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A Systematic Review and Meta-analyses of the Clinical Epidemiology of Carbapenem-Resistant *Enterobacteriaceae*

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ABSTRACT Carbapenem-resistant *Enterobacteriaceae* (CRE) are major health care-associated pathogens and responsible for hospital outbreaks worldwide. To prevent a further increase in CRE infections and to improve infection prevention strategies, it is important to summarize the current knowledge about CRE infection prevention in hospital settings. This systematic review aimed to identify risk factors for CRE acquisition among hospitalized patients. In addition, we summarized the environmental sources/reservoirs and the most successful infection prevention strategies related to CRE. A total of 3,983 potentially relevant articles were identified and screened. Finally, we included 162 studies in the systematic review, of which 69 studies regarding risk factors for CRE acquisition were included in the random-effects meta-analysis studies. The meta-analyses regarding risk factors for CRE acquisition showed that the use of medical devices generated the highest pooled estimate (odds ratio [OR] = 5.09; 95% confidence interval [CI] = 3.38 to 7.67), followed by carbapenem use (OR = 4.71; 95% CI = 3.54 to 6.26). To control hospital outbreaks, bundled interventions, including the use of barrier/contact precautions for patients colonized or infected with CRE, are needed. In addition, it is necessary to optimize the therapeutic approach, which is an important message to infectious disease specialists, who need to be actively involved in a timely manner in the treatment of patients with known CRE infections or suspected carriers of CRE.

KEYWORDS *Enterobacteriaceae*, resistance, carbapenem, risk factors, systematic review, meta-analysis

Over the last 2 decades, a global dissemination of carbapenem-resistant *Enterobacteriaceae* (CRE) has been observed (1, 2). Currently, CRE are responsible for hospital outbreaks worldwide. Infections with these resistant bacteria are associated with high rates of morbidity and mortality, especially in patients with serious underlying disorders or patients admitted to the intensive care unit (ICU) (3).

Carbapenem resistance in *Enterobacteriaceae* is mainly mediated by the horizontal transfer of genes encoding carbapenem-hydrolyzing carbapenemase enzymes, although porin mutations or the overexpression of efflux pumps can also lead to carbapenem resistance, especially in combination with the hyperproduction of β-lactamase enzymes (4, 5). The production of carbapenemase enzymes is plasmid mediated and can be found in multiple different species of *Enterobacteriaceae*, such as *Klebsiella pneumoniae* and *Escherichia coli* (1, 5–7). These conjugative plasmids often carry additional genes conferring resistance to other antibiotics, such as fluoroquinolones and aminoglycosides, limiting the treatment options even more (3, 8).

To prevent a further increase in CRE infections in patients by improving infection prevention strategies, it is important to summarize the current knowledge about CRE in hospital settings. This systematic review and meta-analyses aimed to evaluate the clinical epidemiology of CRE by answering the following questions. First, what are the

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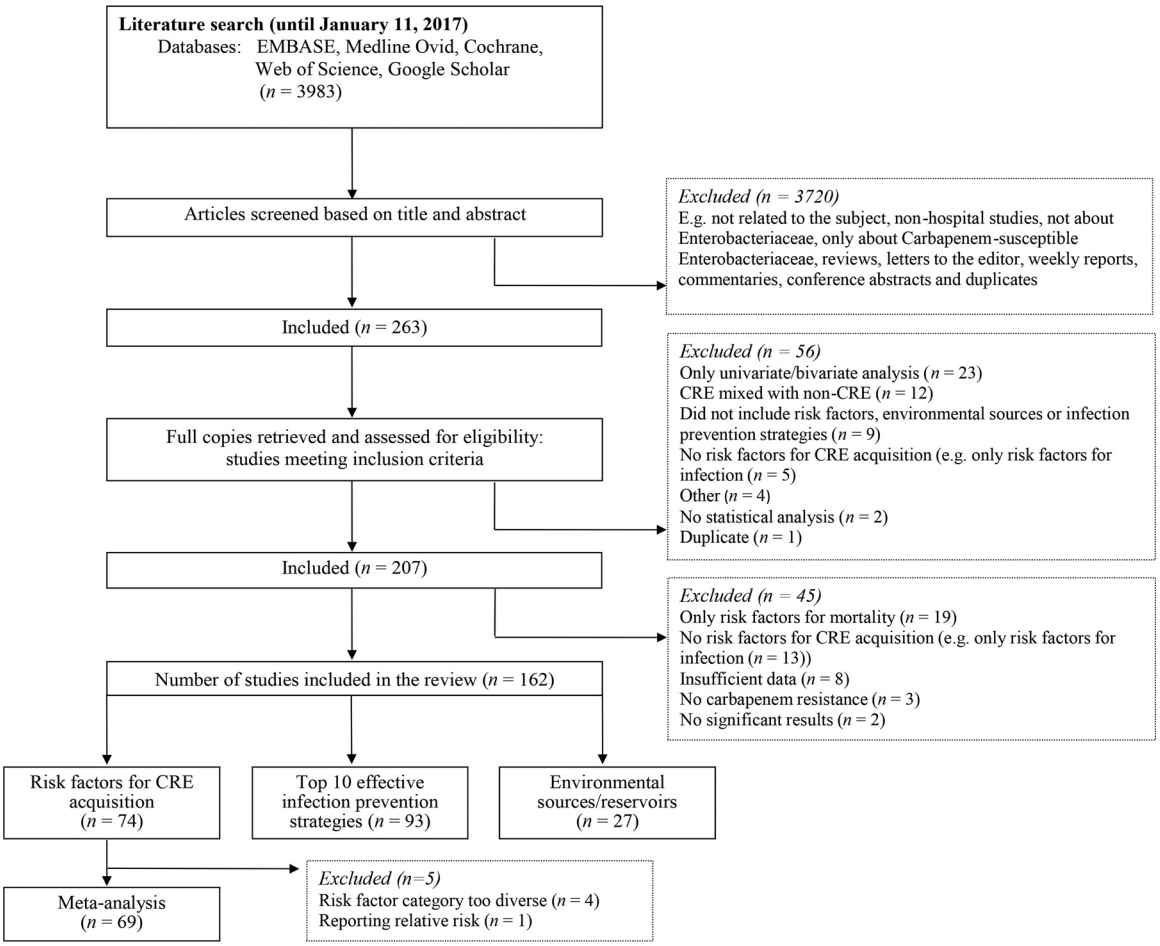

FIG 1 Flow diagram of study selection for the systematic review of studies on carbapenem-resistant *Enterobacteriaceae*.

risk factors associated with CRE acquisition among hospitalized patients? Second, which environmental sources/reservoirs were identified in CRE outbreaks? Third, what were the essential components of effective infection control in preventing or ending hospital outbreaks?

RESULTS

During our literature search we identified 3,983 potentially relevant articles (Fig. 1). All titles and abstracts of the retrieved articles were screened against our inclusion and exclusion criteria, resulting in the exclusion of 3,720 publications. The remaining 263 articles underwent a second screening based on the full text. Seven full-text articles were received by e-mail after we contacted the corresponding authors. Finally, 162 articles were included in the systematic review (Fig. 1). For these studies, the data were extracted and the corresponding author was contacted with a request to check our completed data extraction form. Finally, the corresponding authors of 100 out of 162 articles (61.7%) responded to our request and provided feedback and additional information if necessary.

All included studies were published between 2005 and 2017. Two articles were written in Spanish, one article was written in Chinese, one article was written in Greek, and one article was written in Slovak. All other articles were written in English ($n = 157$, 96.9%). Most studies were conducted in Europe ($n = 62$; 38.3%), mainly in Greece ($n = 14$) and Italy ($n = 11$). A total of 52 studies (32.1%) were conducted in Asia, mainly in Israel ($n = 18$) and China ($n = 16$). The remaining 48 studies were conducted in North America ($n = 31$), South America ($n = 12$), Australia ($n = 3$), and Africa ($n = 2$).

TABLE 1 Summary of studies reporting protective factors for acquisition of CRE, based on multivariable analysis[a]

Authors, yr (reference)	Country	Risk factor	Risk estimate		*P* value	Quality[b]
			OR	95% CI		
Akgul et al., 2016 (31)	Turkey	Nonuse of glycopeptide	0.143	0.031–0.674	<0.05	14
Akgul et al., 2016 (31)	Turkey	Nonuse of steroids	0.244	0.072–0.822	<0.05	14
Akgul et al., 2016 (31)	Turkey	Absence of tracheostomy	0.06	0.006–0.614	<0.05	14
Garbati et al., 2016 (32)	Saudi Arabia	Not being in the ICU	0.027	0.001–0.496	0.015	18
Gasink et al., 2009 (33)	USA	Blood isolate (compared to an isolate from other body sites)	0.33	0.12–0.86	0.02	17
Giuffrè et al., 2013 (34)	Italy	Administration of ampicillin-sulbactam plus gentamicin	0.20	0.03–0.97	0.004	16
Kwak et al., 2005 (19)	South Korea	Use of a fluoroquinolone[c]	0.26	0.07–0.97	0.045	18
Madueño et al., 2017 (35)	Spain	Corticosteroid use	0.33	0.15–0.74	0.007	16
Madueño et al., 2017 (35)	Spain	Antibiotic use	0.20	0.65–0.62	0.01	16
Mittal et al., 2016 (20)	India	Use of aminoglycosides	0.257	0.068–0.975	0.046	13
Mittal et al., 2016 (20)	India	Use of a ventilator[c]	0.291	0.097–0.871	0.027	13
Schwartz-Neiderman et al., 2016 (21)	Israel	Use of cephalosporins[c]	0.2	0.1–0.6	0.005	18
Torres-Gonzalez et al., 2015 (22)	Mexico	Admission to the ICU[c]	0.42	0.20–0.88	<0.05	19

[a]Abbreviations: CRE, carbapenem-resistant *Enterobacteriaceae*; OR, odds radio; CI, confidence interval; ICU, intensive care unit.
[b]According to the STROBE quality assessment scale (30).
[c]Risk factor included in a random-effects meta-analysis study.

Thirty-seven (22.8%) out of the 162 studies used a study design involving only the ICU. The majority of studies focused on a single species of the *Enterobacteriaceae* family: a *Klebsiella* sp. ($n = 103$; 63.6%), an *Enterobacter* sp. ($n = 5$), *E. coli* ($n = 4$), *Citrobacter freundii* ($n = 3$), and *Providencia stuartii* ($n = 2$). The remaining 45 studies (27.8%) involved multiple *Enterobacteriaceae* species.

Carbapenemase production was described by 124 studies (76.5%), and these mainly involved KPC ($n = 91$), NDM ($n = 24$), and OXA ($n = 22$) carbapenemases. Nine studies (5.6%) mentioned the production of β-lactamase enzymes in combination with porin mutations. In addition, one study detected only porin mutations and two studies detected only β-lactamase production in their carbapenem-resistant *Enterobacteriaceae* isolates. Thirty-two studies (19.8%) did not mention or investigate the carbapenem resistance mechanism involved.

Factors associated with CRE acquisition. We identified 74 studies describing factors associated with CRE acquisition with a statistically significant odds ratio (OR) or hazard ratio (HR) obtained from a multivariable analysis. All reported protective factors for CRE acquisition are summarized in Table 1. All reported risk factors were divided into two groups: factors related to antibiotic exposure and other. In addition, five studies reported risk factors associated with mortality among CRE carriers, including nine risk factors and four protective factors (9–13). The highest odds ratio was reported for the risk factor ICU stay (OR = 11.10, 95% confidence interval [CI] = 1.85 to 66.95) (12).

Risk factors related to antibiotic exposure. All factors related to antibiotic exposure were further divided into nine smaller categories (Table 2). Carbapenem exposure ($n = 26$) and cephalosporin exposure ($n = 15$) were the most frequently mentioned risk factors associated with CRE acquisition.

For five out of the nine categories, a random-effects meta-analysis was performed (Table 3 and Fig. 2). For the risk factor carbapenem exposure, one study was excluded because it reported a hazard ratio instead of an odds ratio. The five meta-analyses included 43 studies reporting 63 risk factors (OR > 1) and 2 protective factors (OR < 1). Carbapenem use (OR = 4.71, 95% CI = 3.54 to 6.26) and cephalosporin use (OR = 4.49, 95% CI = 2.42 to 8.33) generated the highest pooled ORs. Both publication bias indicators showed a significant result for the risk factors carbapenem use, cephalosporin use, and glycopeptide use.

In total, 26 additional meta-analyses were performed to assess the effect of the *Enterobacteriaceae* species studied, ICU study setting, the carbapenem resistance mechanism involved, and the study quality on the overall risk estimates (see File S4 in the

TABLE 2 Antibiotic exposure as a risk factor for acquisition of CRE, based on multivariable analysis[c]

Associated risk factor	Frequency	RE	RE range	No. of cases (range)	Study reference(s)
Carbapenem use	25	OR	1.83–29.17	9–100	12, 13, 16, 19, 22, 32, 36–48,[d] 49–53
Carbapenem use	1	HR	2.68	19	22
Cephalosporin use	15	OR	2.24–49.56	15–100	11, 12, 13, 19, 33, 38, 46, 48,[d] 52, 54–57, 58
Quinolone use	9	OR	1.18–28.9	18–88	33, 36, 43, 52, 59–63
Antibiotic exposure (in general)[a,b]	9	OR	1.66–13.37	26–464	41, 43, 61, 64–69
Other β-lactam use	9	OR	1.08–11.71	34–464	49, 52, 57, 60, 65, 70–73
Other[a]	7	OR	1.02–33	25–103	44, 47, 52, 58, 72, 74, 75
Glycopeptide use	5	OR	2.94–43.84	20–203	11, 16, 47, 73, 76
No. of antibiotics administered[a,b]	3	OR	1.6–12.60	59–164	39, 50, 77
Duration of exposure[a,b]	3	OR	1.04–9.8	25–104	74, 78, 79

[a] This category was not included in a random-effects meta-analysis.
[b] Exposure to any antibiotic.
[c] Abbreviations: CRE, carbapenem-resistant *Enterobacteriaceae*; RE, risk estimate; OR, odds ratio; HR, hazard ratio.
[d] This risk factor was identified two times in the study of Orsi et al. (48).

supplemental material). In the additional meta-analyses, all risk factors remained significantly associated with CRE acquisition (pooled OR $>$ 1).

Other risk factors for CRE acquisition. Other risk factors associated with the acquisition of carbapenem-resistant *Enterobacteriaceae* were divided into nine categories and are summarized in Table 4. The risk factor underlying disease or condition (n = 32 times identified) was the most frequently found. For eight out of nine categories, a meta-analysis including 59 studies was performed (Table 3 and Fig. 3). In the categories underlying disease or condition and CRE exposure, one study was excluded because it reported a hazard ratio instead of an odds ratio. In the categories exposure to hospital care and mechanical ventilation, one study was excluded because it reported relative risk instead of an odds ratio.

From the eight different random-effects meta-analyses, the highest pooled OR was found for medical devices (OR = 5.09, 95% CI = 3.38 to 7.67), followed by invasive procedures (OR = 4.67, 95% CI = 3.59 to 6.07) and ICU admission (OR = 4.62, 95% CI = 2.46 to 8.69). Both publication bias indicators showed a significant result for all risk factors, except underlying disease or condition and CRE exposure.

The effects of the different variables (e.g., the CRE species studied, ICU study setting, and the mechanisms of carbapenem resistance) were reviewed by performing 47 additional meta-analyses. Surprisingly, all risk factors showed a decreased (or equal) pooled OR when only studies in which carbapenemase production was shown were included, with the OR difference ranging from 0 to −1.29 (File S5, Fig. SC). The

TABLE 3 Random-effects meta-analyses of antibiotic exposure and other risk factors and/or protective factors for acquisition of CRE[a]

Associated risk factor	No. of times identified	Pooled OR (95% CI)	*P* value for risk of publication bias by use of the indicator of:	
			Egger et al. (28)	Begg and Mazumdar (29)
Antibiotic exposure				
Carbapenem use	25	4.71 (3.54–6.26)	<0.05	<0.05
Cephalosporin use	16	4.49 (2.42–8.33)	<0.05	<0.05
Quinolone use	10	2.46 (1.44–4.23)	<0.05	0.29
Other β-lactam use	9	2.00 (1.49–2.70)	<0.05	0.26
Glycopeptide use	5	4.18 (2.30–7.60)	<0.05	<0.05
Other risk factors				
Underlying disease or condition	31	2.54 (2.08–3.09)	<0.05	0.12
Invasive procedures	20	4.67 (3.59–6.07)	<0.05	<0.05
Medical devices	17	5.09 (3.38–7.67)	<0.05	<0.05
ICU admission	15	4.62 (2.46–8.69)	<0.05	<0.05
Patient demographic characteristics	13	1.08 (1.03–1.14)	<0.05	<0.05
Exposure to hospital care	12	1.05 (1.02–1.08)	<0.05	<0.05
Mechanical ventilation	11	1.96 (1.42–2.69)	<0.05	<0.05
CRE exposure	5	4.10 (1.46–11.52)	<0.05	0.23

[a] Abbreviations: CRE, carbapenem-resistant *Enterobacteriaceae*; OR, odds radio; CI, confidence interval; ICU, intensive care unit.

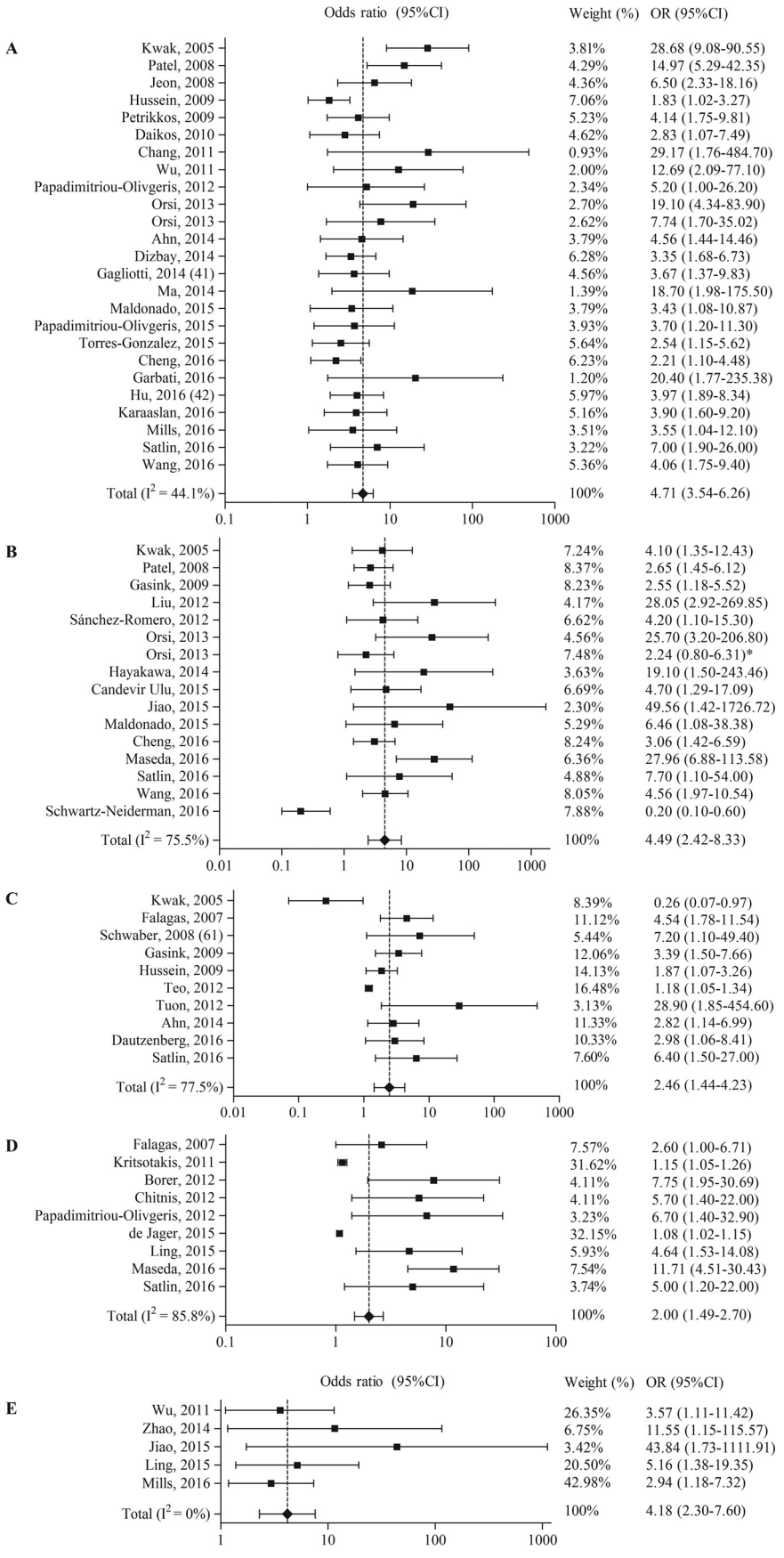
Odds ratio (95%CI)
Weight (%)
OR (95%CI)
A
Kwak, 2005 3.81% 28.68 (9.08-90.55)
Patel, 2008 4.29% 14.97 (5.29-42.35)
Jeon, 2008 4.36% 6.50 (2.33-18.16)
Hussein, 2009 7.06% 1.83 (1.02-3.27)
Petrikkos, 2009 5.23% 4.14 (1.75-9.81)
Daikos, 2010 4.62% 2.83 (1.07-7.49)
Chang, 2011 0.93% 29.17 (1.76-484.70)
Wu, 2011 2.00% 12.69 (2.09-77.10)
Papadimitriou-Olivgeris, 2012 2.34% 5.20 (1.00-26.20)
Orsi, 2013 2.70% 19.10 (4.34-83.90)
Orsi, 2013 2.62% 7.74 (1.70-35.02)
Ahn, 2014 3.79% 4.56 (1.44-14.46)
Dizbay, 2014 6.28% 3.35 (1.68-6.73)
Gagliotti, 2014 (41) 4.56% 3.67 (1.37-9.83)
Ma, 2014 1.39% 18.70 (1.98-175.50)
Maldonado, 2015 3.79% 3.43 (1.08-10.87)
Papadimitriou-Olivgeris, 2015 3.93% 3.70 (1.20-11.30)
Torres-Gonzalez, 2015 5.64% 2.54 (1.15-5.62)
Cheng, 2016 6.23% 2.21 (1.10-4.48)
Garbati, 2016 1.20% 20.40 (1.77-235.38)
Hu, 2016 (42) 5.97% 3.97 (1.89-8.34)
Karaaslan, 2016 5.16% 3.90 (1.60-9.20)
Mills, 2016 3.51% 3.55 (1.04-12.10)
Satlin, 2016 3.22% 7.00 (1.90-26.00)
Wang, 2016 5.36% 4.06 (1.75-9.40)
Total (I^2 = 44.1%) 100% 4.71 (3.54-6.26)
0.1 1 10 100 1000
B
Kwak, 2005 7.24% 4.10 (1.35-12.43)
Patel, 2008 8.37% 2.65 (1.45-6.12)
Gasink, 2009 8.23% 2.55 (1.18-5.52)
Liu, 2012 4.17% 28.05 (2.92-269.85)
Sánchez-Romero, 2012 6.62% 4.20 (1.10-15.30)
Orsi, 2013 4.56% 25.70 (3.20-206.80)
Orsi, 2013 7.48% 2.24 (0.80-6.31)*
Hayakawa, 2014 3.63% 19.10 (1.50-243.46)
Candevir Ulu, 2015 6.69% 4.70 (1.29-17.09)
Jiao, 2015 2.30% 49.56 (1.42-1726.72)
Maldonado, 2015 5.29% 6.46 (1.08-38.38)
Cheng, 2016 8.24% 3.06 (1.42-6.59)
Maseda, 2016 6.36% 27.96 (6.88-113.58)
Satlin, 2016 4.88% 7.70 (1.10-54.00)
Wang, 2016 8.05% 4.56 (1.97-10.54)
Schwartz-Neiderman, 2016 7.88% 0.20 (0.10-0.60)
Total (I^2 = 75.5%) 100% 4.49 (2.42-8.33)
0.01 0.1 1 10 100 1000
C
Kwak, 2005 8.39% 0.26 (0.07-0.97)
Falagas, 2007 11.12% 4.54 (1.78-11.54)
Schwaber, 2008 (61) 5.44% 7.20 (1.10-49.40)
Gasink, 2009 12.06% 3.39 (1.50-7.66)
Hussein, 2009 14.13% 1.87 (1.07-3.26)
Teo, 2012 16.48% 1.18 (1.05-1.34)
Tuon, 2012 3.13% 28.90 (1.85-454.60)
Ahn, 2014 11.33% 2.82 (1.14-6.99)
Dautzenberg, 2016 10.33% 2.98 (1.06-8.41)
Satlin, 2016 7.60% 6.40 (1.50-27.00)
Total (I^2 = 77.5%) 100% 2.46 (1.44-4.23)
0.01 0.1 1 10 100 1000
D
Falagas, 2007 7.57% 2.60 (1.00-6.71)
Kritsotakis, 2011 31.62% 1.15 (1.05-1.26)
Borer, 2012 4.11% 7.75 (1.95-30.69)
Chitnis, 2012 4.11% 5.70 (1.40-22.00)
Papadimitriou-Olivgeris, 2012 3.23% 6.70 (1.40-32.90)
de Jager, 2015 32.15% 1.08 (1.02-1.15)
Ling, 2015 5.93% 4.64 (1.53-14.08)
Maseda, 2016 7.54% 11.71 (4.51-30.43)
Satlin, 2016 3.74% 5.00 (1.20-22.00)
Total (I^2 = 85.8%) 100% 2.00 (1.49-2.70)
0.1 1 10 100
Odds ratio (95%CI)
Weight (%)
OR (95%CI)
E
Wu, 2011 26.35% 3.57 (1.11-11.42)
Zhao, 2014 6.75% 11.55 (1.15-115.57)
Jiao, 2015 3.42% 43.84 (1.73-1111.91)
Ling, 2015 20.50% 5.16 (1.38-19.35)
Mills, 2016 42.98% 2.94 (1.18-7.32)
Total (I^2 = 0%) 100% 4.18 (2.30-7.60)
1 10 100 1000

TABLE 4 Other risk factors associated with acquisition of CRE, based on multivariable analysis[c]

Associated risk factor	Frequency	RE type	RE range	No. of cases (range)	Study reference(s) (no. of different risk factors per reference)
Underlying disease or condition	31	OR	1.07–98.58	17–133	22, 33, 37 (2), 45, 48, 49, 50 (2), 52 (2), 56, 61 67, 68 (2), 70, 71, 79, 80 (2), 81, 82 (6), 83 (3)
	1	HR	5.74	19	22
Other[a]	19	OR	1.35–45.904	20–464	22 (2), 38, 40, 47, 50, 56, 64, 65 (2), 67 (2), 76, 82, 84, 85 (2), 86, 87
	1	RR	5.94	149	88
	1	HR	19.0	26	85
Invasive procedures	20	OR	2.18–35.98	15–99	9, 12, 22, 32, 44, 47, 48 (2), 55, 57 (2), 67, 76, 81, 83, 85, 89–92
Medical devices[b]	17	OR	1.67–677.82	15–203	9, 11, 38, 45 (2), 54, 58, 62, 73, 77, 80, 84, 89 (2), 91, 93, 94
ICU admission	14	OR	1.13–17.4	25–88	16, 39, 40, 43, 49–52, 54, 61, 78, 81, 87, 95
Patient demographic characteristics	13	OR	1.03–10.53	10–164	34, 38, 45, 59 (2), 63, 69, 77, 84, 90, 91 (2), 96
Exposure to hospital care	12	OR	1.014–58.067	15–99	12, 32, 35 (2), 44, 49, 59, 62, 66, 76, 89, 92
	1	RR	1.36	149	88
Mechanical ventilation	10	OR	1.2–17.80	18–164	12, 21, 47, 58, 63, 70, 71, 77, 79, 89
	1	RR	1.99	149	88
CRE exposure	5	OR	1.15–11.9	53–165	21, 22, 77 (2), 79
	1	HR	5.03	19	22

[a]This category was not included in a random-effects meta-analysis.
[b]Mechanical ventilation is excluded from this category.
[c]Abbreviations: CRE, carbapenem-resistant *Enterobacteriaceae*; RE, risk estimate; OR, odds ratio; HR, hazard ratio; RR, relative risk; ICU, intensive care unit.

meta-analyses of the remaining studies that described another resistance mechanism (e.g., porin mutations) or that did not investigate the resistance mechanism involved showed a large increase in the reported pooled ORs for all tested risk factors, with the mean change being +2.89.

Effective infection prevention strategies. We identified 95 studies describing effective infection prevention strategies used to control the spread of carbapenem-resistant *Enterobacteriaceae* in a hospital setting. These were converted to the top 10 most successful intervention strategies (Table 5). The use of barrier and/or contact precautions was found to be the most successful intervention strategy ($n = 71$), followed by patient cohorting ($n = 68$) and active surveillance ($n = 56$). Control of antibiotic use was mentioned in only 17 studies and could be found in ninth place. Besides these 10 strategies, some other interventions were described in the literature, such as restricted/no admission to the affected wards ($n = 9$) and the use of chlorhexidine for patient disinfection ($n = 9$).

Environmental sources and reservoirs. Twenty-seven studies provided information about the environmental sources and reservoirs identified within their hospitals. All hospital locations in which carbapenem-resistant *Enterobacteriaceae* were identified are summarized in Table 6. Contaminated sinks were the most frequently described ($n = 10$ studies), followed by patient beds ($n = 6$ studies) and mechanical ventilation equipment ($n = 5$ studies).

DISCUSSION

Summary of evidence. In this systematic review, we identified 13 risk factors associated with the presence of carbapenem-resistant *Enterobacteriaceae*. These risk factors were, in order of those with the highest to those with the lowest pooled OR, (i)

FIG 2 Forest plots of random-effects meta-analyses of antibiotic exposure as a risk factor and/or protective factor for the acquisition of carbapenem-resistant *Enterobacteriaceae*. (A) Carbapenem use; (B) cephalosporin use; (C) quinolone use; (D) β-lactam use; (E) glycopeptide use. *, nonsignificant confidence interval (Orsi et al. were contacted multiple times to receive the correct numbers; unfortunately, the authors did not respond).

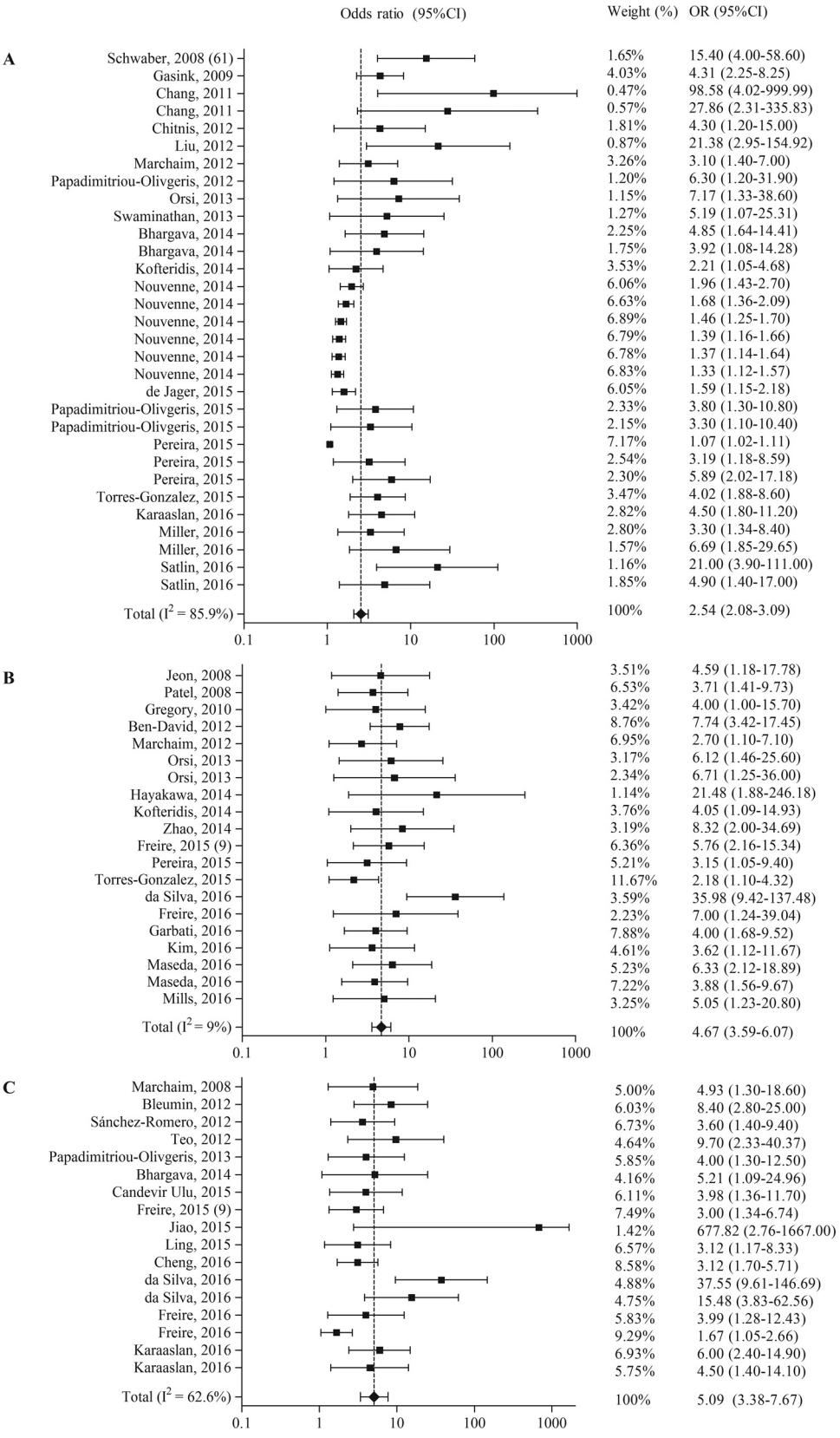

FIG 3 Forest plots of random-effects meta-analyses of other risk factors and/or protective factors for the acquisition of carbapenem-resistant *Enterobacteriaceae*. (A) Underlying disease or condition; (B) invasive procedures; (C) medical devices; (D) ICU admission; (E) demographic patient characteristics; (F) exposure to hospital care; (G) mechanical ventilation; (H) CRE exposure.

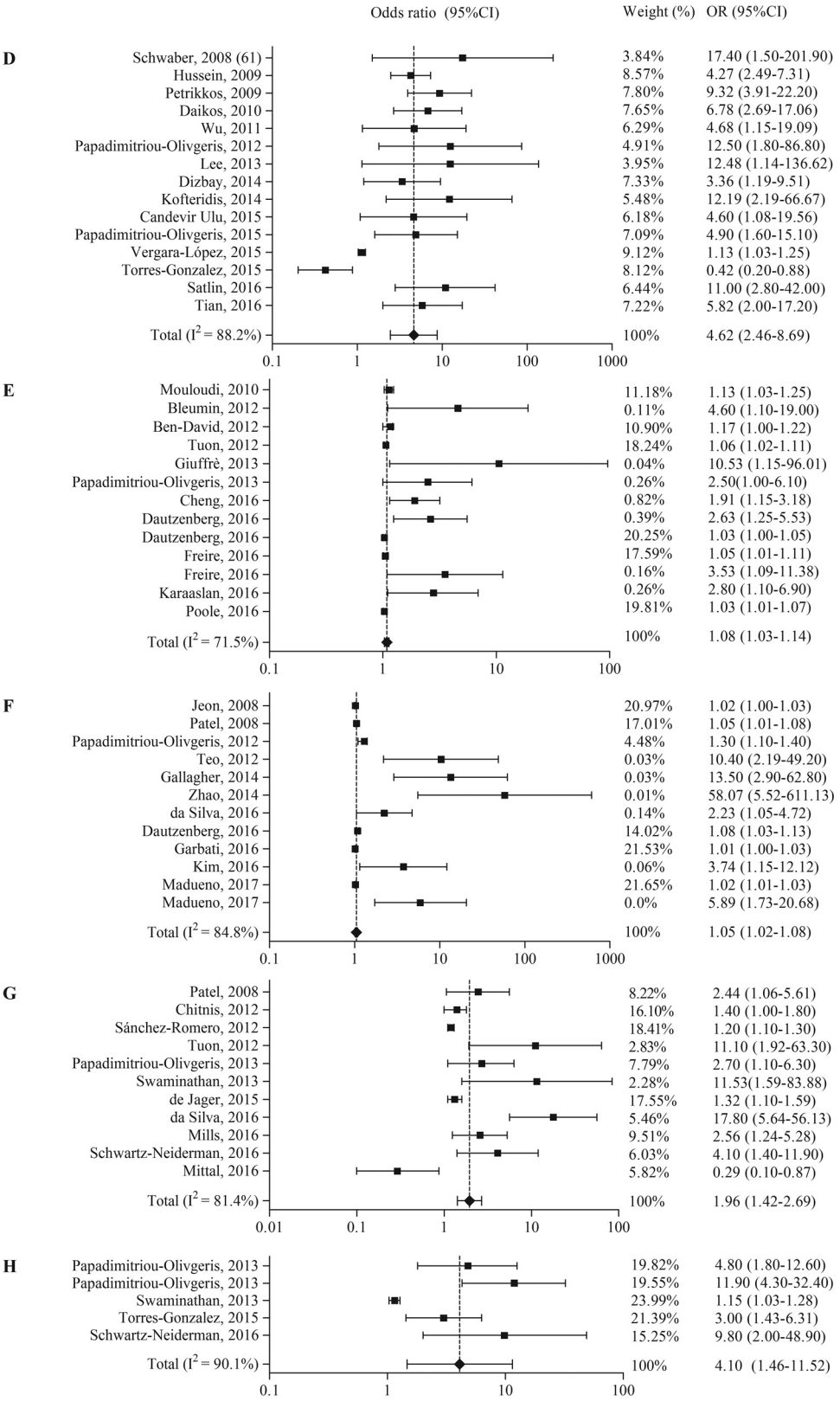

FIG 3 (Continued)

TABLE 5 Top 10 strategies to control hospital outbreaks with CRE[a]

Intervention	No. of studies	Study references
1. Barrier/contact precautions	71	22, 34, 38, 53, 55, 70, 79, 82, 85, 90, 91, 94, 97–155
2. Patient transfer to single room or cohorting	68	22, 34, 38, 53, 70, 82, 85, 90, 91, 94, 97, 98, 102, 103, 105–108, 110–115, 117–122, 124, 126–128, 130–132, 134, 136–141, 143, 146, 148–154, 156–170
3. Active surveillance/screening for CRE	56	53, 70, 75, 79, 82, 97, 100–105, 107, 110–115, 117, 119, 120, 123–126, 128–131, 133, 135–137, 139, 140, 142, 144–146, 148–150, 154, 156–162, 165, 167–169, 171
4. Enhanced hand hygiene	52	22, 34, 38, 53, 70, 85, 91, 94, 97–100, 102, 103, 105, 109, 110, 112, 113, 115–120, 124–129, 131–133, 135, 140, 142, 143, 146, 147, 150, 152, 154, 155, 157, 163, 165, 166, 168, 170, 172, 173
5. Enhanced environmental cleaning	51	22, 34, 38, 70, 71, 97–100, 103, 106, 108, 109, 112, 113, 118–120, 124–126, 129–131, 133–135, 137, 142–147, 149–151, 153, 156, 157, 161, 164–170, 172–174
6. Staff educational programs	34	34, 53, 70, 71, 91, 100, 106, 107, 109–111, 116, 117, 119, 121, 123, 126, 130, 131, 133, 134, 143–146, 148, 151, 157, 161, 164, 167–169, 171
7. Staff cohorting	32	70, 71, 82, 85, 91, 94, 97, 98, 105, 107, 108, 110, 111, 113, 114, 120, 128, 133, 138, 140–143, 145, 149, 155, 157, 159, 162, 165, 167, 168
8. Equipment cohorting/single-use equipment	21	34, 70, 71, 94, 97–99, 108, 111, 112, 121, 128, 130, 131, 135, 138, 142, 153, 156, 157, 168
9. Control of antibiotic use	17	53, 85, 91, 103, 106, 110, 113, 116, 120, 121, 128, 129, 144–146, 172, 175
10. Flagging of CRE patients	14	99, 103, 105, 107, 111, 114, 119, 125, 131, 132, 144, 147, 149, 160

[a]CRE, carbapenem-resistant *Enterobacteriaceae*.

medical devices, (ii) carbapenem use, (iii) invasive procedures, (iv) ICU admission, (v) cephalosporin use, (vi) glycopeptide use, (vii) CRE exposure, (viii) underlying disease or condition, (ix) quinolone use, (x) β-lactam use, (xi) mechanical ventilation, (xii) demographic patient characteristics, and (xiii) exposure to hospital care (Table 3). Medical devices, antibiotic use, ICU admission, exposure to hospital care, and underlying diseases were also identified to be risk factors in systematic reviews regarding the acquisition of extended-spectrum β-lactamase (ESBL)-producing *Klebsiella* spp. (14) and carbapenem-resistant *Pseudomonas aeruginosa* (15).

Plasmids responsible for carbapenem resistance often carry additional genes conferring resistance to other antibiotics, such as fluoroquinolones and aminoglycosides. This can explain why the use of these antibiotic classes is found to be a risk factor for

TABLE 6 Identified environmental sources and reservoirs for CRE[b]

Environmental source or reservoir	Study reference(s)
Sinks	125,[a] 137, 140, 142,[a] 157,[a] 166,[a] 174,[a] 176, 177,[a] 178
Patient bed (e.g., bedrail, mattress)	103, 133,[a] 157,[a] 167,[a] 168,[a] 178
Mechanical ventilation equipment	142,[a] 167[a] 168,[a] 172,[a] 179[a]
Positive cultures from nurses (hands)	103, 151,[a] 152,[a] 157[a]
Endoscope	92, 122, 180[a]
Duodenoscope	105,[a] 181[a]
Urinary catheter	145,[a] 173
Monitor (e.g., vital signs, television)	103, 167[a]
Shower/shower equipment	137, 178
Table	157,[a] 172[a]
Ureteroscope	182[a]
Razor	108[a]
Incubator	151[a]
Radiant warmer	152[a]
Suction equipment	178
Wastewater drainage system	145[a]
Stethoscope	145[a]
Intravenous pole	167[a]
Infusion pump	157[a]
Janet syringe	103
Cabinet	103
Intravenous infusion counter apparatus	103
Enteral feeding formula	103

[a]The study proved the source or reservoir by molecular typing of carbapenem-resistant *Enterobacteriaceae* isolates.
[b]CRE, carbapenem-resistant *Enterobacteriaceae*.

CRE acquisition. However, this explanation cannot be used for glycopeptide antibiotics. Wu et al. (16) and Jiao et al. (11) supposed that vancomycin treatment disrupts the intestinal microflora, promoting the colonization of *Enterobacteriaceae*. Glycopeptide use was also identified to be a risk factor for carbapenem-resistant *P. aeruginosa* (15, 17) and ESBL-producing bacteria (18) acquisition.

On the contrary, 4 out of 13 significant risk factors were also described to be protective against CRE acquisition by other authors: quinolone use (19), mechanical ventilation (20), cephalosporin use (21), and ICU admission (22). Kwak et al. speculated that fluoroquinolone use was found to be a protective factor because this antibiotic was often given as a substitute for carbapenem or cephalosporin antibiotics (19). Torres-Gonzalez et al. reported that ICU admission was protective against CRE acquisition. This observation could be explained by the fact that their CRE outbreak was initially detected in the ICU and a successful bundle of infection prevention measures was initiated in that area (22).

We also performed additional meta-analyses to estimate the influence of the following variables on the overall risk estimate: the *Enterobacteriaceae* species studied, the ICU study setting, the carbapenem resistance mechanism involved, and the study quality. The carbapenem resistance mechanism was found to have the highest influence on the risk estimates, especially in the meta-analyses of non-antibiotic-related risk factors for CRE acquisition (see File S4, Fig. SC, in the supplemental material). We observed that our risk factors showed a lower risk estimate only when studies in which carbapenemase-producing *Enterobacteriaceae* were described were included.

The most successful interventions to stop the spread of CRE were barrier/contact precautions, patient cohorting, and active surveillance. Our findings correspond to the guidelines presented by the Centers for Disease Control and Prevention (CDC), which mainly highlight active surveillance and contact precautions (23, 24). Surprisingly, antimicrobial stewardship was mentioned in only 17 out of 95 studies, although multiple antimicrobial classes were identified to be risk factors for CRE acquisition.

Only 27 out of 95 studies reported environmental sources or reservoirs for CRE within their hospitals (Table 6). This indicates that for many outbreaks the source or reservoir was not determined. Contaminated sinks were the most frequently described and correspond to the reservoirs identified for other nosocomial pathogens, such as carbapenem-resistant *P. aeruginosa* (15) and ESBL-producing *Klebsiella* spp. (14).

Strengths and limitations. A strength of our study was the inclusion of both *Enterobacteriaceae* that showed *in vitro* resistance to any carbapenem antibiotic and *Enterobacteriaceae* that were found to produce carbapenemase enzymes. This is important because carbapenemase production does not always confer high-level carbapenem resistance and therefore leads to false-negative results when only phenotypic tests are used to identify carbapenem-resistant *Enterobacteriaceae* (25). This review included only two studies in which carbapenemase-producing but carbapenem-sensitive and -resistant isolates were studied. However, the mechanism of resistance does influence transmission and, thus, epidemiology, as we showed different risk estimates, especially for the non-antibiotic-related risk factors, when each mechanism was analyzed. With the knowledge that we have up to now, we cannot explain this difference. As we included all kinds of mechanisms, this can also be seen as a limitation of the study.

The study also has some limitations; the first is the large heterogeneity of all studies included. Studies with different target populations, for example, neonates, adults, or transplant patients, were selected. In addition, different microbiological methods were used to identify the CRE isolates, different *Enterobacteriaceae* species were included, and different prevention strategies were installed. To limit the influence of the study heterogeneity, the random-effects model of DerSimonian and Laird (26) was implemented in the meta-analyses, and different subgroup analyses were performed.

Second, we included both studies reporting CRE colonization and studies reporting CRE infections in hospitalized patients. However, not all studies describing risk factors

for CRE infection checked whether the patients were previously colonized with CRE or not. Likewise, they did not check whether patients from the control group were colonized with CRE before or during the infection. For these studies, we cannot rule out the possibility that their reported risk factors are not specific for CRE acquisition but are specific for progression to infection after CRE colonization.

Third, both publication bias indicators showed a significant result for several risk factors (9/13), indicating that publication bias was present. To limit publication bias, the studies that we included were not limited by language, date of publication, country of publication, carbapenem resistance mechanism, study design, or patient characteristics.

Conclusions and implications. This systematic review shows that not only antibiotic use but also many other risk factors are associated with CRE acquisition. The most significant risk estimate found in our meta-analyses was found for the risk factor medical devices, followed by carbapenem use. We identified risk factors related to the emergence/selection of CRE, but also risk factors related to the transmission of the CRE isolates. To prevent or to control hospital outbreaks, bundled interventions are needed. These interventions need to focus on both antibiotic stewardship and reduction of the use of indwelling devices to reduce the spread of CRE within the hospital. Indwelling medical devices do present a very high risk for the acquisition of CRE but are also a risk for the acquisition of infections in general. Therefore, a very useful prevention measure is the active decrease in the rate of use (deimplementation) of medical devices.

MATERIALS AND METHODS

This systematic review and meta-analyses followed the guidelines presented in the PRISMA statement (see File S1 in the supplemental material) (27). Protocol details were submitted to the PROSPERO International Prospective Register of Systematic Reviews (registration number CRD42017055455).

Study selection. Articles related to our research questions were identified through a search of the literature in multiple databases (until 11 January 2017): Embase, Medline Ovid, Cochrane, Web of Science, and Google Scholar (File S2). The search was not limited by language, date of publication, country of publication, carbapenem resistance mechanism, study design, or patient characteristics.

We used the following inclusion criteria during the study selection: (i) studies reporting risk factors for the acquisition of CRE, (ii) studies mentioning environmental sources/reservoirs for CRE, and (iii) studies describing effective infection prevention strategies to halt nosocomial outbreaks. Risk factors for acquisition could include risk factors for infection as well as risk factors for colonization with CRE. *Enterobacteriaceae* were considered resistant to carbapenem antibiotics when this was shown using phenotypic tests and/or when carbapenemase genes could be identified.

We excluded studies related to nonhuman infections, nonhospital studies, conference abstracts, letters to the editor, commentaries, weekly reports, and editorials. Studies were also excluded if patients with CRE infections were compared to patients who were colonized with CRE. First, the titles and abstracts of all retrieved citations were screened independently by K.V.L. and A.F.V. After this screening, K.V.L. and A.F.V. performed a second screening based on the full text.

Data extraction. We designed a data abstraction form, pilot tested it on three randomly selected articles, and redefined it according to the outcomes. The following data were extracted: first author, journal, year published, country, study design, study setting, patient characteristics, the carbapenem-resistant microorganism(s) studied, risk factors for acquisition/mortality, site of colonization/infection, protective factors for acquisition/mortality, potential reservoirs for CRE, and effective infection prevention strategies for CRE. The extracted data were sent to the corresponding author of the original article to verify the extracted data and to gain additional information if relevant. When we did not receive any response after the given deadline (i.e., 2 weeks), a reminder was sent. If no response was received and crucial information was missing, the study was excluded.

Data analysis. (i) Risk factors for CRE acquisition. All risk factors associated with the acquisition of CRE for which an odds ratio (OR) with the 95% confidence interval (CI) was reported were divided into two groups: those related to antibiotic exposure and other. Risk factors that were reported as a hazard ratio or relative risk were not included in a random-effects meta-analysis and were therefore only summarized.

The first category, related to antibiotic exposure, was further divided into the following nine categories: (i) carbapenem use, (ii) cephalosporin use, (iii) quinolone use, (iv) use of other β-lactam antibiotics or β-lactam use in general, (v) glycopeptide use, (vi) antibiotic exposure (in general), (vii) number of antibiotics administered, (viii) duration of exposure, and (ix) other. The second category, other, was also divided into nine categories, as follows: (i) underlying disease or condition, (ii) invasive procedures, (iii) medical devices, (iv) ICU admission, (v) exposure to hospital care, (vi) demographic patient characteristics, (vii) mechanical ventilation, (viii) CRE exposure, and (ix) other.

Studies reporting protective factors for the acquisition of CRE were summarized and included in a meta-analysis if they could be categorized into one of the previously described categories.

(ii) Meta-analysis. The meta-analyses were performed using StatsDirect statistical software (Altrincham, United Kingdom), including the random-effects model of DerSimonian and Laird (26). A *P* value of

<0.05 was considered statistically significant. A meta-analysis was performed only if ≥ 3 studies reported the same risk factor and if the risk factors within the category were not too diverse. Publication bias was examined visually with the use of funnel plots and assessed with the indicators of Egger et al. (28) and Begg and Mazumdar (29). When both indications showed a significant result, it was assumed that publication bias was present.

Eight additional meta-analyses were performed for each risk factor category: 1a, studies including only *K. pneumoniae* isolates; 1b, other studies; 2a, studies with an ICU setting; 2b, studies with a different study setting; 3a, studies describing only carbapenemase production as the carbapenem resistance mechanism; 3b, studies describing another resistance mechanism or not investigating the resistance mechanism involved; 4a, studies with a moderate/high study quality; and 4b, studies with a low study quality.

(iii) Infection prevention strategies and environmental sources/reservoirs. All effective infection prevention strategies mentioned in the included articles were categorized, and a top 10 was created on the basis of the number of studies that reported these infection prevention strategies. In addition, studies describing sources and/or reservoirs for CRE in a hospital setting were reviewed and summarized.

Study quality. A quality assessment was performed for all studies included in a meta-analysis using the strengthening the reporting of observational studies in epidemiology (STROBE) guideline (File S3) (30). Studies with a score of ≤ 15 points were considered to be of relatively low methodological quality, studies receiving a quality score of 16, 17, or 18 points were rated to be of moderate quality, and studies with a score of ≥ 19 points were considered to have a relatively high study quality. Study quality was not considered an exclusion criterion.

SUPPLEMENTAL MATERIAL

Supplemental material for this article may be found at https://doi.org/10.1128/AAC.01730-17.

SUPPLEMENTAL FILE 1, PDF file, 0.6 MB.

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M.C.V. and A.F.V. designed the study. A.F.V. and K.V.L. conducted the literature search and selected the studies. K.V.L. performed the data extraction. M.C.V., K.V.L., and A.F.V. performed the data interpretation and analysis. K.V.L., M.C.V., and A.F.V. wrote the manuscript.

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