complex medical history, requiring high-level nursing and medical care, mechanical ventilation, respiratory therapy	56
S. Tedeschi, 2016	150	Spinal cord injury	Mean: (2011) 113.5, (2012) 84.5, (2013) 76.8, (2014) 74.7	**A. Mushtaq, 2017**	76	NR	NR
A. Cheung, 2017	270	Chronic lung diseases, diabetes mellitus, stroke, amputation, musculoskeletal illness.	NR	**B. Brakovich, 2013**	50	Patients admitted from other hospitals, most of them on mechanical ventilation	NR
K. Shigemura, 2014	330	spinal cord injury, neurogenic bladder	Mean 70.1	**G.R. Madden, 2018**	40	NR	NR
A. Widner, 2014	75	Orthopedic Conditions, Stroke, Brain Dysfunction, Debility, Spinal Cord Dysfunction, Neurologic Conditions, Cardiac	baseline: 14.7 intervention: 16.7	**T. Ethington, 2021**	123	All patients on mechanical ventilation	NR

E. Chipps, 2013	60	post-stroke	NR	**E.A. Hooker, 2015**	Hospital A :74 Hospital B: 30	NR	Hospital A: 31-34 Hospital B: 31-30
A. Chow, 2018	HospitalA : 100 Hospital B: 360 Hospital C (no interventi on): 116	Hospital A stroke, brain injury, spinal and musculoskeletal conditions. Hospital B: stroke and debilitating medical conditions. Hospital C (no intervention): stroke and subacute medical conditions.	median A: 16 B: 26 C: 18				
F. Arena, 2018	100	1) patients admitted directly from ICU, complex rehabilitation practices, significant comorbidities, mechanical ventilation, ventilator weaning. 2) patients with orthopedic, cardiologic, respiratory, neurologic conditions, requiring functional and/or cognitive rehabilitation	1) mean±SD : 97±72 2) mean±SD 24±12	**J. Benson, 2014**	41	nearly all patients referred from other health care facilities (primarily traditional acute care hospitals)	Baseline: 31.4 Interventi on: 28.6

NR: not reported

Table 3. Types of rehabilitation settings and patient populations in the included studies

The selected publications evaluated the effectiveness of different interventions to prevent MDR hospital acquired full-blown infections (HAI) or colonization, and/or their impact on antimicrobial consumption and on the expenditure in antimicrobials. Such kinds of interventions were grouped into the three identified categories: AMS programs, SEC i.e., interventions aimed at decreasing the rate of contamination of the environment, surfaces or patients' skin and mucosae, and, finally, BP interventions. These interventions and their outcomes are described in the following sections and summaries of the main characteristics of the included studies are reported according to the type of intervention in Table 4.

Antimicrobial Stewardship Interventions

Antimicrobial stewardship interventions were introduced in eight facilities: three rehabilitation hospitals, one rehabilitation ward of a hospital, and four LTACHs (Table 4). The implementation consisted, in six studies (M. Rawlins et al., 2017; JA Curran et al., 2022; S. Tedeschi et al., 2016; J. Benson et al., 2014, K. Beaulac et al., 2016; A. Mushtaq et al., 2017) of the adoption of periodic perspective audit and feedback rounds, based on the evaluation of antimicrobial prescriptions' data. Regarding LTACH, Beaulac et al., 2016 reported a significant reduction in the overall antimicrobial consumption over the intervention period, similarly. A. Mushtaq, 2017 reported a decrease in the use of daptomycin and tigecycline but statistical significance was not tested. A significant decrease in antibiotic use was also observed by J. Benson, 2014, notwithstanding the use of an indirect outcome.

As for Rehabilitation Facilities, S. Tedeschi et al., 2016, reported a significant decrease of carbapenems consumption in the intervention cohort, however, providing no information on the degree of uncertainty of these findings; M. Rawlins, 2017 showed a significant reduction in piperacillin–tazobactam consumption albeit with increases in carbapenems, cephalosporins, and fluoroquinolone consumption compared to baseline. Curran et al. reported non-statistically significant variations.

The impact of ASP on CD infections was analyzed by three studies. A positive effect on reducing infection rate was found by Beaulac et al. in Brakovic's three-tiered approach (LTACH) and Tedeschi et al. (Rehabilitation Facility) although the latter two did not provide information on the uncertainty of the findings.

Antimicrobial Stewardship Interventions					
Author, year	Intervention	Setting	Sample size	outcome(s) of Interest (Unit)	Relevant Results
J. Benson, 2014	Antimicrobial optimization, based on patients' individual	LTACH	baseline: 311 intervention: 767	antimicrobial costs per patient/day (USD)	baseline: 75.37 (SD: ±11.85) intervention:

	characteristics and on the result of microbiological tests.				64.13 (SD: ± 13.78)*
A. Mushtaq, 2017	Prospective review and feedback	LTACH	baseline: 88 intervention: 28	total antibiotic cost per patient in 3 months (USD) Δ daptomycin consumption (%) Δ tigecycline consumption (%)	baseline: 57,168.00 intervention: 22,397.15 -42% -58%
B. Brakovich, 2013	optimization of the frequency and duration of antimicrobial therapy and restriction of clindamycin and cephalosporin prescription.	LTACH	NR	rates of CDI (per 10,000 days)	baseline: 56.52 intervention: 31.51
K. Beaulac, 2016	off-site review of the medical records followed by daily reports and recommendations from the AMS team	LTACH	baseline: NR intervention: 734	Δ antimicrobial consumption from baseline (DDD/1,000 PD) incidence rate ratio of HA-CDI (cases per 1,000 PD)	−6.58 DDD/1,000 PD per month (95% CI, −11.48 to −1.67)* 0.57 (95% CI, 0.35–0.92)*
S. Tedeschi, 2016	prospective audit and feedback therapeutic dose-monitoring	Rehabilitation hospital	baseline: 485 intervention: 740	antibiotic consumption (DDD/100 PD) incidence of CDI (cases/10,000 PD)	baseline: 42* intervention: 22* baseline: 3.6* intervention: 1.2*
Cheung A, 2017	Institution-specific UTI guideline, based on reviewing local antibiagrams. education for the personnnel	Rehabilitation hospital	NR	antibiotic consumption (DDD/1,000 PD)	NS
JA Curran, 2022	prospective audit and feedback performed in 2 sequential intervention periods to the baseline by: (1) a dedicated AMS pharmacist, (2) a ward pharmacist	Rehabilitation hospital	baseline: 2,569 intervention 1: 2,836 intervention 2: 2,525	antimicrobial consumption (DOT/1,000 PD)	NS
M. Rawlins, 2017	Prospective audit and feedback	Rehabilitation ward/unit of a hospital	NR	Δ Carbapenems consumption compared to baseline (%)	+8.4*

				Δ Cephalosporins consumption compared to baseline (%) Δ Fluoroquinolone consumption compared to baseline (%) Δ Piperacillin–tazobactam consumption (%)	+11.2* +5.7* −8.9*
Behaviour preventive interventions					
Author, year	**Setting**	**Sample size**	**Method of Detection**	**Management of cases**	**Outcome measure (Unit)**	**Value**
F. Arena, 2018	Inpatient Rehabilitation Facility	1,084	Rectal swab at the admission and on a weekly basis	contact precautions, cohorting, dedicated rehabilitation programs, restricted access to common gyms.	point-prevalence of CRE carriage CRE colonization incidence (cases/100 PW)	NS NS
A. Widner, 2014	Inpatient Rehabilitation Facility	baseline: 2028 intervention: 4003	PCR-based rapid screening upon admission	Contact precautions, Decolonization therapy through nasal mupirocin-based ointment and bathing with chlorhexidin-based soap. nasal mupirocin	Δ MRSA HAI incidence rate (%)	-38.8*
A. Chow, 2018	Rehabilitation Hospital	1255	screening for MRSA colonization on admission and discharge for MRSA acquisition. Screening swabs obtained from the nares, axillae, and groin	contact precautions, universal daily chlorhexidine bathing and intranasal octenidine for MRSA-colonisers	OR MRSA prevalence	Hospital A: 0.42, (95% CI 0.20 –0.89) Hospital B 0.57, (95% CI 0.39 –0.84) Hospital C (no intervention) 1.19, (95% CI 0.60 – 2.33)
B. Brakovich, 2013	LTACH	NR	new testing methodology for CDI (antigen marker, C. difficile glutamate	new testing methodology, contact isolation for all patients with a positive diagnosis of CDI	rates of CDI (per 10,000 days)	baseline: 56.52 intervention: 31.51

			dehydrogenase , and both toxins A and B.)			
MK. Hayden, 2015	LTACH	baseline: 3894 intervention: 2951	rectal culture surveillance upon admission and every two weeks	contact isolation and geographic separation of positive patients in a ward cohort or single room; universal contact isolation of all patients in high-acuity units.	prevalence of KPC rectal colonization (%) attributable risk of KPC in any clinical culture (cases/1.000 PW) attributable risk of KPC bloodstream infection (cases/1.000 PW)	Baseline: 45.8%; 95% (CI 42.1%–49.5%) Interventions: 34.3%; (95% CI, 32.4%–36.2%;) * −1.2* −0.5*
K. Shigemura , 2014	Rehabilitation ward/unit of a hospital	38	Urine culture tests for all hospitalized patients with catheters or on clean intermittent catheterization every month.	contact precautions in infected patients Fitting up automatic flushing toilet system.	MDR P. aeruginosa isolation ratio (cases 1000/Total days of catheter use)	Decreasing trend

Sanitation and Environmental cleaning

Author, year	Setting	Sample size	Intervention	Outcome measure (Unit)	Value
E. Chipps, 2013	Rehabilitation Hospital	29	Oral Care Protocol	MRSA colonization incidence	NS
G.R. Madden, 2018	LTACH	NR	copper-impregnated linens, hand hygiene	HO-CDI, (cases/1000 PD) HO-MDRO (cases/1000 PD) acquisition, MRSA acquisition, (cases/1000 PD) VRE, acquisition, (cases/1000 PD) CRE, acquisition (cases/1000 PD)	Baseline: 1,5 intervention : 2,8 Baseline: 3.9 intervention : 6.3 NS Baseline: 2,1 intervention : 3,8

				Acinetobacter (cases/1000 PD) MDRO HAIs (cases/1000 PD)	Baseline: 0.3 intervention : 0.7 NS NS
B. Brakovich , 2013	LTACH	NR	Lipstick Challenge on high touch areas, Implement daily and terminal cleaning checklist, HPV equipment, Color-coded microfiber cloths, Training on the use of ES chemical, Use of bleach	rates of CDI (per 10,000 days)	baseline: 56.52 intervention : 31.51
T. Ethington , 2021	LTACH	NR	removing bacteria from the air with ultraviolet germicidal irradiation (UV-C)	CDI (number of cases)	Baseline: 8 Intervention 1
E.A. Hooker, 2015	LTACH	NR	launderable mattress and bed deck covers, hand hygiene	IRR of CDI (cases/per 10,000 PD)	-50%, in the intervention period, compared to baseline (95% CI 47.5 – 52.7),

NR: not reported

NS: not significant

**p<0.05*

Table 4. Types of interventions, main characteristics, and outcomes in the included studies

Behaviour preventive interventions

Five study implemented colonization screening and contact precautions for patients tested positive to MDROs. Regarding LTACH, two were aimed at preventing MRSA infections (A. Widner, 2014; A. Chow, 2018), one (MK. Hayden, 2015) was designed to address CRE transmission. and Concerning Rehabilitation Facilities, F. Arena, 2018 also investigated CRE, while K. Shigemura, 2014 focused on preventing UTIs caused by MDR Pseudomonas (Table 4).

All the interventions were designed to have two distinct phases: a screening phase upon patients' admission and a second phase, which consisted of the employment of

contact precautions or contact isolation for the colonized patients; interventions to which decolonization treatment was added in the studies concerning MRSA (A. Widner, 2014; A. Chow, 2018) .

According to Chow 2018, the implementation of intranasal octenidine treatment and universal antiseptic bathing was effective in reducing prevalence of MRSA at two rehabilitation hospitals; similar intervention of case detection and decontamination therapy with mupirocin was proven effective to reduce MRSA HAI incidence rate in Widner 2014 study.

MK. Hayden, 2015 noted a decrease in the prevalence of KPC rectal colonization throughout the intervention period involving contact precautions and cohorting.

With regard to Rehabilitation Facilities, an intervention similar to that of Hayden, 2015, showed no significant changes in the study by Arena et al. Finally, a reduction in MDR *Pseudomonas aeruginosa* isolation rates among catheterized spinal cord injury patients was documented by Shigemura et al., 2014, after introducing contact precautions for patients identified through urine screening.

Contact isolation measures were also proposed by B. Brakovich, 2013, but coupled with a new testing methodology rather than preventive screening; these measures resulted in a decrease in CDI incidence (without information on the uncertainty of the findings).

Sanitation and Environmental cleaning

As for the category of sanitation and environmental cleaning, four studies concerning LTACH were identified (Table 4); however, these studies describe highly heterogeneous interventions. Madden et al., 2018, found that the use of copper impregnated linen was ineffective in preventing HAI and it was associated with a significant increase of hospital acquired colonization from MDRO and CDIs.

According to authors' interpretation of findings, the mean lower monthly hand hygiene compliance occurring during the intervention compared to the control period significantly impacted the total hospital MDRO acquisition rate.

In E.A. Hooker et al., 2015 study, the use of launderable mattress cover was associated with a reduction of hospital onset CDI, although changes in hand washing compliance, were also found to have a significant impact on the results.

Germicidal irradiation with UV-C was proven to be effective against the spread of HAIs, including CD infections in T. Ethington et al., 2021, study.

Finally, B. Brakovich et al., 2013, evaluating a three-tiered approach comprising a multifaceted strategy of cleaning and disinfection intervention, observed a reduction in CDI incidence (without information on the uncertainty of the findings).

With regard to Rehabilitation Facilities, a RCT by E. Chipps et al., 2013, failed to demonstrate the effectiveness of an oral care-based protocol in preventing MRSA colonization.

Consequently, most AMS studies showed a statistically significant reduction in antibiotic consumption.

BP studies report findings associated with colonization screening and contact precautions albeit with varying degrees of significance.

SEC studies report a wide array of highly diverse interventions where hand hygiene often acts as a confounding factor.

The following table presents the proportion of studies reporting positive outcomes in addressing MDRO infections by type of intervention.

Intervention type	Setting	Number of studies	Proportion showing benefit
adoption of periodic perspective audit and feedback rounds	LTACH	3	67%
	Rehabilitation Facilities	3	33%
colonization screening and contact precautions	LTACH	3	100%

	Rehabilitation Facilities	2	50%

Table 5. Types of interventions and proportion of studies reporting positive outcomes

Discussion

The present systematic review provides a comprehensive insight of the current evidence concerning the strategies to tackle MDROs in inpatient rehabilitation settings. A panel of indicators that are recognized by the CDC as being of objective parameters of infection, prevention and control have been considered [16].

An interpretative framework comprised of scientific findings across the three pre-existing categories borrowed from CDC/WHO guidance emerges from this systematic review. As for antimicrobial stewardship interventions, the decrease in antimicrobial consumption can contribute to a reduction in CD colonizations. Regarding of behavior preventive interventions, colonization screening and contact precautions can reduce MDRO colonization and infections. Finally, sanitation, environmental cleaning and hand hygiene-based interventions may lead to a decrease in the frequency of CD cases.

To the best of our knowledge, this is the first review conducted on this topic that specifically considers a population of patients in inpatient intensive rehabilitation settings with a marked vulnerability to developing colonization or infection by MDROs, due to the previously mentioned individual clinical characteristics and the specific features of the inpatient rehabilitation setting.

In line with previous literature [5, 6] showing that the introduction of ASPs is associated with a reduction of total antimicrobial consumption, antimicrobial costs, and LOS, we also found a positive effect of ASPs in four of the included studies, although statistical significance of estimates was not always proven or tested.

The majority of the selected studies analysed interventions aimed at changing the behaviour of clinicians, healthcare providers, and patients. One study (M. Rawlins, 2017) highlighted higher compliance among clinicians in a rehabilitation hospital compared to a traditional acute care hospital, leading to better outcomes.

Our findings are broadly consistent with previous reviews on IPC and AMS strategies targeting MDROs in acute and extended-care settings. Systematic reviews conducted in acute care hospitals have consistently shown that AMS programs are associated with reductions in antimicrobial consumption, Clostridioides difficile infections, and MDRO colonization and infection rates [38]. Similarly, reviews focusing on long-term care facilities and nursing homes have highlighted the role of contact precautions, hand hygiene, environmental cleaning, and screening strategies in mitigating MDRO transmission, although within care models characterized by lower rehabilitation intensity and different organizational structures [39-41].

Conversely, evidence from some studies in our review (e.g., Madden et al., 2018) suggests that the implementation of some infection control measures may produce an inverse effect. By fostering a false sense of safety, these measures, like copper-impregnated linens, can inadvertently lead to the neglect of core interventions like hand hygiene.

Compared with these previous reviews, the present systematic review specifically addresses post-acute inpatient rehabilitation settings, a transitional care context that has received limited dedicated attention in the IPC literature. While the core preventive strategies identified are largely consistent across settings, their implementation in inpatient rehabilitation environments should account for several setting specific factors such as higher patient mobility, intensive multidisciplinary

therapy, prolonged lengths of stay, and frequent patient–staff interactions. These features may influence both MDRO transmission dynamics and the feasibility of IPC interventions, underscoring the need for setting-specific IPC models tailored to post-acute inpatient rehabilitation contexts.

Indeed, several of the challenges intrinsic to inpatient rehabilitation settings may help explain the variable effectiveness of IPC interventions observed across studies. The frequent use of shared equipment and group-based therapies increases opportunities for cross-transmission, potentially enhancing the impact of interventions focused on environmental cleaning, equipment disinfection, and contact precautions. Conversely, prolonged lengths of stay and lower staff-to-patient ratios compared with acute care settings may limit adherence to resource-intensive measures, such as repeated screening or isolation procedures, thereby reducing their effectiveness. In this context, interventions embedded in standard care processes, such as antimicrobial stewardship and routine hygiene and sanitation practices, are better aligned with the operational realities of inpatient rehabilitation and therefore more likely to achieve sustained impact.

Given the complexity of post-acute inpatient rehabilitation settings and the evidence emerging from both this review and the existing literature, policies and programs in IRUs should systematically evaluate the feasibility of interventions across the three domains identified in our framework. This evaluation should encompass both the micro level (departments responsible for implementation) and the meso level (general management, due to its strategic role). Multi-component interventions combining pharmacological and non-pharmacological strategies are likely to be most effective in addressing these interrelated areas.

Some limitations of the present review need to be mentioned. Chief among these is the absence of prior registration of the study protocol in a public database. The current literature on this topic is quite fragmentary and the level of studies heterogeneity is high; the marked diversity of outcome definitions across the included studies complicates the direct comparison of results and may introduce measurement bias. For these reasons, we could not perform a meta-analysis of findings. The retrieved interventions were all conducted in high income Countries and therefore findings from the included studies cannot be generalized to populations from other geographical or income level areas. Furthermore, the literature search was restricted to publications in the English language, which may have resulted in the omission of relevant data from non-English speaking regions. A potential important source of heterogeneity in the included studies relates to the diversity of inpatient settings, encompassing both rehabilitation hospitals and long-term acute care hospitals. While LTACHs are often conceptualized as step-down units from acute or intensive care, in several healthcare systems they also deliver structured and intensive inpatient rehabilitation to patients with high clinical complexity. In the present review, this heterogeneity was addressed by avoiding pooled quantitative analyses and by interpreting findings within their specific organizational and clinical contexts. Nevertheless, differences in staffing models, patient case-mix, and care intensity across settings should be considered when interpreting and generalizing these findings, and future studies may benefit from stratified or setting-specific evaluations of IPC and AMS strategies.

The present review has several strengths related to the applied methodological approach. The risk of bias was assessed for each study using a scale relevant to the study design. The interpretation of the findings was informed by the risk-of-bias

assessment conducted using ROBINS-I and RoB 2. Although no study was judged to be at high risk of bias, most studies presented methodological limitations related to study design, outcome measurement, or statistical reporting, which warranted a cautious narrative synthesis. For this reason, greater interpretative weight was assigned to studies with more robust designs and clearly reported effect estimates, while evidence from studies with higher uncertainty was considered supportive but not decisive in shaping the overall conclusions. Additionally, we adhered to the PRISMA reporting guidelines for systematic reviews and meta-analyses. Finally, it was possible to provide a systematic and comprehensive overview of various interventions while also considering the value of integrating different areas of preventive programs. Such integrated programs should be further evaluated according to a multidimensional perspective of health technology assessment, as suggested by the EUnetHTA core model [42].

These integrated programmes should be evaluated according to a multidimensional perspective of Health Technology Assessment (HTA), as suggested by EUnetHTA core model for conducting HTA analyses, which organizes the assessment into 9 core domains: 4 technical aspects (including safety and clinical effectiveness implications), and 5 multidisciplinary aspects (ethical, social, legal, economic, and organizational implications).

Conclusion

This review has provided a systematic overview of strategies to promote the prevention and control of MDRO infections in inpatient rehabilitation settings. The available evidence suggests that interventions targeting antimicrobial stewardship, behavioural prevention, and sanitation and environmental cleaning may contribute to the prevention and control of MDROs in inpatient rehabilitation settings.

However, given the heterogeneity of the evidence and the predominance of observational studies, these findings should be interpreted with caution and considered as a framework to guide future research and context-specific implementation rather than as definitive recommendations.

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Appendix 1

Search query: "Subacute Care"[MeSH Terms] OR "hospitals, rehabilitation"[MeSH Terms] OR "Neurological Rehabilitation"[MeSH Terms] OR "Cardiac Rehabilitation"[MeSH Terms] OR "Rehabilitation Centers"[MeSH Terms] OR "Inpatient rehabilitation" OR "extended care" OR "post-intensive care unit" OR "post intensive care" OR "post-intensive care unit" OR "postintensive care" OR

"postintensive care" OR "aftercare" OR "post acute care" OR "care post acute" OR "post-acute care" OR "Postacute Care" OR "care post-acute" OR "convalescent care" OR "rehabilitation hospital" OR "rehabilitation clinic" OR "Subacute Care" OR "Hospital Rehabilitation" OR "Neurological Rehabilitation" OR "Cardiac Rehabilitation" OR "rehabilitation center*" OR "Long-term Acute Care" "LTCH"[Title/Abstract] OR "LTACH"[Title/Abstract] OR "long term care hospital"[Title/Abstract]
"Hygiene"[MeSH Terms] OR "Communicable Disease Control"[MeSH Terms] OR "Cross Infection"[MeSH Terms] OR "Sanitation"[MeSH Terms] OR "Handwashing" OR "Hand sanitation" OR "Hand disinfection" OR "infection prevention" OR "infection control" OR "disinfection" OR "Hygiene" OR "isolation" OR "contact precaution*" OR "universal precaution*" OR "Antimicrobial Stewardship"[MeSH Terms] OR "Drug Utilization"[MeSH Terms] OR "quality assurance, health care"[MeSH Terms] OR "Audit" OR "feedback" OR "Microbial Sensitivity Tests"[MeSH Terms] OR "Disk Diffusion Antimicrobial Tests" OR "antibiogram*" OR "Clinical Governance"[MeSH Terms] OR "Disease Management"[MeSH Terms] OR "Clinical Governance" OR "Disease Management" OR "Clinical Management" OR ("data" OR "use" OR "utilization" OR "utilisation" OR "utilisations" OR "utilise" OR "utilised" OR "utilises" OR "utilising" OR "utilities" OR "utility" OR "utilizations" OR "utilize" OR "utilized" OR "utilizer" OR "utilizers" OR "utilizes" OR "utilizing" AND "Consumption" OR "prescription*") OR "protective equipment" OR “practice guidelines”
"Antimicrobial resistant"[All Fields] OR "XDRO"[Title/Abstract] OR "PDR"[Title/Abstract] OR "XDR"[Title/Abstract] OR "MDR"[Title/Abstract] OR "AMR"[Title/Abstract] "MRSA"[Title/Abstract] OR "VRE"[Title/Abstract] OR "CRE"[Title/Abstract] OR "CDI"[Title/Abstract] OR "AMR"[Title/Abstract]OR "Clostridium difficile"[All Fields] OR "Clostridioides difficile"[All Fields] OR "drug resistance, microbial"[MeSH Terms] OR "antimicrobial resist*"[All Fields] OR "multi drug resistan*"[All Fields] OR "drug resistance"[All Fields] OR "drug resistant"[All Fields] OR "methicillin resistant"[All Fields] OR "beta lactamase*"[All Fields] OR "carbapenem resistant"[All Fields] OR "carbapenemase*"[All Fields] OR "methicillin resistant"[All Fields] OR "vancomycin resistan*"[All Fields] OR "carbapenem resistant"[All Fields] OR "antibiotic resistant"[All Fields] OR "antibiotic resistant"[All Fields]

Appendix 2: Detailed Risk-of-Bias Assessment

This appendix provides a detailed study-level evaluation of the risk of bias for all included studies. Non-randomized studies were assessed using ROBINS-I, which covers seven domains: confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of reported results. Randomized trials were assessed using RoB 2, which includes five domains. Each domain was rated as Low, Moderate, High, or Some concerns, and the overall risk of bias for each study is reported. Interpretative comments highlight how each study's risk-of-bias profile informed the narrative synthesis.

Author, Year	Study Design	Confounding	Selection	Classification	Deviations	Missing Data	Outcome Measurement	Reported Results	Overall Risk	Interpretative Comments
K. Shigemura, 2014	Prospective cohort	Low	Low	Moderate	Low	Moderate	Moderate	Moderate	Moderate	Study conducted in a rehabilitation ward; outcome measures generally reliable, slight uncertainty in intervention classification.
F. Arena, 2018	Prospective cohort	Low	Low	Moderate	Low	Low	Moderate	Moderate	Moderate	Overall good quality; some limitations in outcome measurement.
A. Widner, 2014	Retrospective cohort	Low	Moderate	Low	Low	Moderate	Moderate	Moderate	Moderate	Retrospective study; uncertainty in missing

										data and outcome reporting.
M. Rawlins, 2017	Pre-post	Low	Moderate	Moderate	Low	Low	Moderate	Moderate	Moderate	Pre-post design; interpretation cautious due to lack of control group.
J.A. Curran, 2022	Retrospective interrupted time series	Low	Moderate	Low	Low	Moderate	Moderate	Low	Moderate	Time-series design with sequential interventions; outcomes reasonably reliable.
S. Tedeschi, 2016	Quasi-experimental before-and-after	Low	Moderate	Low	Low	Low	Moderate	Moderate	Moderate	Some domains limited; descriptive reporting for outcomes without full statistical testing.
E. Chipps, 2013	RCT	–	–	–	–	–	–	–	Low	Randomized trial; low risk in RoB 2 domains, providing reliable evidence.
A. Cheung, 2017	Prospective cohort	Low	Moderate	Moderate	Low	Moderate	Moderate	Low	Moderate	Moderate risk overall; descriptive reporting of infection management outcomes.
A. Chow, 2018	Controlled before–after	Low	Moderate	Low	Low	Moderate	Low	Moderate	Moderate	Some uncertainty in confounding; reasonable control of bias in outcome measurement.
B. Brakovich, 2013	Prospective cohort	Low	Moderate	Low	Low	Moderate	Moderate	Moderate	Moderate	Moderate risk due to potential confounding; outcomes reported clearly.
T. Ethington, 2021	Prospective cohort	Low	Low	Low	Moderate	Moderate	Moderate	Low	Moderate	Air disinfection study; low-to-moderate risk, descriptive outcome reporting.
E.A. Hooker, 2015	Prospective cohort	Low	Low	Moderate	Low	Moderate	Moderate	Low	Moderate	Intervention with launderable covers; low risk for most domains, moderate in outcome measurement.
G.R. Madden, 2018	Retrospective cohort	Low	Moderate	Low	Low	Moderate	Moderate	Low	Moderate	Retrospective study; moderate risk due to missing data and reporting domains.
M.K. Hayden, 2015	Pre-post	Low	Low	Low	Moderate	Moderate	Low	Moderate	Moderate	Pre-post design; cautious interpretation of effect due to study design limitations.

J. Benson, 2014	Retrospective cohort	Low	Moderate	Low	Moderate	Moderate	Moderate	Moderate	Moderate	Outcomes reported clearly; moderate risk due to confounding and missing data.
K. Beaulac, 2016	Interrupted time-series	Low	Low	Moderate	Low	Low	Moderate	Moderate	Moderate	Interrupted time-series; robust design, effect estimates reliable.
A. Mushtaq, 2017	Prospective cohort	Low	Low	Moderate	Low	Low	Moderate	Moderate	Moderate	Short-term cohort; moderate risk due to confounding; outcomes descriptive but supportive.

Appendix 3

Full set of indicators used:

- Methicillin-resistant Staphylococcus aureus (MRSA) infection/colonization rates,
- Vancomycin-resistant Enterococci (VRE) infection/colonization rates,
- Carbapenem-resistant Enterobacteriaceae (CRE) infection/colonization rates,
- Carbapenemase-producing Klebsiella pneumoniae (KPC) infection/colonization rates,
- Carbapenemase-producing Acinetobacter baumannii (CRAB) infection/colonization rates,
- Clostridioides difficile (CD) infection/colonization rates,
- incidence rate of resistant Hospital Acquired-Infections,
- antimicrobial consumption per patient/day,
- antibiotic costs per patient/day.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

MR, RM, SM and GS participated in searching for the scientific literature, selection and quality assessment of articles and data collection. MCN performed the data analysis. PL, GD and RL drafted the Discussion and conclusions and supervised the work. All authors participated in the study design and in writing of the manuscript. All authors read and approved the final manuscript.

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