Clinical Infectious Diseases

INVITED ARTICLE

HEALTHCARE EPIDEMIOLOGY: Robert A. Weinstein, Section Editor

Control of Carbapenem-resistant Enterobacteriaceae, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* in Healthcare Facilities: A Systematic Review and Reanalysis of Quasi-experimental Studies

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(See the Editorial Commentary by Bleasdale on pages 885–6.)

Carbapenem-resistant Enterobacteriaceae (CRE), *Acinetobacter baumannii* (CRAB), and *Pseudomonas aeruginosa* (CRPsA) are a serious cause of healthcare-associated infections, although the evidence for their control remains uncertain. We conducted a systematic review and reanalysis to assess infection prevention and control (IPC) interventions on CRE-CRAB-CRPsA in inpatient healthcare facilities to inform World Health Organization guidelines. Six major databases and conference abstracts were searched. Before-and-after studies were reanalyzed as interrupted time series if possible. Effective practice and organization of care (EPOC) quality criteria were used. Seventy-six studies were identified, of which 17 (22%) were EPOC-compatible and interrupted time series analyses, assessing CRE (n = 11; 65%), CRAB (n = 5; 29%) and CRPsA (n = 3; 18%). IPC measures were often implemented using a multimodal approach (CRE: 10/11; CRAB: 4/5; CRPsA: 3/3). Among all CRE-CRAB-CRPsA EPOC studies, the most frequent intervention components included contact precautions (90%), active surveillance cultures (80%), monitoring, audit and feedback of measures (80%), patient isolation or cohorting (70%), hand hygiene (50%), and environmental cleaning (40%); nearly all studies with these interventions reported a significant reduction in slope and/or level. The quality of EPOC studies was very low to low.

Keywords. prevention and control; carbapenem resistance; Enterobacteriaceae; *Acinetobacter*; *Pseudomonas*.

Healthcare-associated infections (HAI) are one of the most common adverse events in healthcare delivery [1]. Carbapenem-resistant Gram-negative bacilli, namely, carbapenem-resistant Enterobacteriaceae (CRE), carbapenem-resistant *Acinetobacter baumannii* (CRAB), and carbapenem-resistant *Pseudomonas aeruginosa* (CRPsA), are a serious cause of HAI and an emerging health threat worldwide. CRE-CRAB-CRPsA have been highlighted as critical pathogens in the World Health Organization (WHO) prioritization of pathogens to guide discovery, research and development of new antibiotics for drug-resistant bacterial infections [2]. These bacteria are difficult to treat due to high levels of antimicrobial resistance and associated with high mortality [3–5]. Some strains have the potential for widespread transmission of resistance via mobile genetic elements that result in the production of carbapenemase enzymes [6]. This can lead to significant outbreaks in healthcare settings and a strain on infection prevention and control (IPC) resources that may be limited [7].

Effective and targeted IPC interventions are essential in CRE-CRAB-CRPsA outbreak and endemic settings [8]. Published IPC strategies for carbapenem-resistant Gram-negative bacilli emphasize the importance of multifaceted approaches and timeliness [9–11]. Various national and international CRE-CRAB-CRPsA guidance documents exist but they vary significantly in scope and evidence base [12]. Most were not based on a methodologically rigorous evaluation of the published literature. Furthermore, ongoing controversy exists about the most pragmatic and evidence-based approach to prevent CRE-CRAB-CRPsA cross-transmission, especially in resource-limited settings [13].

Thus, WHO identified the prevention and control of CRE-CRAB-CRPsA as an urgent priority for the global health agenda. To provide the evidence for global guideline recommendations, we conducted a systematic review to assess the impact of practices and procedures to prevent and control

Received 27 March 2018; editorial decision 23 July 2018; accepted 26 September 2018; published online November 23, 2018.

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Clinical Infectious Diseases® 2019;68(5):873–84

DOI: 10.1093/cid/ciy752

CRE-CRAB-CRPsA transmission in healthcare facilities both in endemic and epidemic settings.

METHODS

We followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) [14]. The protocol was registered at PROSPERO, an international prospective register of systematic reviews (no. 42016052355).

Search Strategy and Eligibility Criteria

We performed a comprehensive search of 6 major databases from their date of inception to January 2017 and 5 international scientific conferences from 2012 to 2016. The search strategy used the concepts: (1) carbapenemase or carbapenem resistance, (2) core infection control measures, and (3) primary infection outcomes including CRE-CRAB-CRPsA colonization and/or infection rates. We included studies that assessed the impact of any IPC measure on CRE-CRAB-CRPsA transmission in inpatient facilities (ie, acute and long-term care) including both endemic and epidemic settings. Outcomes included incidence or prevalence of CRE-CRAB-CRPsA infection or colonization (see Supplementary Table 1 for more on search strategy and eligibility criteria).

Screening and Data Abstraction

Using a standardized form, studies were screened in 2 stages. At the first stage, one reviewer screened all titles and abstracts retrieved from the search strategy, and a second reviewer independently screened a random subset of 30%. At the second stage, all identified full-text manuscripts were independently screened by 2 reviewers. Disagreements between reviewers were resolved by discussion to reach consensus. Data extraction was performed using a standardized form, and DistillerSR® software (Evidence partners, Ottawa, Canada) was used for all screening and abstraction.

Assessment of Bias and Quality

For included studies, risk of bias was assessed using design-specific effective practice and organization of care (EPOC) quality criteria using the EPOC data collection checklist [15]. Eligible EPOC-study designs include non-randomized controlled trials, controlled before-after studies and interrupted time series (ITS) with sufficient data to statistically assess trends before and after the intervention. Sufficient ITS data criteria include: clearly defined intervention time points, at least 3 data points before and 3 after the main intervention, objective measurement of outcome(s), and relevant and interpretable data obtainable among other quality criteria [16]. For all EPOC-compatible studies, grading of recommendations assessment, development and evaluation (GRADE) evidence profiles were created for each measured outcome [17]. All decisions about EPOC and GRADE classifications were discussed within the review team until a consensus was reached.

Reanalysis of ITS Studies

ITS analyses assess the impact of interventions by estimating the change in slope (ie, trend) and level (ie, immediate change) of the outcome from the pre- to post-intervention period. This is a strong quasi-experimental design that can control for the effect of underlying secular trends in data over time, which may bias estimates from before-after studies [18]. In an effort to increase the number of suitable identified studies meeting the requirements of an EPOC-compatible ITS analysis, we contacted authors of before-after studies who potentially had sufficient ITS data (ie, minimum 3 data points pre- and 3 data points post-intervention) and requested raw data for further analysis. In total, we were able to reanalyze 13 (72%) studies, using autoregressive moving average regression models for each outcome. Model specifications were determined using autocorrelation and partial autocorrelation functions, residual plots, Durbin-Watson statistics, and likelihood ratio tests [19]. Studies with at least 10 data points in the pre-intervention and 10 in the post-intervention periods were considered reasonably well powered [19].

RESULTS

We identified 9247 potential articles/abstracts, of which 180 (1.9%) assessing CRE and 126 (1.3%) assessing CRAB-CRPsA were suitable for full-text screening (Figure 1). Seventy-six of these met the inclusion criteria upon full text review (CRE: 46 studies, CRAB: 26 studies and CRPsA: 13 studies; 6 studies assessed more than 1 pathogen outcome). Most were conducted in the Americas or Europe and described locally led hospital or intensive care unit (ICU)-specific interventions (Table 1). The most common outcome was incidence of infection (Table 1). Seventeen (22%) studies were classified as EPOC-standard including 11 (14.5%) that assessed CRE (10 CRE alone, 1 CRE and CRAB), 5 (6.6%) that assessed CRAB (3 CRAB alone, 1 CRE and CRAB, 1 CRAB and CRPsA) and 3 (3.9%) that assessed CRPsA (2 CRPsA alone, 1 CRAB and CRPsA). All 17 were ITS, with study durations ranging from 15.6 months to 7.0 years; none were conducted in low-income countries. Fifteen of 17 studies were reasonably well powered. Results for EPOC studies are presented below (see Supplemental Appendix Table 3 for non-EPOC studies).

IPC Intervention Components and Reanalysis

Multimodal strategies (ie, ≥3 components implemented in an integrated way to achieve outcome improvement and change behavior as defined in WHO guidelines on core components of IPC programs) were used in most studies [20]. Among all studies, ten (91%) CRE, 4 (80%) CRAB, and 3 (100%) CRPsA studies of EPOC-standard used a multimodal approach, of which

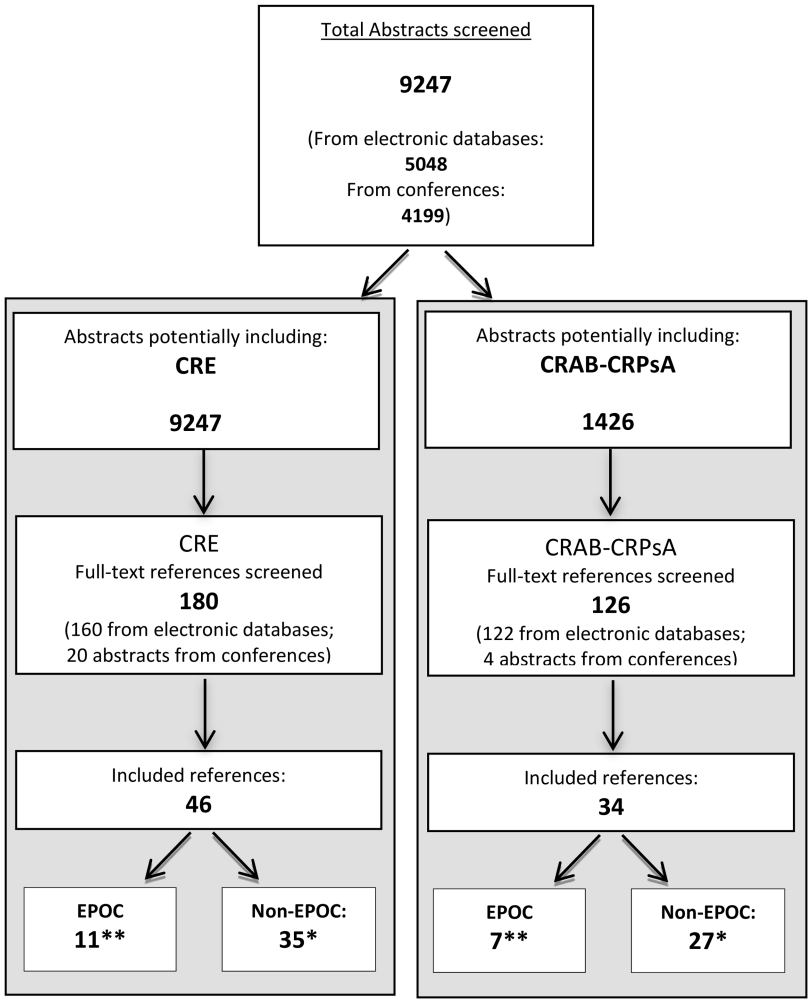

Figure 1. Flow chart of study selection. Abbreviations: CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRE, carbapenem-resistant Enterobacteriaceae; CRPsA, carbapenem-resistant *Pseudomonas aeruginosa*; EPOC, effective practice and organization of care. *Includes 3 studies that described CRE, CRAB and CRPsA; 1 study that described CRE and CRAB; and 2 studies that described CRAB and CRPsA. **Includes one study that described both CRE and CRAB.

9 (90%), 3 (75%), and 2 (67%) studies (respectively) reported a significant reduction in outcomes post-intervention, respectively (range for change in slope [trend over time]: −0.01 to −4.81; and level [immediate change]: −0.02 to −48.86; Tables 2 and 3, Figures 2 and 3).

Among all CRE-CRAB-CRPsA EPOC studies, the most frequently implemented IPC measures were contact precautions (90%), active surveillance cultures (80%), monitoring, audit and feedback of preventive measures (80%), patient isolation or cohorting (70%), hand hygiene (50%), and environmental cleaning (40%); nearly all studies with these intervention components reported a significant reduction in slope and/or level (Table 3). Contact precautions were often defined as "at least the use of disposable gowns and gloves" and the intervention was commonly described as "strict contact precautions." Among studies which included contact precautions, 9/10 CRE, 3/4 CRAB, and 2/3 CRPsA studies reported a significant reduction in slope (range: −0.01 to −4.81) and/or level (range: −0.02 to −48.86; Tables 2 and 3). Active surveillance strategies varied but commonly included culture of feces and/or rectal swab collection from all patients or high-risk patients only (eg, ICU, previous history of colonization/infection) on admission and/or at regular frequencies (eg, weekly to biweekly) as well as from contacts of index cases; and often focused on CRE. Among studies which included active surveillance as part of their IPC intervention, 8/10 CRE, 2/3 CRAB, and 2/3 CRPsA studies reported a significant reduction in slope (range: −0.01 to −4.81) and/or level (range: −0.02 to −48.86; Tables 2 and 3).

Monitoring and audits focused on IPC practices and often included feedback to staff, IPC committees and/or hospital leadership. Among studies that included monitoring, audit, and feedback, 8/9 CRE, 3/4 CRAB and 2/3 CRPsA studies reported a significant reduction in slope (range: −0.01 to −4.81) and/or level (range: −0.02 to −48.86; Tables 2 and 3). Patient isolation strategies included cohorting (ie, wards or separate locations) or single room isolation when feasible. Some studies specified

Table 1. Descriptive Characteristics of Included Effective Practice and Organization of Care (EPOC) and Non-EPOC Studies (N = 76)

Study Characteristic	CRE		CRAB		CRPsA	
	EPOC (n = 11[a])	Non-EPOC (n = 35[b])	EPOC (n = 5[a])	Non-EPOC (n = 21[b])	EPOC (n = 3)	Non-EPOC (n = 10[b])
Region[c]						
Africa	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Americas	4 (0.4)	14 (0.4)	3 (0.6)	5 (0.2)	1 (0.3)	3 (0.3)
Eastern Mediterranean	4 (0.4)	3 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)
Europe	2 (0.2)	17 (0.5)	0 (0)	10 (0.5)	1 (0.3)	6 (0.6)
South-East Asia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.1)
Western Pacific	1 (0.1)	1 (0.02)	2 (0.4)	6 (0.3)	1 (0.3)	0 (0)
Setting						
National	1 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Regional/State	1 (0.1)	1 (0.02)	0 (0)	1 (0.05)	0 (0)	1 (0.1)
Hospital	6 (0.5)	12 (0.3)	2 (0.4)	8 (0.4)	1 (0.3)	4 (0.4)
Intensive Care Unit	2 (0.2)	8 (0.2)	3 (0.6)	9 (0.4)	1 (0.3)	3 (0.3)
Neonatal Intensive Care Unit	0 (0)	2 (0.1)	0 (0)	2 (0.1)	0 (0)	0 (0)
Hematology	0 (0)	8 (0.2)	0 (0)	0 (0)	1 (0.3)	1 (0.1)
Burns	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.1)
Long-term care facilities	1 (0.1)	4 (0.1)	0 (0)	1 (0.05)	0 (0)	0 (0)
Design						
Non-randomized controlled trials	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Controlled before-after studies[d]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Interrupted time series studies	11 (1)	1 (0.02)	5 (1)	2 (0.1)	3 (1)	1 (0.1)
Before-after case count studies[d]	0 (0)	14 (0.4)	0 (0)	15 (0.7)	0 (0)	9 (0.9)
Longitudinal studies	0 (0)	2 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)
Mathematical modeling studies	0 (0)	3 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)
Non-controlled before-after studies[d]	0 (0)	15 (0.4)	0 (0)	4 (0.2)	0 (0)	0 (0)
Outcome[e]						
Incidence of infection[f]	8 (0.7)	12 (0.3)	2 (0.4)	5 (0.2)	2 (0.7)	3 (0.3)
Prevalence of infection[f]	0 (0)	5 (0.1)	0 (0)	1 (0.05)	0 (0)	0 (0)
Incidence of bloodstream infections[f]	2 (0.2)	4 (0.1)	0 (0)	1 (0.05)	0 (0)	0 (0)
Incidence of colonization	0 (0)	9 (0.3)	1 (0.2)	4 (0.2)	1 (0.3)	3 (0.3)
Prevalence of colonization	1 (0.1)	13 (0.4)	0 (0)	0 (0)	0 (0)	0 (0)
Incidence of colonization or infection[f]	1 (0.1)	13 (0.4)	2 (0.4)	12 (0.6)	0 (0)	5 (0.4)

Abbreviations: CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRE, carbapenem-resistant Enterobacteriaceae; CRPsA, carbapenem-resistant *Pseudomonas aeruginosa*; EPOC, effective practice and organization of care.

[a]Includes 1 study assessing both CRE and CRAB.

[b]Includes 3 studies that described CRE, CRAB, and CRPsA; 1 study that described CRE and CRAB; and 1 study that described CRAB and CRPsA.

[c]Defined as World Health Organization regions: http://www.who.int/about/regions/en/.

[d]Before-after case counts: cases were counted before and after implementation of an intervention with no statistical test performed to compare the change; noncontrolled before-after studies: observations made before and after implementation of an intervention and a statistical analysis conducted to compare the 2 periods.

[e]Some studies reported multiple outcomes and are therefore listed more than once.

[f]Infections: Most of studies defined infection as any positive clinical sample.

dedicated nursing staff and equipment. Among studies that included patient isolation or cohorting, 8/9 CRE, 3/3 CRAB, and 1/1 CRPsA studies reported a significant reduction in slope (range: −0.01 to −4.81) and/or level (−1.19 to −48.86; Tables 2 and 3). Hand hygiene improvement interventions often included education and monitoring of best practices. Among studies that included hand hygiene promotion, 5/6 CRE and 3/4 CRAB studies reported a significant reduction in slope (range: −0.01 to −4.81) and/or level (range: −0.02 to −48.86; Tables 2 and 3).

Three (30%) CRE studies included environmental cleaning as part of their intervention, whereas 3 (60%) CRAB and 2 (70%) CRPsA studies emphasized the importance of this component. One cleaning agent that was commonly reported was hypochlorite 1000 parts per million (ppm). Among these, 2/3 CRE, 3/3 CRAB, and 2/2 CRPsA studies reported a significant reduction in slope (range: −0.01 to −4.81) and/or level (range: −0.02 to −48.86; Tables 2 and 3). Additionally, 1 CRE, 1 CRAB, and 2 CRPsA studies included environmental surveillance. Other less common interventions included antibiotic stewardship, medical record flagging or alerts, chlorhexidine gluconate baths, temporary ward closure, multidisciplinary task force meetings, and analysis of work flow to identify common objects shared between patients and staff (Tables 2 and 3).

Table 2. Results of Effective Practice and Organization of Care Studies by Outcome for Change in Slope (ie, Trend) and Level (ie, Immediate Change) From Pre-intervention to Post-intervention Periods

Study	Intervention Package	Slope Change (95% CI)[a]	Level Change (95% CI)[a]
Incidence of CRE infection per 10 000 patient days			
Ben-David et al [34]	Active surveillance using rectal swabs of ICU and step-down unit patients on admission/weekly and contacts; Infected patient database to identify readmissions; Contact precautions; Daily prevalence reporting to management	**−0.57 (−0.58, −0.55)**	**−2.56 (−2.77, −2.33)**
Borer et al [35]	Active surveillance of high-risk patients on admission/weekly; Emergency department flagging to identify high-risk patients; Contact precautions; Cohort ward for positive cases with dedicated staff/equipment; Cultures of environment and healthcare worker hands; Carbapenem prescribing restriction policy; Management reporting	**−0.32 (−0.58, −0.06)**	**−3.93 (−5.95, −1.91)**
Campbell et al [36]	Expanded CRE surveillance: High-risk populations screened on admission/weekly	−0.09 (−1.04, 0.87)	**7.23 (1.89, 12.57)**
Ciobotaro et al [37]	Active surveillance using rectal swabs of index case roommates and ICU patients; Audit and feedback; Electronic database of positive patients and flagging in electronic medical record; Immediate laboratory notification of cases; Contact precautions; Cohorting including rotation of staff to prevent overload; Environmental cleaning; Education and training of patients and caregivers	**−0.91 (−0.97, −0.85)[c]**	Not calculated
Gagliotti et al [38][b]	Active surveillance of asymptomatic carriers on admission and contacts; Contact precautions; Cohorting or single room isolation; Communication of CRE status on hospital transfer or discharge; Monthly reporting of prevalent cases to the regional health authority; Monitoring by hospital directors; Survey to evaluate implementation of CRE guidelines and feedback	**−0.01 (−0.02, −0.002)**	0.17 (−0.18, 0.51)
Hayden et al [39]			
Facility 1	Active surveillance of patients for *Klebsiella Pneumoniae* carbapenemase rectal colonization on admission and every other week; Pre-emptive isoation pending culture results; Contact isolation; Chlorhexidine gluconate baths; Healthcare worker education and adherence monitoring including a focus on hand hygiene	−0.13 (−2.70, 2.43)	−17.43 (−42.29, 7.43)
Facility 2		**−2.39 (−3.13, −1.66)**	−5.71 (−13.99, 2.60)
Facility 3		0.55 (−1.89, 2.99)	**−25.33 (−38.27, 12.40)**
Facility 4		−0.38 (−2.33, 1.57)	**−20.94 (−37.60, −4.28)**
Kim et al [40]	Contact precautions; Cohorting; Hand hygiene enforcement and compliance monitoring; Enhanced antimicrobial stewardship	**−3.55 (−4.25, −2.86)**	**−31.80 (−52.77, −10.84)**
Schwaber et al [41]	Contact isolation measures; Single rooms or cohorts including dedicated staff/equipment; Re-isolation of known carriers on admission; Creation of a Task Force on Antimicrobial Resistance and Infection Control that performed regular site visits; Feedback to appointed hospital representatives; Mandatory reporting to public health authorities; Distribution of guidelines for active CRE surveillance in acute-care hospitals later in the intervention period	**−0.30 (−0.45, −0.15)**	**−1.19 (−1.95, −0.44)**
Incidence of CRE infection or colonization per 10 000 patient days			
Enfield et al [42]	Active surveillance using wound and respiratory samples of all patients twice weekly and all at-risk patients in ICU; Audit and feedback (on hand hygiene, contact precautions, environmental cleaning); Enhanced staff education on contact precautions; Pre-emptive isolation for all patients; Patient and staff cohorting; Chlorhexidine baths; Limit public access to rooms and common areas; Environmental cleaning education; Terminal cleaning rooms of all patients; Enhanced antibiotic stewardship	9.11 (−2.80, 21.02)	−10.69 (−108.14, 86.77)
Incidence of CRE BSI infection per 10 000 patient days			
Hayden et al [39]			
Facility 1	Active surveillance of *Klebsiella pneumoniae* carbapenemase using rectal swabs of patients on admission and every other week; Pre-emptive isolation pending culture results; Contact isolation; Chlorhexidine gluconate baths; Healthcare worker education and adherence monitoring (on hand hygiene)	**−1.00 (−1.71, −0.29)**	**−17.72 (24.91, −10.53)**
Facility 2		**−0.91 (−1.13, −0.70)**	**−4.80 (−7.40, −2.20)**
Facility 3		0.28 (−0.73, 1.30)	−4.95 (−12.64, 2.75)
Facility 4		−0.21 (−1.25, 0.83)	−5.46 (−14.32, 3.39)
Viale et al [43]	Active surveillance of high-risk patients and contacts; Contact precautions; Cohorting; Enhanced education, cleaning and hand-washing program; Antibiotic stewardship focused on carbapenem use	**−0.09 (−0.12, −0.06)**	1.20 (0.86, 1.55)
Prevalence of CRE colonization			
DalBen et al [44]	Active surveillance using rectal cultures of all admitted patients on admission/weekly/ discharge; Monitoring of hand hygiene and contact precautions compliance; Weekly staff meetings for feedback; ICU closure	0.63 (−0.01, 1.26)	**−17.89 (−20.12, −15.65)**
Incidence of CRAB infection per 10 000 patient days			
Chung et al [45]	Daily chlorhexidine bathing in medical ICU	0.003 (−0.04, 0.04)[c]	**−0.60 (−0.90, −0.31)[c]**
Munoz-Price et al [46]	Weekly electronic communication with case notification to hospital leadership; Environmental cultures; Hand hygiene education and enforcement; Identifying and limiting shared objects; Multidisciplinary task force meetings	**−0.09 (−0.14, −0.04)[c]**	Not calculated

Table 2. Continued

Study	Intervention Package	Slope Change (95% CI)[a]	Level Change (95% CI)[a]
Incidence of CRAB infection or colonization per 10 000 patient days			
Enfield et al [42]	Active surveillance using wound and respiratory samples of all patients twice weekly and all at-risk patients in ICU; Audit and feedback (on hand hygiene, contact precautions, environmental cleaning); Enhanced staff education on contact precautions; Pre-emptive isolation for all patients; Patient and staff cohorting; Chlorhexidine baths; Limit public access to rooms and common areas; Environmental cleaning education; Terminal cleaning rooms of all patients; Enhanced antibiotic stewardship	**−4.81 (−7.00, −2.61)**	**−48.86 (−67.18, −30.54)**
Cho et al [47]	Active surveillance using nasal swabs of all ICU patients on admission and weekly; Contact precautions and isolation; Hand hygiene using alcohol-based hand rub; Environmental cleaning using a sodium dichloroisocyanurate (NaDCC)-containing solution; Education biweekly onsite; Monitoring of infection control measures for hospital accreditation	**−0.01 (−0.02, −0.003)[c]**	0.34 (0.14, 0.54)[c]
Incidence of CRPsA infection per 10 000 patient days			
Nagao et al [48][b]	Active surveillance using rectal swabs; Contact precautions; Environmental cleaning and surveillance; Automatic urine collection machines removed; Staff meetings for feedback; Restriction of carbapenem use	−0.002 (−0.004, −0.0004)	**−0.02 (−0.03, −0.01)**
Suarez et al [49]	Active surveillance of patients and environment; Strict compliance with cross-transmission protocols; Patient isolation; Closure of ICU and urology wards for decontamination; Disposable aprons and gloves; Room cleaning with hypochlorite twice daily for colonized patients; Audits; Restriction of carbapenem use in ICU;	**−1.36 (−1.88, −0.84)[c]**	−1.58 (−3.5, 0.33)[c]
Incidence of CRAB and CRPsA colonization per 10 000 patient days			
DalBen et al [50]	Active surveillance using rectal, oro-pharyngeal and axilla swabs of patients on admission/regularly; Contact precautions but no single rooms; Education on use of gloves and alcohol-based hand rub; Hand hygiene audits	−37.17 (−102.13, 27.80)	458.40 (−236.26, 1153.05)

Abbreviations: CI, confidence interval; CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRE, carbapenem-resistant Enterobacteriaceae; CRPsA, carbapenem-resistant *Pseudomonas aeruginosa*; ICU, intensive care unit.

[a]"Slope change" is the change in the trend of the outcome from the pre- to post-intervention period. "Level change" is the immediate change in the outcome from the pre- to post-intervention period. Significant reductions (negative estimates) in slope and/or level could be considered a rough proxy for more effective studies. Bold numbers represent significant estimates.

[b]Studies were analyzed according to week (Gagliotti et al) or biannually (Nagao et al).

[c]Data not available to reanalyze so estimates are as reported in the published manuscript using Poisson segmented regression (Ciobotaro et al, Chung et al, Munoz-Price et al) or linear segmented regression (Suzarez et al, Cho et al).

Risk of Bias and Quality of the Evidence

All EPOC-standard CRE-CRAB-CRPsA studies were classified as having a high risk of bias (Table 4) due to the unknown likelihood that interventions (eg, surveillance) affected outcome data collection or were independent of other measures implemented at the same time, an important methodological consideration for ITS studies; lack of blinding or control; and failure to explicitly address missing outcome measures. According to GRADE methodology, evidence was graded as "low quality" for incidence of CRE infection, CRE blood stream infection, CRAB infection and/or colonization and CRPsA infection. Evidence was graded as "very low quality" for prevalence of CRE colonization and incidence of CRE infection and/or colonization, CRAB infection, and CRAB and CRPsA colonization (Supplemental Appendix Table 2).

DISCUSSION

In contrast to previous reviews, the current article provides a methodologically focused, rigorous systematic review with a reanalysis of quasi-experimental studies to assess the impact of practices and procedures to prevent and control CRE-CRAB-CRPsA transmission in healthcare facilities [11, 21–23]. We were able to obtain additional data from many authors to reanalyze studies using ITS analyses and apply strict evidence quality assessment methodology to obtain higher quality evidence as a basis for more robust recommendations. These studies reported effective interventions including strict contact precautions, active surveillance cultures (ie, not only passive surveillance of CRE infection), monitoring, audit and feedback of preventive measures, patient isolation or cohorting, hand hygiene, and environmental cleaning.

Overall, multimodal IPC strategies (ie, ≥3 components implemented in an integrated way) appear to be highly effective for CRE-CRAB-CRPsA prevention and control. This is also highlighted by the recent evidence-based WHO Guidelines on core components of IPC programs, which strongly recommend multimodal strategies to translate IPC measures into practice and achieve behavioral change [20]. Other toolkits to control carbapenem-resistant Gram-negatives have similarly emphasized the importance of multifaceted approaches or bundles for early detection, education and implementation of strict IPC measures [9, 10, 24, 25].

Strong evidence on the role of active surveillance for infection and asymptomatic colonization was found for CRE,

Table 3. Most Frequent Components in Infection Prevention and Control Multimodal Interventions Implemented in Effective Practice and Organization of Care Studies

Intervention	Studies *WITH* Intervention (%)[a]	Studies *WITH* Intervention AND Reporting Significant Reduction in Slope and/or Level (%)[b]	Studies *WITHOUT* Intervention *AND* Reporting Significant Reduction in Slope and/or Level (%)[c]
All studies (N = 17)			
Contact precautions (ie, at least use of disposable gowns and gloves) education/ monitoring	15/17 (0.9)	14/15 (0.9)[d]	2/2 (1)
Active surveillance cultures[e]	14/17 (0.8)	12/14 (0.9)[d]	3/3 (1)
Monitoring/audit of infection prevention and control practices and feedback	14/17 (0.8)	13/14 (0.9)[d]	3/3 (1)
Patient isolation or cohorting[f]	12/17 (0.7)	12/12 (1)[d]	4/5 (0.8)
Hand hygiene education/monitoring	9/17 (0.5)	8/9 (0.9)[d]	8/8 (1)
Environmental cleaning[g]	7/17 (0.4)	7/7 (1)[d]	9/10 (0.9)
Antibiotic stewardship (eg, carbapenem restriction)	6/17 (0.4)	6/6 (1)[d]	10/11 (0.9)
Environmental surveillance	4/17 (0.2)	4/4 (1)	12/13 (0.9)[d]
Flagging positive patients in medical record (alerts) to promptly recognize readmissions/transfers	4/17 (0.2)	4/4 (1)	12/13 (0.9)[d]
Daily chlorhexidine gluconate baths	3/17 (0.2)	3/3 (1)[d]	13/14 (0.9)
Temporary ward closure	2/17 (0.1)	2/2 (1)	14/15 (0.9)[d]
Multidisciplinary task force meetings	2/17 (0.1)	2/2 (1)	14/15 (0.9)[d]
Analysis of work flow to identify common objects shared between patients and staff	1/17 (0.1)	1/1 (1)	15/16 (0.9)[d]
CRE studies (n = 11)			
Contact precautions (ie, at least use of disposable gowns and gloves) education/ monitoring	10/11 (0.9)	9/10 (0.9)	1/1 (1)
Active surveillance cultures[e]	10/11 (0.9)	8/10 (0.8)	1/1 (1)
Patient isolation or cohorting[f]	9/11 (0.8)	8/9 (0.9)	2/2 (1)
Monitoring/audit of infection prevention and control practices and feedback	9/11 (0.8)	8/9 (0.9)	2/2 (1)
Hand hygiene education/monitoring	6/11 (0.5)	5/6 (0.8)	5/5 (1)
Antibiotic stewardship (eg, carbapenem restriction)	4/11 (0.4)	3/4 (0.8)	7/7 (1)
Flagging positive patients in medical record (alerts) to promptly recognize readmissions/transfers	3/11 (0.3)	3/3 (1)	7/8 (0.9)
Environmental cleaning[g]	3/11 (0.3)	2/3 (0.7)	8/8 (1)
Daily chlorhexidine gluconate baths	2/11 (0.2)	2/2 (1)	8/9 (0.9)
Environmental surveillance	1/11 (0.1)	1/1 (1)	9/10 (0.9)
Temporary ward closure	1/11 (0.1)	1/1 (1)	9/10 (0.9)
CRAB studies (n = 5)			
Contact precautions (ie, at least use of disposable gowns and gloves) education/ monitoring	4/5 (0.8)	3/4 (0.8)	1/1 (1)
Monitoring/audit of infection prevention and control practices and feedback	4/5 (0.8)	3/4 (0.8)	1/1 (1)
Hand hygiene education/monitoring	4/5 (0.8)	3/4 (0.8)	1/1 (1)
Patient isolation or cohorting[f]	3/5 (0.6)	3/3 (1)	1/2 (0.5)
Environmental cleaning[g]	3/5 (0.6)	3/3 (1)	1/2 (0.5)
Active surveillance cultures[e]	3/5 (0.6)	2/3 (0.7)	2/2 (1)
Daily chlorhexidine gluconate baths	2/5 (0.4)	2/2 (1)	2/3 (0.7)
Environmental surveillance	1/5 (0.2)	1/1 (1)	3/4 (0.8)
Flagging positive patients in medical record (alerts) to promptly recognize readmissions/transfers	1/5 (0.2)	1/1 (1)	3/4 (0.8)
Analysis of work flow to identify common objects shared between patients and staff	1/5 (0.2)	1/1 (1)	3/4 (0.8)
Multidisciplinary task force meetings	1/5 (0.2)	1/1 (1)	3/4 (0.8)
Antibiotic stewardship (eg, carbapenem restriction)	1/5 (0.2)	1/1 (1)	3/4 (0.8)
CRPsA studies (n = 3)			
Contact precautions (ie, at least use of disposable gowns and gloves) education/ monitoring	3/3 (1)	2/3 (0.7)	0 (0)
Active surveillance cultures[e]	3/3 (1)	2/3 (0.7)	0 (0)
Monitoring/audit of infection prevention and control practices and feedback	3/3 (1)	2/3 (0.7)	0 (0)
Environmental cleaning[g]	2/3 (0.7)	2/2 (1)	0/1 (0)

Table 3. Continued

Intervention	Studies *WITH* Intervention (%)[a]	Studies *WITH* Intervention AND Reporting Significant Reduction in Slope and/or Level (%)[b]	Studies *WITHOUT* Intervention *AND* Reporting Significant Reduction in Slope and/or Level (%)[c]
Antibiotic stewardship (eg, carbapenem restriction)	2/3 (0.7)	2/2 (1)	0/1 (0)
Environmental surveillance	2/3 (0.7)	2/2 (1)	0/1 (0)
Patient isolation or cohorting[f]	1/3 (0.3)	1/1 (1)	1/2 (0.5)
Multidisciplinary task force meetings	1/3 (0.3)	1/1 (1)	1/2 (0.5)
Temporary ward closure	1/3 (0.3)	1/1 (1)	1/2 (0.5)
Hand hygiene education/monitoring	1/3 (0.3)	0/1 (0)	2/2 (1)

Abbreviations: CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRE, carbapenem-resistant Enterobacteriaceae; CRPsA, carbapenem-resistant *Pseudomonas aeruginosa*; ICU, intensive care unit.

[a]Studies *with* the intervention component *AMONG* all studies of the respective pathogen outcome(s);

[b]Studies *with* the intervention component *and* reporting a significant reduction in slope and/or level *AMONG* studies *with* the intervention;

[c]Studies *without* the intervention component *and* reporting a significant reduction in slope and/or level *AMONG* studies *without* the intervention.

[d]Enfield et al reported a significant reduction in slope and/or level of CRAB, not CRE.

[e]Target populations included all patients, high-risk patients only (eg, ICU), and contacts of a case. Strategies included on admission and/or with a regular ongoing frequency (eg, weekly or biweekly).

[f]Strategies included single room when feasible or cohort ward (or separate location) for positive cases. Some specified dedicated nursing staff and equipment.

[g]Some noted Hypochlorite 1000 ppm as one cleaning agent.

allowing timely recognition and identification of the local epidemiology. Specific surveillance strategies varied across studies. However, common target populations (eg, all patients, high-risk patients, index case contacts), type of culture/swab (eg, culture of feces, rectal swab), and frequency (eg, on admission, weekly) were noted. Recent European Centre for Disease Control and Prevention (ECDC) guidance specifically defined "high-risk patients" for CRE carriage as those (1) with a history of overnight stay in a healthcare setting in the last 12 months, (2) who are dialysis-dependent or received cancer chemotherapy in the last 12 months, (3) have known previous colonization of CRE in the last 12 months, and/or (4) epidemiological linkage to a known colonization of CRE [22]. In the United States, long-term care facility residence and mechanical ventilation have also been highlighted as important risk factors [26]. Similar to our review findings, ECDC suggests that the optimal specimens for microbiological cultures are feces and active infection sites, but rectal swabs appeared to be acceptable due to their correlation with the sensitivity of fecal specimens and the logistical challenges of sampling fecal specimens [22]. They recommend preemptive isolation and contact precautions for these "at-risk" patients on admission [22]. Studies did not assess types of clinical laboratory testing to identify carbapenem resistance or carbapenemases as highlighted in other reviews [27], but such testing would need to be routine in microbiology laboratories to ensure accurate and timely recognition.

Details reported for contact precautions and patient isolation (eg, single room) or cohorting varied across studies in our

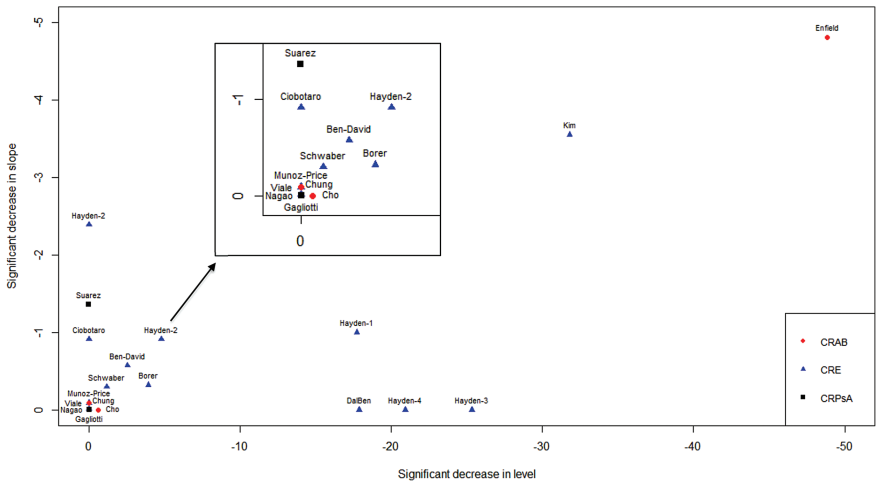

Figure 2. Summary of effective practice and organization of care studies showing significant decrease in slope (ie, trend) or level (ie, immediate change) from pre-intervention to post-intervention periods. Abbreviations: CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRE, carbapenem-resistant Enterobacteriaceae; CRPsA, carbapenem-resistant *Pseudomonas aeruginosa*.

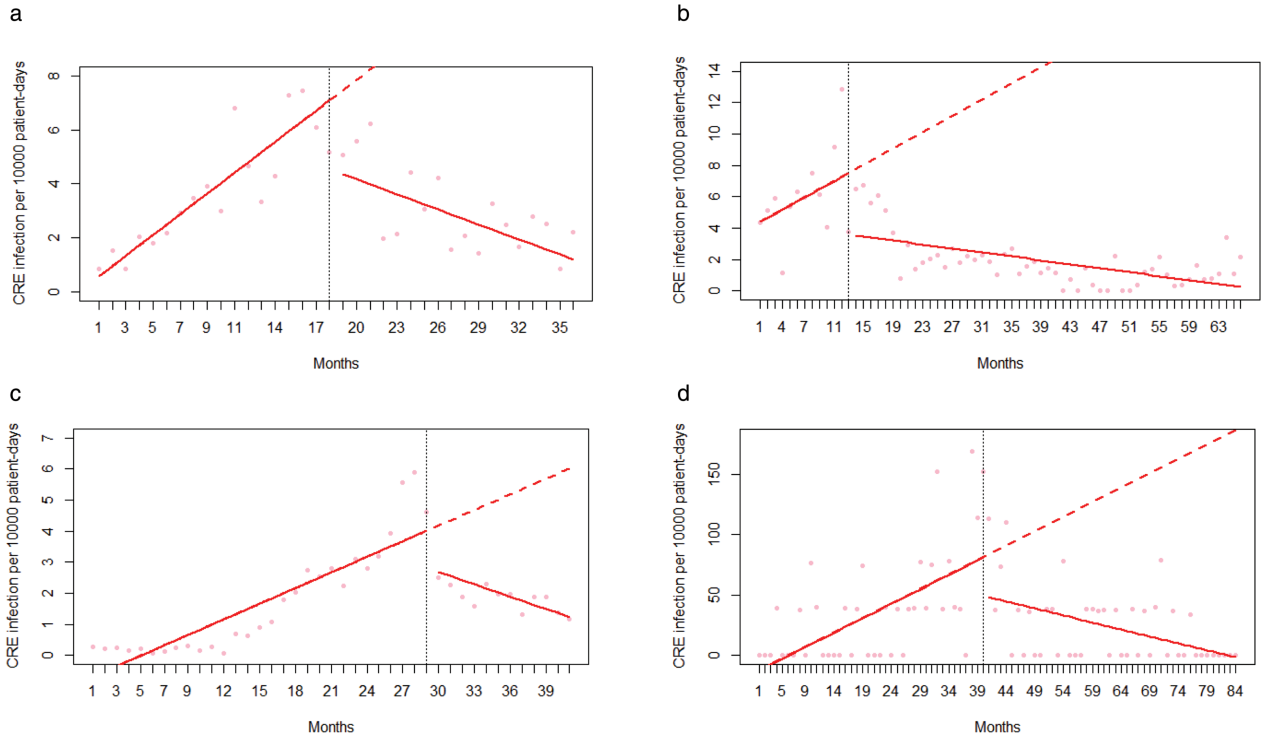

Figure 3. Selected results of high-quality carbapenem-resistant Enterobacteriaceae (CRE) studies with change in both slope (ie, trend) and level (ie, immediate change) from pre-intervention to post-intervention. *A*, Ben-David et al: Intervention included active surveillance using rectal swabs of intensive care unit and step-down unit patients on admission/weekly and contacts; infected patient database to identify readmissions; contact precautions; daily prevalence reporting to management. *B*, Borer et al: Intervention included active surveillance of high-risk patients on admission/weekly; emergency department flagging to identify high-risk patients; contact precautions; cohort ward for positive cases with dedicated staff/equipment; cultures of environment and healthcare worker hands; carbapenem prescribing restriction policy; management reporting. *C*, Schwaber et al: Intervention included isolation measures; single rooms or cohorts including dedicated staff/equipment; re-isolation of known carriers on admission; creation of a task force on antimicrobial resistance and infection control that performed regular site visits; feedback to appointed hospital representatives; mandatory reporting to public health authorities; and distribution of guidelines for active CRE surveillance in acute-care hospitals later in the intervention period. *D*, Kim at al: Intervention included contact precautions; cohorting; hand hygiene enforcement and compliance monitoring; enhanced antimicrobial stewardship. Abbreviation: CRE, carbapenem-resistant Enterobacteriaceae.

review. Definitions reflecting the Centers for Disease Control and Prevention (CDC) Guidelines for Isolation Precautions were commonly noted [28]. Many studies emphasized the need for "enhanced" contact precautions and principles of geographical separation of patients, including isolation or cohorting as essential components of outbreak control. A review by Campos et al on the occurrence of outbreaks caused by carbapenemase-producing *K. pneumoniae* (KPC) found that surveillance cultures and contact precautions were the two most cited interventions, although they did not quantify the effectiveness results of summarized interventions [21]. A recent infection control roadmap for CRE based on expert input highlighted the importance of active surveillance, contact precautions and patient isolation as described in the following steps: (1) determine whether CRE have been isolated, (2) determine affected wards and occurrence of intrafacility transmission, (3) implement early CRE detection and containment measures, (4) enhance existing infection control requirements (ie, education, decontamination, minimize patient transfers and use of invasive devices), (5) develop a regional strategy, and (6) investigate community CRE spread [10].

Interestingly, implementation of hand hygiene best practices was reported in fewer studies. Effective hand hygiene compliance is widely recognized and strongly recommended by WHO to reduce transmission of pathogenic microorganisms in healthcare [29], so it may be assumed as standard of care and not explicitly stated in interventions. The importance of environmental cleaning and environmental surveillance cultures was most often reported in CRAB and CRPsA studies, pathogens that can be more often associated with environmental contamination involving water/waste systems such as sinks and faucets [30].

Various national and regional guidance documents exist for the prevention and control of CRE and carbapenem-resistant Gram-negative bacteria, but they vary in scope and few use a robust evidence-based approach such as ours. One of the most comprehensive guidelines is the 2013 European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Guidelines for the management of infection control measures to reduce transmission of multidrug-resistant (MDR) Gram-negative bacteria, which also used a systematic review and

Table 4. Risk of Bias Assessment of Effective Practice and Organization of Care Studies

Study	Intervention Independent of Other Changes[a]	Shape of Intervention Effect Pre-specified[a]	Intervention Unlikely to Affect Data Collection[a]	Knowledge of Allocated Interventions Prevented [a]	Incomplete Outcome Data Addressed[a]	No Selective Outcome Reporting[a]	No Other Risk of Bias[a]	Risk of Bias[a]
CRE (n = 11)								
Ben-David et al	++	+	++	++	++	+	++	High
Borer et al	++	+	++	++	++	+	++	High
Campbell et al	++	+	++	++	++	++	++	High
Ciobotaro et al	++	+	++	++	++	+	++	High
Gagliotti et al	++	+	++	++	++	+	++	High
Hayden et al	++	+	++	++	++	+	++	High
Kim et al	++	+	++	++	++	+	++	High
Schwaber et al	++	+	++	++	++	++	++	High
Enfield et al	++	+	++	++	++	++	++	High
Viale et al	++	+	++	++	++	+	++	High
DalBen et al	++	+	++	++	++	+	++	High
CRAB (n = 5)								
Chung et al	++	+	++	++	++	+	++	High
Munoz-Priceet al	++	+	++	++	++	++	++	High
Enfield et al	++	+	++	++	++	+	++	High
Cho et al	++	+	++	++	++	+	++	High
DalBen et al	++	+	++	++	++	+	++	High
CRPsA (n = 3)								
Nagao et al	++	+	++	++	++	+	++	High
Suarez et al	++	+	++	++	++	+	++	High
DalBen et al	++	+	++	++	++	+	++	High

The interpretation of these criteria was done according to the "Suggested risk of bias criteria tool for EPOC reviews" for interrupted time series available at: (https://epoc.cochrane.org/sites/epoc.cochrane.org/files/public/uploads/Suggested%20risk%20of%20bias%20criteria%20for%20EPOC%20reviews.pdf.

Abbreviations: CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRE, carbapenem-resistant Enterobacteriaceae; CRPsA, carbapenem-resistant *Pseudomonas aeruginosa*; EPOC, Effective practice and organization of care.

[a]Legend: +: low risk of bias, ++: high risk of bias.

GRADE approach [11]. ESCMID recommendations were specific to endemic or epidemic settings and varied slightly to the findings of our review. In endemic settings, hand hygiene and contact precautions were the only two interventions that were strongly recommended for all three pathogens (MDR-*Klebsiella pneumoniae*, MDR-*P. aeruginosa*, and MDR-*A. baumannii*) in addition to isolation for MDR-*K. pneumoniae* and isolation, alert codes, education, and environmental cleaning for MDR-*A. baumannii*. In epidemic settings, hand hygiene, contact precautions, active screening, isolation and environmental cleaning were strongly recommended for all three pathogens in addition to alert codes and cohorting for MDR-*K. pneumoniae*. In the US CDC CRE toolkit, similar interventions are recommended (ie, hand hygiene, contact precautions, education, minimize use of invasive devices, timely notification, communication, antimicrobial stewardship, environmental cleaning, cohorting, active surveillance, chlorhexidine bathing, and surveillance) [24]; however, the toolkit does not present recommendations according to the results of a systematic review or GRADE approach to determine relative importance of interventions according to current evidence for a direct comparison with this study.

This review has several limitations to consider. Potential publication bias of studies found in the systematic literature review could have influenced the results (ie, over- or under-estimate of intervention effects) and it was difficult to assess the potential for publication bias (eg, funnel plot) given the heterogeneity in studies. Most studies assessed multimodal IPC strategies, making it difficult to elucidate the effectiveness of single interventions and leading to inherent heterogeneity and indirectness. This prevents an adequate quantitative synthesis of results and contributes to lower study quality ratings, a challenge which has been acknowledged in other complex intervention reviews [31]. However, we believe the results including the frequency to which strategies included a respective component, the fact that most studies reported a significant reduction in slope and/or level, and the magnitude of these reductions can be used to inform practice. We focused this review on pathogen-specific results for CRE-CRAB-CRPsA given their high burden and impact [12]. However, additional consideration may be needed to the role of pathogen-specific differences in epidemiology and transmission dynamics. We were unable to stratify results according to endemic or epidemic settings because the classification appeared to be locally subjective. ESCMID MDR recommendations define endemic as "settings where there are constant challenges from admissions of patients colonized or infected with MDR-GNB" and epidemic as "settings where there is an unusual or unexpected increase of cases of infections due

to MDR-GNB already isolated in the hospital or an emergence of cases of infection due to a new MDR-GNB, with or without molecular analysis of strains" [11]. The results of this analysis should be considered in the context of the local epidemiological setting, resource implications, acceptability, values, and preferences which are described in detail in the WHO Guidelines for the prevention and control of CRE-CRAB-CRPsA in health care facilities [12]. Most studies were conducted at acute care hospitals in high-income settings so there may be other concerns regarding cost implications and prioritization in low-resource settings or other facilities such as long-term care. Lastly, we conducted secondary ITS reanalyses of previously conducted studies. Although we did a robust study quality assessment, we did not conduct the original studies so were unable to fully assess methods that may have affected the statistical certainty of the analyses.

To assess complex IPC interventions, particularly in settings of outbreaks or emerging pathogens, it is often not possible to conduct a randomized controlled trial. Quasi-experimental studies can be more feasible, but we found that most studies were incorrectly analyzed as simple before-after studies subject to bias. Robust quasi-experimental designs such as ITS, which are increasingly being used for evaluation of healthcare quality improvement, should be considered early and reported transparently [18, 32]. Reporting standards should be used to improve the quality of hospital epidemiology/research so that it is robust enough to influence policy and practice. The ORION (Outbreak Reports of Intervention Studies of Nosocomial infection) statement provides a useful checklist of key standards relevant to CRE-CRAB-CRPsA outbreaks [33].

Our comprehensive, methodologically rigorous systematic review and re-analysis of quasi-experimental studies describes the current evidence on measures to prevent and control CRE-CRAB-CRPsA transmission, and provides the basis for international recommendations to prevent and control this healthcare threat [12]. Multimodal IPC strategies with specific components are critical to consider in the context of local epidemiology and resources.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgments. We especially thank the collaborating authors who provided their raw data for the reanalysis and contributed to the evidence base for the World Health Organization (WHO) Guideline development process: Debby Ben David, Abraham Borer, Eileen Campbell, Mirian de Freitas Dalben, Kyle B. Enfield, Carlo Gagliotti, Maddalena Giannella, Mary Hayden, Hong Bin Kim, Nak-Hyun Kim, Russel Edward Lewis, Maria Luisa Moro, Miki Nagao, Catherine Passaretti, Monica Schmidt, Mitchell J Schwaber, Anna Sara Shaferman Levin, Costi D. Sifri, Pierluigi Viale. Additionally, we thank Lukas Buetikofer for his statistical review as well as Thomas Allen, the WHO librarian, for his assistance with the development of the systematic review search strategy.

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Financial support. This work was supported by the WHO.

Potential conflicts of interest. S. H. reports personal fees from Takeda, personal fees from Bayer, personal fees from Sandoz, personal fees from GlaxoSmithKline, personal fees from DNA Electronics, grants from Pfizer, outside the submitted work. D. P. is supported by the Swiss National Science Foundation (32003B_163262) for hand hygiene research activities and by Fundação para a Ciência e Tecnologia (SFRH/SINT/95317/2013), outside the submitted work. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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