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Review

The global prevalence of multidrug-resistance among *Acinetobacter baumannii* causing hospital-acquired and ventilator-associated pneumonia and its associated mortality: A systematic review and meta-analysis

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SUMMARY

Objective: The objective of this works was to assess the global prevalence of multidrug-resistance among *A. baumannii* causing hospital-acquired (HAP) and ventilator-associated pneumonia (VAP), and describe its associated mortality.
Methods: We performed a systematic search of four databases for relevant studies. Meta-analysis was done based on United Nations geoscheme regions, individual countries and study period. We used a random-effects model to calculate pooled prevalence and mortality estimates with 95% confidence intervals (CIs), weighted by study size.
Results: Among 6445 reports screened, we identified 126 relevant studies, comprising data from 29 countries. The overall prevalence of multidrug-resistance among *A. baumannii* causing HAP and VAP pooled from 114 studies was 79.9% (95% CI 73.9–85.4%). Central America (100%) and Latin America and the Caribbean (100%) had the highest prevalence, whereas Eastern Asia had the lowest (64.6%; 95% CI, 50.2–77.6%). The overall mortality estimate pooled from 27 studies was 42.6% (95% CI, 37.2–48.1%).
Conclusions: We observed large amounts of variation in the prevalence of multidrug-resistance among *A. baumannii* causing HAP and VAP and its mortality rate among regions and lack of data from many countries. Data from this review can be used in the development of customized strategies for infection control and antimicrobial stewardship.

Introduction

Hospital-acquired pneumonia (HAP) is a lung infection that develops after more than 48 h of hospitalization, and, if associated with mechanical ventilation, it is termed ventilator-associated pneumonia (VAP).[1] They are the second most common nosocomial infections and are important causes of morbidity and mortality around the world.[2,3] These nosocomial pneumonias increase duration of hospitalization and healthcare costs. A matched case-control study demonstrated that having VAP prolonged duration of mechanical ventilation, intensive care unit (ICU) stay and hospitalization.[4] Mortality rate and hospital costs are two and three times higher respectively, in patients with VAP compared to the non-infected ones.[5,6] A higher mortality rate is seen in cases caused by Gram-negative infections such as *Pseudomonas aeruginosa* and *Acinetobacter spp*.[7,8]

Acinetobacter baumannii is intrinsically highly resistant to many antibiotics, enabling it to emerge as an important cause of nosocomial infections.[9] From being an organism initially regarded as having low-grade pathogenicity, it has now become one of the important nosocomial pathogens, particularly in the ICU.[10,11] Prevalence of multidrug-resistant *A. baumannii* (MDRAB) in patients with nosocomial pneumonia has been reported to range between

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40 and 95%,[12–14] and its associated mortality has been reported to range between 45 and 85%.[15,16]

Although numerous studies have reported the prevalence and clinical epidemiology of MDRAB HAP or VAP,[17–19] these studies were limited by geographical location. Comprehensive data on the global prevalence and clinical epidemiology of MDRAB in patients with HAP and VAP are lacking. A systematic search and analysis on research looking at the epidemiology of MDRAB in HAP and VAP would allow us to understand the extent of the problem, which, in turn, would allow for better planning of research and use of resources. This systematic review aimed to provide a global picture of the prevalence of multidrug-resistance among *A. baumannii* causing HAP and VAP and its mortality rate.

Methodology

The protocol for this systematic review was registered on PROSPERO (CRD42019120178). The whole process followed the PRISMA guideline.[20] The outcomes of interest were the proportions of multidrug-resistance among *A. baumannii* causing HAP and VAP and mortality rate associated with MDRAB HAP and VAP.

Literature search

We searched four databases (PubMed, Cochrane, Web of Science, and Embase) systematically for relevant studies, from inception until December 2018. No language restriction was applied. The detailed search strategy was developed in consultation with a research librarian and is listed in Appendix 1. The reference lists of all selected articles were also searched for other potentially relevant studies.

Study selection

Two independent reviewers (SMSL and AZA) performed the study selection based on the predefined inclusion and exclusion criteria. The reviewers independently screened all titles and abstracts of the articles to identify potentially eligible studies. The full texts of these potentially eligible studies were then evaluated to determine eligibility for inclusion into the review. Any discrepancies and inconsistencies were discussed and sorted out by consensus. If unable to come to a consensus, a third reviewer was consulted.

The studies were included if they: (1) Included patients with HAP and VAP infected by *A. baumannii* or MDRAB, and (2) MDRAB is defined as *A. baumannii* strains that are non-susceptible to at least one agent in ≥ 3 antimicrobial categories.[21] The studies were excluded if they: (1) were conference abstracts, case reports, meta-analyses or reviews on the topic; (2) reported data from animals or environmental studies; (3) reported on the prevalence of MDRAB colonization; (4) reported on *Acinetobacter spp*. and not *A. baumannii* specifically; (5) had insufficient information to calculate prevalence of multidrug-resistance among *A. baumannii* causing HAP and VAP or its mortality rate; (6) focused only on specific sub-groups that were not reflective of the general population (e.g., migrants, prisoners, refugees); and (7) did not document the origin of the samples; meaning that the reviewers could not determine which country or population (i.e., inpatients, personnel or outpatients) the specimens were gathered from.

Data extraction

Two reviewers (SMSL and AZA) independently extracted data from each included article using a standardized data extraction form.

Quality appraisal

The studies that met the inclusion criteria were rated for methodological quality by two members (SMSL and AZA), independently. Quality assessment of the selected studies was done according to the Newcastle-Ottawa Scale for assessing the quality of nonrandomized studies in meta-analyses.[22] For this review, each study was assessed on how the study cohort was derived, i.e. the representativeness of the study cohort.[23] The quality appraisal of each included study was reported, but no exclusion was done based on the findings of the appraisal, to include all potentially valuable insights.[24]

Data analysis

The statistical analyses were carried out with MedCalc for Windows, version 18.11.3 (MedCalc Software, Ostend, Belgium) and Comprehensive Meta-Analysis (Version 3; Borenstein, M., Hedges, L., Higgins, J., & Rothstein, H.; Biostat, Englewood, NJ 2013). The formulae used to calculate the prevalence of MDRAB isolates in HAP or VAP and associated mortality rate are listed in Appendix 2.

Considering the probable heterogeneity across observational studies, a random-effects model was applied to calculate pooled estimates with 95% confidence intervals (CIs) using the DerSimonian–Laird method.[25,26] Studies were assessed for heterogeneity using I^2 statistic and Cochran's Q test (taking $p < 0.10$ to indicate statistically significant heterogeneity). We classified heterogeneity as low, moderate, or high by the I^2 statistics value of 25%, 50%, or 75%, respectively.[27] We also used forest plots to depict the pooled estimates. A funnel plot was used to determine the probability of publication bias by visual inspection.

The results of the pooled estimates were organized by United Nations (UN) geoscheme regions and individual countries.[28] Furthermore, the pooled estimates at different time intervals were investigated and compared. When prevalence was reported for a multi-year period that extended over more than one year, the study was included in the period that captured the most updated data. Only studies which reported the year in which the study was done were included in the meta-analysis. To graphically demonstrate the geographic distribution of multidrug-resistance among *A. baumannii* causing HAP and VAP and its mortality, choropleth maps were created using Microsoft Excel (version 16.22) based on the subgroup analyses by country.

Meta-regression analyses using a restricted maximum likelihood (REML) method were done to evaluate the impact of predefined factors on the prevalence of multidrug-resistance among *A. baumannii* causing HAP and VAP and the mortality in MDRAB HAP/VAP.[26] Studies with missing data were excluded from the multivariate meta-regression analyses. The adjusted R^2 was used to evaluate the meta-regression model. The statistical significance of a single coefficient was tested using a Z-test, and $p < 0.05$ was considered statistically significant.

Results

A total of 6445 records were identified from four databases, of which 126 studies were included for analysis (Fig. 1). A majority of the included reports were research articles ($n = 115$), followed by brief reports ($n = 7$) and letter to the editor ($n = 4$).

We found published data from 29 countries, leaving 166 countries (85%) unrepresented (Appendix 3). We did not find any relevant published data from Oceania. Most studies were carried out between the year 2011 and 2015 ($n = 54$, 42.5%), followed by 2006 to 2010 ($n = 34$, 26.8%). The duration of the study ranged from 1 to 15 years. There were variations in the susceptibility testing methods, which included automated methods such as VITEK, and

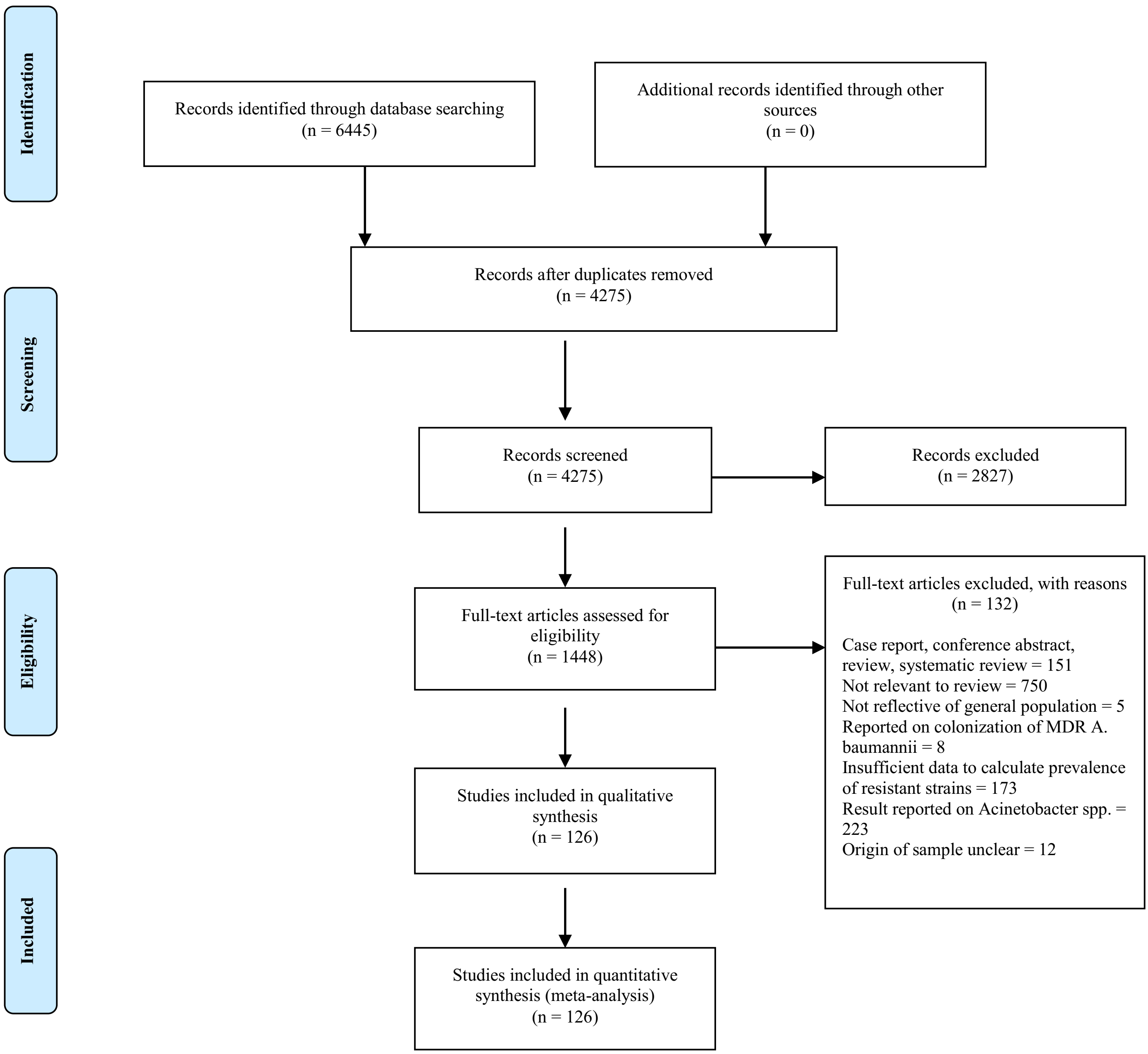

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 flow diagram.

other assays including E-test, disk diffusion, and broth microdilution. Details and quality appraisal of individual studies are shown in Appendix 5 and 6. Overall, most of the studies ($n = 112$, 88.9%) were truly representative of the prevalence of multidrug-resistance among *A. baumannii* causing HAP and VAP. Significant heterogeneity and publication bias was observed in the subgroup analyses (Appendix 7–14).

Prevalence of multidrug-resistance among A. baumannii *causing HAP and VAP*

The overall prevalence of multidrug-resistance among *A. baumannii* causing HAP and VAP pooled from 114 studies was 79.9% (95% CI 73.9–85.4%). The top three regions with the highest reported prevalence were Central America (100%), Latin America and the Caribbean (100%) and Western Europe (91.4%; 95% CI, 70–99.9%). Regions with the lowest reported prevalence were Eastern Asia (64.6%; 95% CI, 50.2–77.6%), Northern America (69.8%; 95% CI, 36.6–94.2%) and Eastern Europe (70.6%; 95% CI, 42.9–91.9%) (Table 1 and Appendix 15).

The countries with the highest burden of multidrug-resistance among *A. baumannii* causing HAP and VAP were Mexico (100%), Cuba (100%), Uruguay (100%), Nepal (100%), Pakistan (100%), Lebanon (100%), Qatar (100%) and Croatia (100%). The countries with the lowest burden of multidrug-resistance among *A. baumannii* causing HAP and VAP were Argentina (56.5%), Taiwan (61.8%; 95% CI, 34.8–85.3%) and Romania (63.1%; 95% CI, 3.4–99.3%).

Over the past two decades, the rate of multidrug-resistance among *A. baumannii* causing HAP and VAP globally had ranged between 60 and 87% (Table 2 and Appendix 16). For the Americas and European region, we observed an increase in this prevalence by as much as 15%. On the other hand, in the African and Asian

Table 1
Pooled prevalence of multidrug-resistance among *Acinetobacter baumannii* causing hospital-acquired and ventilator-associated pneumonia, stratified by country/region.

Region/Country	Number of studies	Number of AB	Number of MDRAB strains	Prevalence estimates (%)	95% CI (%)	I^2 (%)
Africa	3	131	115	88.3	67.6–99.2	83.5
Northern Africa	3	131	115	88.3	67.6–99.2	83.5
Egypt	2	39	36	88.5	41–96.6	88.7
Tunisia	1	92	79	85.9	–	–
Americas	10	770	661	82.7	59.6–97.1	97.3
Central America	1	12	12	100	–	–
Mexico	1	12	12	100	–	–
Latin America and the Caribbean	1	53	53	100	–	–
Cuba	1	53	53	100	–	–
Northern America	3	180	106	69.8	36.6–94.2	94.5
United States of America	3	180	106	69.8	36.6–94.2	94.5
South America	5	525	490	79.6	41.6–99.5	97
Argentina	1	46	26	56.5	–	–
Brazil	3	475	460	81.2	33.4–99.6	96.8
Uruguay	1	4	4	100	–	–
Asia	78	6455	4425	77.6	69.8–84.6	98
Eastern Asia	30	2655	1232	64.6	50.2–77.6	98
China	18	1770	672	63.8	43.2–82	98.2
Korea	5	304	219	70.8	54.4–84.8	88.3
Taiwan	7	581	341	61.8	34.7–85.3	97.5
South-eastern Asia	6	1605	1447	87.5	83.2–91.1	73.6
Thailand	4	669	584	86.2	81.8–90	49.8
Vietnam	2	936	863	89.8	80.8–96.2	60.7
Southern Asia	27	748	522	81.4	66.6–92.6	95.5
India	20	569	349	74.7	55.8–89.7	95.6
Iran	5	145	139	95.2	85–99.7	74.5
Nepal	1	25	25	100	–	–
Pakistan	1	9	9	100	–	–
Western Asia	15	1447	1224	89.6	79.2–96.7	96.3
Jordan	1	121	119	98.3	–	–
Lebanon	1	28	28	100	–	–
Qatar	1	23	23	100	–	–
Saudi Arabia	1	11	10	90.9	–	–
Turkey	11	1264	1044	86	71.6–95.8	97.1
Europe	23	1907	1219	85.1	73–94	97
Eastern Europe	7	1454	831	70.6	42.9–91.9	98.8
Poland	5	1388	774	72.6	40.2–95.3	99.1
Romania	2	66	57	63.1	3.3–99.3	91.8
Southern Europe	10	385	327	89	81.2–94.9	77.2
Croatia	1	16	16	100	–	–
Greece	5	237	205	91.6	82–97.7	77.1
Italy	1	68	61	89.7	–	–
Spain	3	64	45	77.8	52.8–95	74.4
Western Europe	6	68	61	91.4	70–99.9	82.7
France	6	68	61	91.4	70–99.9	82.7
Grand Total	**114**	**9263**	**6420**	**79.9**	**73.9–85.4**	**97.8**

MDR, multidrug-resistant; AB, *A. baumannii*; CI, confidence interval.

Table 2
Pooled prevalence of multidrug-resistance among *Acinetobacter baumannii* causing hospital-acquired and ventilator-associated pneumonia, stratified by time period.

Time period	Number of studies	Number of AB	Number of MDRAB strains	Prevalence estimates (%)	95% CI (%)	I^2 (%)
Prior to 2001	5	121	98	85.3	60.4–98.8	87.2
2001–2005	14	1414	384	60.6	38.5–80.5	97.6
2006–2010	28	2429	1659	73.5	63.7–82.3	96.1
2011–2015	51	4491	3602	87.7	80.8–93.2	97.2
2016–2018	8	532	451	76.5	52.7–93.7	96

MDR, multidrug-resistant; AB, *A. baumannii*; CI, confidence interval.

regions the prevalence decreased by about 20% (Table 3 and Appendix 17). However, there was also a lack of data for a number of countries from the Americas and the African region.

Based on the univariate meta-regression, the prevalence of multidrug-resistance among *A. baumannii* causing HAP and VAP varied significantly relative to the period during which the studies were carried out. The significant effect of the study period on the prevalence held through in the multivariate meta-regression as well (Appendix 18).

Mortality associated with MDRAB HAP and VAP

The overall mortality estimate pooled from 27 studies was 42.6% (95% CI, 37.2–48.1%) (Table 4 and Appendix 19). The regions with highest reported mortality rates were Western Asia (56.2%; 95% CI, 42.1–69.7%), Southern Europe (55.7%; 95% CI, 32.9–77.2%) and Northern Africa (53.3%). The regions with the lowest mortality rates were Northern America (28.6%; 95% CI, 22.6–35.1%), South-eastern Asia (31.9%, 95% CI, 14.2–52.9%) and Western

Table 3
Pooled prevalence of multidrug-resistance among *Acinetobacter baumannii* causing hospital-acquired and ventilator-associated pneumonia, stratified by time period and region.

Region/Time period	Number of studies	Number of AB	Number of MDRAB strains	Prevalence estimates (%)	95% CI (%)	I^2 (%)
Africa						
2006–2010	1	92	79	85.9	–	–
2016–2018	1	9	6	66.7	–	–
Americas						
Prior to 2001	1	73	57	78.1	–	–
2001–2005	2	139	62	46.8	30.1–63.8	74.4
2006–2010	3	41	33	84.2	51.7–99.7	83.1
2011–2015	4	517	509	95.3	80–99.9	91.1
Asia						
Prior to 2001	1	8	8	100	–	–
2001–2005	8	1202	264	45.2	17.2–75	98.1
2006–2010	22	2286	1541	72	60.8–82	96.8
2011–2015	38	2419	2164	87.6	82.3–92.1	90.7
2016–2018	6	508	430	73	44–94	97
Europe						
Prior to 2001	3	40	33	82.4	28.8–98	92.4
2001–2005	4	73	58	91.7	67.8–99.9	84.5
2006–2010	2	10	6	65.1	1.2–96.2	88.2
2011–2015	9	1555	929	84.4	62.8–97.5	98.6
2016–2018	1	15	15	100	–	–

MDR, multidrug-resistant; AB, *A. baumannii*; CI, confidence interval.

Table 4
Pooled mortality estimates in multidrug-resistant *Acinetobacter baumannii* in hospital-acquired and ventilator-associated pneumonia, according to country and UN region.

Region/Country	Number of studies	Number of patient with MDRAB	Number of patients that died	Mortality estimates (%)	95% CI (%)	I^2 (%)
Africa	1	30	16	53.3	–	–
Northern Africa	1	30	16	53.3	–	–
Egypt	1	30	16	53.3	–	–
Americas	4	267	83	32.5	24.3–41.1	48.5
Northern America	3	218	62	28.6	22.6–35.1	6.6
United States of America	3	218	62	28.6	22.6–35.1	6.6
South America	1	49	21	42.9	–	–
Brazil	1	49	21	42.9	–	–
Asia	19	1959	860	43.1	36.7–49.6	87.2
Eastern Asia	9	616	255	42.8	33.9–52	80.4
China	6	418	153	38.4	27.6–49.7	81.6
Korea	2	105	53	50.4	41–59.8	0
Taiwan	1	93	49	52.7	–	–
South-eastern Asia	3	536	215	31.9	14.2–52.8	95.3
Thailand	3	536	215	31.9	14.2–52.8	95.3
Southern Asia	3	151	60	38.1	27.6–49.1	43.3
India	2	119	51	42.4	32.3–52.8	20.1
Iran	1	32	9	28.1	–	–
Western Asia	4	656	330	56.2	42.1–69.7	91.4
Jordan	1	119	50	42	–	–
Turkey	3	537	280	61.4	42.9–78.3	93.5
Europe	3	59	30	49.9	31.2–68.5	55.7
Southern Europe	2	47	26	55.7	32.9–77.2	63.1
Greece	1	22	15	68.2	–	–
Spain	1	25	11	44	–	–
Western Europe	1	12	4	33.3	–	–
France	1	12	4	33.3	–	–
Grand Total	**27**	**2315**	**989**	**42.6**	**37.2–48.1**	**84.7**

MDR, multidrug-resistant; AB, *A. baumannii*; CI, confidence interval.

Europe (33.3%). The countries with the highest reported mortality rate were Greece (68.2%), Turkey (61.4; 95% CI, 42.9–78.3%) and Egypt (53.3%). The countries with the lowest reported mortality rate were Iran (28.1%), the United States of America (28.6%; 95% CI, 22.6–35.1%) and Thailand (31.9%; 95% CI, 14.2–52.9%) (Table 4).

Over the last two decades, the global rate of mortality in MDRAB HAP and VAP ranged between 38 and 48% (Table 5 and Appendix 20). Conversely, our meta-analysis according to region demonstrated an increase in mortality rate in Europe, from 44% before 2001, to 68% between 2011 and 2015. In contrast, a reduction in mortality rate was seen in the Americas and Asian region (42.9 to 24.4% and 50.4 to 37.8%, respectively) (Table 6 and Appendix 21). There was a lack of recent data for the Americas and European regions and lack of published data on mortality in HAP and VAP due to MDRAB from the African region. Based on the multivariate meta-regression, quality of the study, multicentricity, and study design had a significant impact on the mortality estimates (Appendix 22).

Discussion

We observed a wide variation in the prevalence of multidrug-resistance among *A. baumannii* causing HAP and VAP (ranging from 55% to 100%) and mortality rates (ranging from 28% to 68%), be-

Table 5
Pooled mortality estimates in multidrug-resistant *Acinetobacter baumannii* in hospital-acquired and ventilator-associated pneumonia, stratified by time period.

Time period	Number of studies	Number of patient with MDRAB	Number of patients that died	Mortality estimates (%)	95% CI (%)	I^2 (%)
Prior to 2001	2	39	17	43.8	29.2–59.1	0
2001–2005	3	117	57	48.7	39.8–57.6	0
2006–2010	10	1286	572	45.2	35.2–55.4	92.4
2011–2015	9	756	293	38	30–46.2	78.2
2016–2018	2	87	34	37.8	22.3–54.6	60.4

MDR, multidrug-resistant; AB, *A. baumannii*; CI, confidence interval.

Table 6
Pooled mortality estimates in multidrug-resistant *Acinetobacter baumannii* in hospital-acquired and ventilator-associated pneumonia, stratified by time period and region.

Region/Time period	Number of studies	Number of patient with MDRAB	Number of patients that died	Mortality estimates (%)	95% CI (%)	I^2 (%)
Americas						
Prior to 2001	1	14	6	42.9	–	–
2006–2010	2	171	57	35.1	23–48.4	63.6
2011–2015	1	82	20	24.4	–	–
Asia						
2001–2005	2	105	53	50.4	41–59.8	0
2006–2010	8	1115	515	47.5	35.9–59.3	93.4
2011–2015	7	652	258	37.3	29.7–45.2	71.8
2016–2018	2	87	34	37.8	22.3–54.6	60.4
Europe						
Prior to 2001	1	25	11	44	–	–
2001–2005	1	12	4	33.3	–	–
2011–2015	1	22	15	68.2	–	–

MDR, multidrug-resistant; AB, *A. baumannii*; CI, confidence interval.

tween regions and countries. These differences in prevalence likely reflect the level of urbanization, sanitation, different socioeconomic status and variation in medical practice or resources.

There is still a significant burden of MDRAB in most of the world. Our review demonstrated that four out of five *A. baumannii* strains, globally, are resistant to multiple antibiotics. Moreover, 40% of patients with MDRAB HAP or VAP are likely to succumb to the infection. Although there was not much change in the temporal trend of multidrug-resistance among *A. baumannii* causing HAP and VAP and its associated mortality, the rates were already high, to begin with. The high rate of MDRAB strains is unsurprising, as *A. baumannii* is innately resistant to numerous antibiotics effective against Gram-negative pathogens.[29,30] In addition to natural resistance, *A. baumannii* can also acquire other resistance mechanisms.[31]

Our review revealed Central and Latin America as having the highest burden of multidrug-resistance among *A. baumannii* causing HAP and VAP (100% for both) whereas Eastern Asia has the lowest prevalence (64.6%). However, the Central and Latin American regions were represented by only one country, and the estimates were derived from one study each as data from these regions were limited. A multiregional surveillance and a recent systematic review reported the rates of CR strains of *A. baumannii* from VAP and other clinical samples to be about 52 to 57%.[19,32] However, the multiregional surveillance was done between 2003 and 2008. A considerable variation in the susceptibility of *A. baumannii* was also observed in a sizeable multiregional surveillance of clinical isolates from ICUs in North America, Europe, the Asia-Pacific Rim, Latin America, the Middle East, and Africa which was carried out between 2004 and 2009.[33] The results of this surveillance demonstrated that 73.4% of the *A. baumannii* isolates from Latin America, 39.6% from North America, 46.7% from Europe, 68.7% from Asia-Pacific Rim, 78.9% from the Middle East and 84.1% from Africa, were resistant to meropenem. These findings support what we observed in our review suggesting that the rates of resistance in *A. baumannii* have not changed much in the past years.

Our review revealed Greece (68.2%) as having the highest mortality of MDRAB in HAP, and VAP, whereas Iran (28.1%) has the lowest mortality. However, the estimates for Greece and Iran were based on one study each only. We also found the overall mortality rate of MDRAB HAP and VAP to be 42.6%. Our finding is similar to a systematic review which reported the attributable mortality in the ICU, of patients with *A. baumannii* infection, ranged from 10% to 43%.[34] The overall mortality rate observed in this study is also close to the rate observed in a multiregional surveillance carried by Rosenthal et al., which reported a crude mortality rate of 43.9% in ICU patients with VAP.[32] The high rate of mortality could be attributable to the resistance of the infecting *A. baumannii* strains. A meta-analysis on mortality in CR *A. baumannii* infections suggests that patients infected with carbapenem-resistant strains have higher mortality rates compared to patients with carbapenem-sensitive *A. baumannii* in both the pooled crude (OR=2.22; 95% CI=1.66–2.98; I^2=55) and adjusted (OR=2.49;95% CI=1.61–3.84; I^2= 32%) effect estimate.[35] Higher mortality rates found in patients with CR *A. baumannii* may be due to greater severity of illness and the likelihood of receiving inappropriate empirical antibiotic treatment, which results in increased risk of mortality. This notion is further supported by a few retrospective studies which also found that inappropriate antibiotic treatment in patients with *A. baumannii* pneumonia is associated with higher mortality[36,37] and that having an MDR *A. baumannii* is strongly predictive of receiving inappropriate empirical treatment.[37] Joung et al. also demonstrated that MDRAB infection in itself is associated with mortality.[36]

We noticed the lack of epidemiological and recent data from many countries, with only 29 out of 195 countries having any publish data at all. There is a dearth of comprehensive regional data on the prevalence of multidrug-resistance among *A. baumannii* causing HAP and VAP. Most studies either reported on *Acinetobacter spp*. or reported the epidemiology of *A. baumannii* based on various other clinical samples. Other published reviews, on the other hand, focused on specific regions of the world or other aspects of the clinical epidemiology of *A. baumannii* or MDRAB.

This review has several limitations. It contains reports from only 29 of 195 countries globally, and several countries/regions were only represented by a single study, one country or small sample size. This limits the accuracy of the meta-analysis to reflect the country's or region's true prevalence or mortality estimate. The included studies were also conducted at different periods, with several countries lacking recent data, limiting precision for inter-region comparison. We assumed that countries with missing data in a region have a comparable prevalence to our pooled mean prevalence or mortality rate. It is likely these reports may under- or overestimate the actual prevalence or mortality rate.

A. baumannii is one of many species of the *A. baumannii-calcoaceticus* complex, which includes *A. calcoaceiticus, A. nosocomialis*, and *A. pittii*. Thus, what is termed *A. baumannii* may include pathogens within this group that are not *A. baumannii*. Furthermore, the studies used different methods for the susceptibility testing of *A. baumannii*, with different sensitivities and specificities, and, different definitions of mortality. Also, there was a large degree of heterogeneity in our studies, which we have endeavored to compensate for by using the random-effects model for meta-analysis, but the underlying differences in the studies remain. To further explore is any covariates had a significant effect on the outcomes of interest, we performed meta-regression analyses. However, the multivariate meta-regression was performed on a fraction of the studies included in this review as about 40 to 50% of studies had to be excluded due to missing data (excluded: 47/114 studies for the prevalence of multidrug-resistance among *A. baumannii* causing HAP and VAP, and 12/27 studies for mortality in MDRAB HAP and VAP). Due to the publication bias, heterogeneity and study limitations, any conclusions and extrapolations to other populations should be undertaken with caution.

Despite these limitations, this systematic review provides a comprehensive overview of the prevalence of multidrug-resistance among *A. baumannii* causing HAP and VAP and its mortality rate, worldwide. Consequently, these data can be used to support regional initiatives to enhance infection control practices and antimicrobial stewardship, by facilitating available and inexpensive tools and resources to tackle this problem effectively and systematically.

Conclusion

In summary, this review highlights the critical need for a comprehensive worldwide survey to monitor *A. baumannii* isolates in general and in HAP and VAP specifically as there is a lack of data from many countries. It is clear that the burden of MDRAB in HAP and VAP and the mortality rate is high. Continuous monitoring of drug resistance and strict infection control are recommended for the prevention and control of MDRAB in HAP and VAP.

Declaration of Competing Interest

None to declare.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2019.09.012.

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