Clinical Microbiology and Infection xxx (xxxx) xxx

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Systematic Review

A systematic review on the excess health risk of antibiotic-resistant bloodstream infections for six key pathogens in Europe

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ARTICLE INFO

Article history:
Received 10 July 2023
Received in revised form
1 September 2023
Accepted 3 September 2023
Available online xxx

Editor: L. Leibovici

Keywords:
Antimicrobial resistance
Bloodstream infections
Burden
Health outcomes
Health technology
Mortality

ABSTRACT

Background: Antimicrobial resistance is a global threat, which requires novel intervention strategies, for which priority pathogens and settings need to be determined.
Objectives: We evaluated pathogen-specific excess health burden of drug-resistant bloodstream infections (BSIs) in Europe.
Methods: A systematic review and meta-analysis.
Data sources: MEDLINE, Embase, and grey literature for the period January 1990 to May 2022.
Study eligibility criteria: Studies that reported burden data for six key drug-resistant pathogens: carbapenem-resistant (CR) *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, third-generation cephalosporin or CR *Escherichia coli* and *Klebsiella pneumoniae*, methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecium*. Excess health outcomes compared with drug-susceptible BSIs or uninfected patients. For MRSA and third-generation cephalosporin *E. coli* and *K. pneumoniae* BSIs, five or more European studies were identified. For all others, the search was extended to high-income countries.
Participants: Paediatric and adult patients diagnosed with drug-resistant BSI.
Interventions: Not applicable.
Assessment of risk of bias: An adapted version of the Joanna-Briggs Institute assessment tool.
Methods of data synthesis: Random-effect models were used to pool pathogen-specific burden estimates.
Results: We screened 7154 titles, 1078 full-texts and found 56 studies on BSIs. Most studies compared outcomes of drug-resistant to drug-susceptible BSIs (46/56, 82.1%), and reported mortality (55/56 studies, 98.6%). The pooled crude estimate for excess all-cause mortality of drug-resistant versus drug-susceptible BSIs ranged from OR 1.31 (95% CI 1.03–1.68) for CR *P. aeruginosa* to OR 3.44 (95% CI 1.62

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https://doi.org/10.1016/j.cmi.2023.09.001
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Please cite this article as: Hassoun-Kheir N et al., A systematic review on the excess health risk of antibiotic-resistant bloodstream infections for six key pathogens in Europe, Clinical Microbiology and Infection, https://doi.org/10.1016/j.cmi.2023.09.001

−7.32) for CR *K. pneumoniae*. Pooled crude estimates comparing mortality to uninfected patients were available for vancomycin-resistant *Enterococcus* and MRSA BSIs (OR of 11.19 [95% CI 6.92−18.09] and OR 6.18 [95% CI 2.10−18.17], respectively).

Conclusions: Drug-resistant BSIs are associated with increased mortality, with the magnitude of the effect influenced by pathogen type and comparator. Future research should address crucial knowledge gaps in pathogen- and infection-specific burdens to guide development of novel interventions.

Nasreen Hassoun-Kheir, Clin Microbiol Infect 2023;■:1

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Introduction

Antimicrobial resistance (AMR) is a global threat with severe implications for patient safety [1]. For drug-resistant bloodstream infections (BSIs), 47 000 AMR attributable deaths and 195 000 AMR-associated deaths were estimated in Europe in 2019; corresponding to incidence rates of 21 associated deaths (95% uncertainty interval 11−36) and five attributable deaths (95% uncertainty interval 3−9) per 100 000 population [2]. Considering all infection types, the highest AMR burden was found for multi-drug-resistant *Escherichia coli* (27.3% of attributable deaths) and *Staphylococcus aureus* (14.4% of attributable deaths) [2]. Over time, the number of difficult-to-treat infections and their clinical burden have been increasing [3]. The increasing threat of AMR combined with the complexities of developing and marketing novel antibiotics, has stimulated the search for alternative preventive and therapeutic strategies to reduce the burden of AMR, such as vaccination and humanized monoclonal antibodies (mAbs). Vaccines have the potential to reduce the number of drug-resistant, as well as drug-susceptible, infections, and subsequently decrease antibiotic use and emergence of antibiotic resistance [4]. mAbs could reduce the burden of AMR by prevention of infections through pre-emptive treatment strategies in specific risk groups, or by increasing treatment efficacy once an infection occurs [5]. To date, there are several novel vaccines and mAbs at different stages in the clinical development pipeline [6].

To guide prioritization in research and development, and subsequent implementation strategies for novel vaccines and mAbs, detailed and stratified AMR burden data are required to determine the most critical drug-resistant pathogens, infection types, and the possible target populations. Most studies, so far, either focused on the clinical impact of a single pathogen and infection type [7], on one specific pathogen causing multiple infection types [8], or on a specific infection type associated with different pathogens [9]. Little empirical data is available comparing the clinical impact of different drug-resistant pathogens stratified by infection type, or population, whereas these data are crucial to support clinical development of vaccines and mAbs. In addition, this information will support the effective implementation of proven infection prevention and control strategies, as well as antimicrobial stewardship programmes.

Predicting the Impact of Monoclonal Antibodies & Vaccines on Antimicrobial Resistance (PrIMAVeRa, https://www.primavera-amr.eu/), is a European project funded by the Innovative Medicines Initiative 2. Its main goal is to develop mathematical models to study the efficacy of different implementation strategies for specific vaccines and mAbs, aiming to reduce the burden of AMR at population level. These models will be able to inform data-driven decisions regarding the prioritization of development and implementation of specific vaccines and mAbs. For parametrization of the models, three systematic reviews were completed on AMR frequency measures, excess health risks, and incremental costs associated with six frequent infection types caused by six key drug-resistant pathogens in Europe. Here, we report on the systematic review and meta-analysis, which assessed the excess health risks associated with drug-resistant BSIs. Data about excess health risks associated with other infection types was heterogeneous and scarce and will be reported elsewhere.

Methods

Search strategy and selection criteria

A detailed study protocol was published on the PROSPERO website (CRD42022322586, publication date 6 May 2022) [10]. In short, we searched MEDLINE® (PubMed), Embase (Ovid), and grey literature including the Global Index Medicus, and websites from the Center for Disease Prevention and Control (CDC) and the European CDC for articles published between 1 January 1990 and 3 May 2022, with no language restriction. We completed a reference check of identified systematic reviews in the search, as well as important previous publications on the topic [1,3,11,12]. The MEDLINE search included a combination of MeSH terms and keywords combining infection type, pathogen, resistance profile, health outcomes, and an extensive European geographical filter. The search terms were modified as required for each of the other databases (Supplement 1, Search strategies).

The population included adult patients with bloodstream, respiratory tract, urinary tract, skin and soft tissue, surgical site, or intraabdominal infections caused by the selected drug-resistant pathogens. The exposures of interest were carbapenem-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, third-generation cephalosporin- (3GCR) or carbapenem-resistant *E. coli* and *Klebsiella pneumoniae*, methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant *Enterococcus faecium* (VRE). This prioritization was based on ranking of relevance by the CDC, the priority pathogen list from WHO, previous AMR burden estimates [3], prevalence of resistance [13], and availability of vaccines or mAbs in the clinical development pipeline [6]. Comparator groups included patients with a similar drug-susceptible pathogen-infection combination or uninfected patients. Our primary outcome was pathogen-specific, excess all-cause mortality. Secondary outcomes included mortality at specific time-points, infection-related mortality, cognitive or physical impairment, organ failure, recurrence of infection, ICU admission, and infection-specific complications (Supplement 1, Review outcomes).

Eligibility criteria included: cohort studies, case-control studies, and secondary analysis of randomized controlled trials, reporting on relevant health outcomes for at least 40 patients with a specific drug-resistant-pathogen-infection combination compared with patients with drug-susceptible-infections or uninfected patients. We excluded studies without pathogen-infection-specific data, studies with other comparators, without health outcomes, and studies conducted outside of Europe. Single reviewing of titles and

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abstracts and double reviewing of full-texts was completed by three independent reviewers (NHK, MTNN, and MG) using Covidence [14]. Disagreements were resolved by an additional reviewer (MEAdK).

For *S. aureus*, (3GCR) *K. pneumoniae,* and *E. coli* BSIs, five or more European studies reporting relevant outcome data were identified. For all the other resistant pathogens-infection combinations, we extended the search to all high-income countries to improve sample size, as pre-specified in the protocol.

Data collection and analysis

Single data extraction was completed by two independent reviewers (NHK and MG) using REDCap electronic data capture tools hosted by the University Hospital of Verona [15]. Study design, setting, and population characteristics were recorded. Information on diagnosis, infection onset, presence of catheters, infection source, and clinical outcomes were also collected. For all outcomes, crude results per study arm (numerator, denominator, proportions), unadjusted and adjusted hazard ratios, OR, and/or risk ratios were recorded, whenever available. Information on the analytical methods and adjustment for confounders, including antibiotic treatment appropriateness, was collected. Single assessment of risk-of-bias (ROB) was performed using an adapted version of the Joanna Briggs Institute (JBI) risk-of-bias assessment tool by two reviewers (NHK and MG) (Supplement 1, Risk of bias assessment tools) [16]. Specific ROB items on methods and variables used to reduce confounding were assigned as critical items required for high-quality assignment. As pre-specified in the protocol, double full-text data extraction, and ROB assessment of 15% randomly selected studies was completed to verify quality, no major disagreements were identified, thus no further verification was performed.

We defined a minimum of five studies reporting on the same pathogen-infection combination per outcome to be pooled in a meta-analysis in the protocol, which was ultimately reduced to three studies because of data scarcity. Estimates were pooled separately according to the comparator group (no infection and infection by drug-susceptible pathogens, respectively). On the basis of outcome data availability, we performed the following meta-analyses: (a) crude analysis pooling unadjusted effect estimates, if needed calculated from crude data; (b) combined analysis, including adjusted effect estimates if reported, and unadjusted effect estimates otherwise; and (c) adjusted analysis—pooling only adjusted effect estimates. On the basis of data availability, we pooled OR estimates. Estimates from matched case-control studies were regarded as crude estimates, a post-hoc sensitivity analysis excluding these studies from the crude analyses estimates was done. For the primary mortality outcome, different time-points (e.g. 30-day mortality, in-hospital mortality) were combined in one meta-analysis. When more than three studies reported mortality for a specific timepoint for one pathogen, we reported separately specific-timepoint pooled mortality estimates as well. For secondary outcomes, only crude data were pooled.

All meta-analyses were conducted and reported using random-effects models, assuming a priori significant heterogeneity resulting from diverse study populations and statistical methods. A sensitivity analysis was provided for pooled estimates including only three studies, using fixed-effects (Peto) models, assuming that different studies have indeed different effect sizes, but estimating the weighted average of the included studies only, ignoring the distribution of effect sizes beyond the included studies. We assessed statistical heterogeneity using the I^2 statistic measure and prediction intervals (PrIs, reported for >3 studies), and non-reporting bias using Funnel plots (≥10 studies) [17,18]. Suspected Funnel plot asymmetry was interpreted through visual inspection and Egger's test. We also completed stratified analysis for different subgroups to address heterogeneity, if at least three studies reported on similar subgroups. Analysis was completed using Rstudio (Version 1.3.1093), packages 'meta', 'robvis', and 'highcharter' [19].

Results

Study selection and characteristics

For the full review, including all six infection types, we screened 7153 non-duplicate records (4013 from Europe and 3140 from high-income countries). Of these, 1078 full text reports were assessed for inclusion. Ninety-eight studies fulfilled the inclusion criteria, and 56 included clinical outcome data for BSIs and were included in this review (Fig. 1). The main reasons for exclusion were aggregate reporting on outcomes of multiple infection types/pathogens ($n = 275$), comparator groups not of interest ($n = 136$), and lack of outcome data ($n = 125$).

Most included studies evaluated clinical BSI outcomes among hospitalized patients (54/56, 96.4%), and were reported as cohort studies (45/56, 80.4%), with 25 retrospective and 20 prospective studies (Table 1) [20–67]. Half of the studies were multicentre studies (28/56, 50%), which had a median of two sites (interquartile range [IQR] 1–10), and seven studies were multinational studies (median of nine countries, IQR 6–11 countries). Overall, 31 of 56 studies (55.4%) included at least one European site, and 25 of 56 (44.6% of studies) included only non-European high-income countries site(s). In Europe, the United Kingdom was the country contributing most data ($n = 14$ studies), followed by Spain ($n = 9$), and Italy and Germany ($n = 8$ each, Fig. 2). For MRSA, (3GCR) *K. pneumoniae,* and *E. coli* BSIs, the review included only European studies, for the other pathogens studies from other high-income countries were added to overcome data scarcity.

Excess health risks of drug-resistant BSIs were compared only to drug-susceptible BSIs in 46 of 56 (82.1%) studies, only to uninfected patients in two studies (2/56, 3.6%), and to both control groups in eight studies (8/56, 14.3%). Ten studies (10/56, 17.9%) reported pathogen-specific BSI health outcomes for more than one selected pathogen. Overall, from 56 studies, we extracted data on 75 different comparisons (combinations of resistant-pathogen and comparator group). We were able to include data on BSIs caused by carbapenem-resistant *P. aeruginosa* (8 comparisons), *A. baumannii* (7 comparisons), and *K. pneumoniae* (5 comparisons), and 3GCR *E. coli* (13 comparisons), *K. pneumoniae* (3 comparisons), and Enterobacterales BSI (3 comparisons), MRSA (18 comparisons) and VRE (18 comparisons). No studies on carbapenem-resistant *E. coli* were identified (Supplement 2, Table S1). In total, for the different comparisons, 122 outcome records were collected evaluating different health outcomes.

Overall, the 56 studies included 15 210 patients infected with a key drug-resistant pathogen, 149 487 infected with a susceptible pathogen, and 703 758 uninfected controls (mainly driven by three large studies [68–70]), with a median of 100 (IQR 62–167), 222 (IQR 100–599), and 552 (IQR 223–15 823) per study, respectively. Most of the included patients were male (median percentage 57.9%, IQR 51.0–63.6%). Resistant and susceptible BSI patients had a similar mean age, 60.0 (standard deviation 7.6) vs. 60.9 (standard deviation 8.9) years (18 comparisons, p 0.76), but drug-resistant BSI patients more frequently had a vascular device (mean percentage 62.9% versus 48.3%, 23 comparisons, p 0.24), and a haemato-oncological malignancy (mean percentage of 34.2% vs. 25.5%, 15 comparisons, p 0.083) (Supplement 2, Table S3 and S4).

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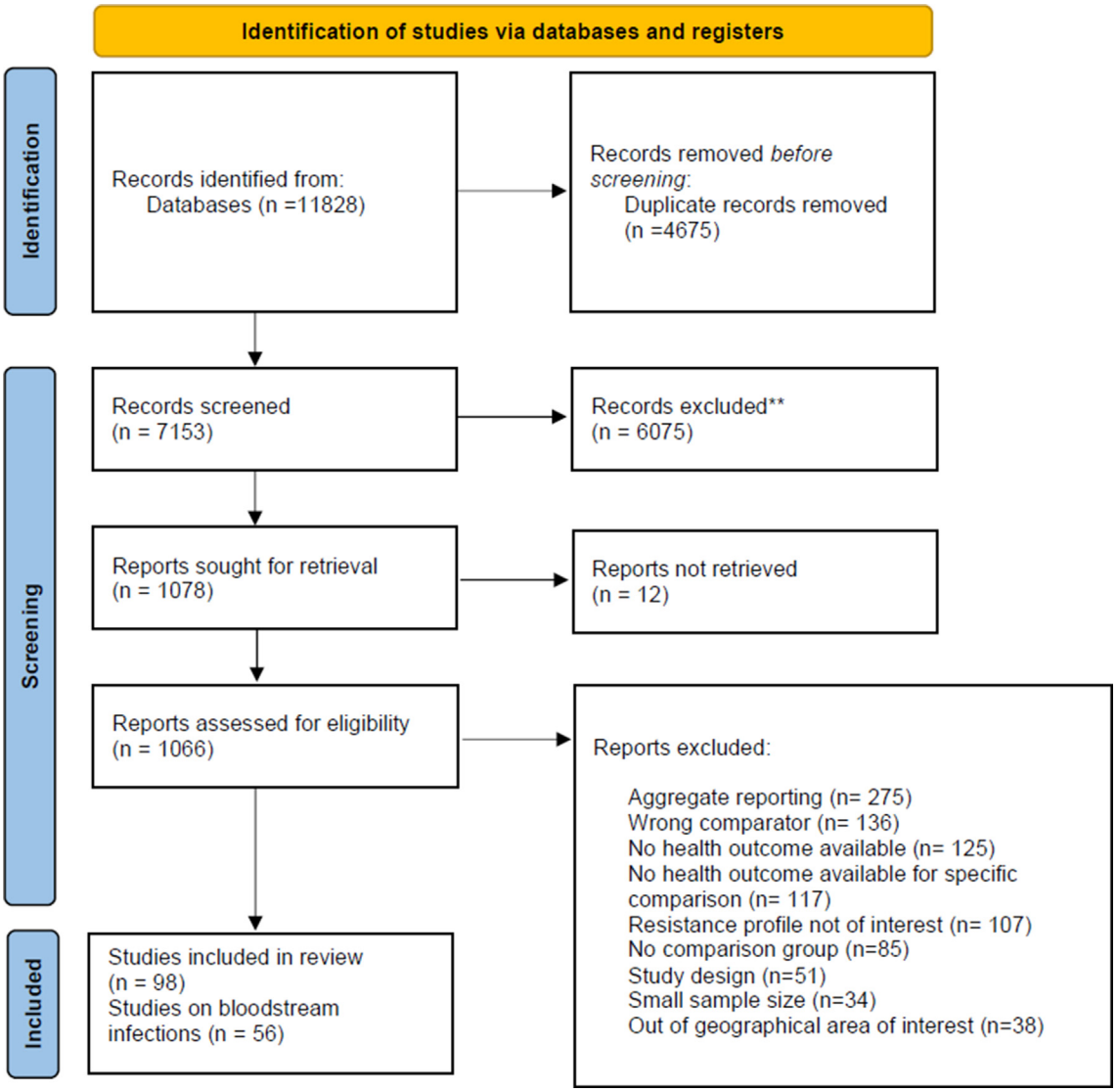

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart for the systematic review.

Review outcomes

Mortality was the outcome most frequently evaluated (55/56 studies, 98.2%). From these studies, a total of 98 mortality outcome records were collected, including all-cause mortality (86/98 records, 87.8%) and infection-related mortality (12/98 records, 12.2%), mostly measured at 3–4 weeks after infection (35/98 records, 35.7%) or on hospital-discharge (31/98 records, 31.6%). For VRE BSI, clinical failure/recurrence were also reported, compared with vancomycin-susceptible *E. faecium* BSI ($n = 3$ studies). Other review outcomes were completely absent or reported only in 1–2 studies per pathogen, precluding meta-analysis (Supplement 2, Table S2).

Meta-analysis results

Of 56 reviewed studies, 50 studies provided data for the meta-analysis (see Supplement 3, Table S8). Pooled, all-cause mortality among patients with the selected drug-resistant BSIs ranged between 20.9% and 46.6%, as compared with 13.0% and 27.7% in patients with drug-susceptible BSIs and 1.7% and 5.3% in uninfected controls (Table 2). In crude analysis, the pooled, excess all-cause mortality associated with drug-resistance ranged between an OR of 1.31 (95% CI 1.03–1.68) for carbapenem-resistant *P. aeruginosa* to an OR of 3.44 (95% CI 1.62–7.32) for carbapenem-resistant *K. pneumoniae*, both compared with susceptible infections (Table 2). Pooled estimates, on the basis of crude data, comparing mortality to uninfected patients were available for VRE and MRSA BSIs only (Table 2). Forest plots of studies reporting all-cause mortality because of MRSA and 3GC E. *coli* each compared with susceptible infection, on the basis of crude data, are shown in Fig.. 3(a) and (b). Other Forest plots are reported in the supplement per pathogen type (Supplement 3), including specific pooled estimates for in-hospital and 3–4 weeks mortality, if available (Supplement 3, Table S9).

For clinical failure/infection recurrence for VRE BSI, the pooled estimate compared with vancomycin-susceptible *E. faecium* was OR 2.38 (95% CI 1.60–3.54, three studies, $I^2 = 24\%$).

For those estimates with a high degree of heterogeneity, we excluded two studies from the meta-analysis (one study that included only haemato-oncological patients and another clear outlier [71,72]), and assessed outcomes per specific mortality timepoint. However, this did not reduce heterogeneity levels (Supplement 3, Table S9).

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Table 1
Characteristics of included studies reporting on health outcomes of drug-resistant bloodstream infections (BSI) compared with susceptible infection or uninfected patients

Study	Reported design	Study sites	Country[a]	Study period	Overall study size[b]	Pathogen(s)	Comparison[c]	Reported outcomes
Abernethy 2015 [20]	National registry—European	Multicentre	United Kingdom	2011–2012	28 616	3GC-resistant *E. coli*	S	Mortality
Abu-Lybdeh 2022 [21]	Cohort-retrospective	Multicentre	Israel	2009–2020	282	VRE	S	Mortality, LOS
Ammerlaan 2009 [22]	Cohort-retrospective	Multicentre	European	2007–2007	334	MRSA	S	Mortality
Aviv 2018 [23]	Case-control	Single centre	Israel	2007–2012	255	Carbapenem-resistant *P. aeruginosa*	S, N	Mortality, LOS, Functional deterioration
Balkhair 2019 [72][d]	Cohort-retrospective	Single centre	Oman	2007–2016	775	Carbapenem-resistant *P. aeruginosa, A. baumannii,* and *K. pneumoniae*	S	Mortality
Bassetti 2017 [24]	Cohort-retrospective	Multicentre	Italy	2011–2014	337	MRSA	S	Mortality
Ben-David 2011 [25]	Cohort-retrospective	Single centre	Israel	2006	192	Carbapenem-resistant *K. pneumoniae*	S	Mortality, LOS
Bhavnani 2000 [26]	Case-control	Multicentre	United States	1995–1997	300	VRE	S	Mortality, Clinical failure
Blandy 2019 [27]	Cohort-retrospective	Multicentre	United Kingdom	2011–2015	978	3GC-resistant *E. coli*	S	Mortality, LOS, ICU admission
Butler 2010 [68]	Cohort-retrospective	Single centre	United States	2002–2003	21 154	VRE	S, N	Mortality, LOS, ICU admission, Costs
Cheah 2014 [28]	Case-control	Multicentre	Australia	2002–2010	348	VRE	S, N	Mortality, LOS
Contreras 2022 [29]	Cohort-prospective	Multicentre	United States	2016–2018	232	VRE	S	Mortality, ICU admission
Daikos 2009 [30]	Cohort-prospective	Multicentre	Greece	2004–2006	162	Carbapenem-resistant *K. pneumoniae*	S	Mortality
Das 2007 [31]	Cohort-prospective	Single centre	United Kingdom	2001–2002	140	MRSA	S	Mortality, Relapse
De Kraker 2011 [32]	Cohort-prospective	Multicentre	European	2007–2008	2489	MRSA	S, N	Mortality, LOS
De Kraker 2011 [33]	Cohort-prospective	Multicentre	European	2007–2008	3509	3GC-resistant *E. coli*	S, N	Mortality, LOS
Evans 2020 [34]	Cohort-prospective	Multicentre	United Kingdom	2010–2012	1676	3GC-resistant *E. coli*	S	Mortality
Holmbom 2020 [35]	Cohort-retrospective	Multicentre	Sweden	2008–2016	9268	3GC-resistant *E. coli*	S	Mortality
Huang 2012 [36]	Cohort-retrospective	Single centre	Taiwan	2002–2007	226	Carbapenem-resistant *A. baumannii*	S	Mortality
Hussein 2013 [37]	Cohort-retrospective	Single centre	Israel	2006–2008	317	Carbapenem-resistant *K. pneumoniae*	S	Mortality
Johnstone 2018 [38]	Case-control	Multicentre	Canada	2009–2013	868	VRE	N	Mortality, LOS, ICU admission
Joo 2011 [39]	Cohort-retrospective	Single centre	Korea	2006–2009	202	Carbapenem-resistant *P. aeruginosa*	S	Mortality, LOS, Clinical failure
Kang 2021 [40]	Cohort-retrospective	Single centre	Korea	2009–2020	295	Carbapenem-resistant *P. aeruginosa*	S	Mortality, LOS
Kim 2020 [41]	Cohort-prospective	Multicentre	Korea	2016–2018	509	VRE	S	Mortality
Kim 2012 [42][d]	Cohort-retrospective	Single centre	Korea	2007–2010	95	Carbapenem-resistant *A. baumannii*	S	Mortality
Kim 2014 [43]	Cohort-retrospective	Single centre	Korea	2010–2012	234	Carbapenem-resistant *P. aeruginosa*	S	Mortality, LOS
Kwon 2007 [44]	Cohort-retrospective	Multicentre	Korea	2000–2005	80	Carbapenem-resistant *A. baumannii*	S	Mortality
Lambert 2011 [9]	Cohort-prospective	Multicentre	European	2005–2008	119 699	3GC-resistant *E. coli*, MRSA	S	Mortality, LOS
Lautenbach 1999 [45]	Cohort-retrospective	Single centre	United States	1993–1995	260	VRE	S	Mortality
Lee 2021 [69]	Case-control	Multicentre	Australia	2012–2016	92 025	MRSA, VRE, 3GC-resistant *E. coli*	S, N	Mortality, LOS, Costs
Leistner 2014 [46]	Cohort-retrospective	Single centre	Germany	2008–2010	1098	3GC-resistant *E. coli*	S	Mortality, LOS, Costs
Martinez 2010 [47]	Cohort-prospective	Single centre	Spain	1997–2008	4863	3GC-resistant *E. coli* and *K. pneumoniae*	S	Mortality
Melzer 2003 [48]	Cohort-prospective	Single centre	United Kingdom	1995–2000	815	MRSA	S	Mortality, deep seated infection
Melzer 2007 [49]	Cohort-prospective	Single centre	United Kingdom	2003–2005	354	3GC-resistant *E. coli*	S	Mortality, LOS
Nambiar 2018 [50][d]	Cohort-prospective	Multicentre	Global	2013–2015	1851	MRSA	S	Mortality
Pena 2012 [51]	Cohort-prospective	Multicentre	Spain	2008–2009	632	Carbapenem-resistant *P. aeruginosa*	S	Mortality
Pogue 2022 [52]	Cohort-retrospective	Multicentre	United States	2014–2019	5523	Carbapenem-resistant *A. baumannii*	S	Mortality, LOS, ICU admission
Richelsen 2020 [53]	Cohort-retrospective	Multicentre	Denmark	2007–2017	22 350	3GC-resistant *E. coli*	S	Mortality, LOS
Rodreigues Bano 2010 [54]	Case-control	Multicentre	Spain	2004–2006	95	3GC-resistant *E. coli*	S	Mortality
Romero-Vivas 1995 [74]	Cohort-prospective	Single centre	Spain	1990–1993	184	MRSA	S	Mortality
Rubio-Terrés 2010 [55]	Cohort-retrospective	Multicentre	Spain	2005	366	MRSA	S	Mortality, LOS, ICU admission, Costs
Schneider 2020 [56]	Cohort-retrospective	Single centre	Germany	2012–2015	467	MRSA	S	Mortality, LOS, Other
Shay 1995 [57]	Case-control	Single centre	United States	1992–1993	46	VRE	S	Mortality
Sheng 2010 [58][d]	Cohort-prospective	Multicentre	Taiwan	2004–2006	148	Carbapenem-resistant *A. baumannii*	S	Mortality, LOS
Smolyakov 2003 [59]	Cohort-retrospective	Single centre	Israel	2000	94	Carbapenem-resistant *A. baumannii*	S	Mortality, LOS
Stewardson 2016 [70]	Cohort-retrospective	Multicentre	European	2010–2011	606 649	MRSA, 3GC-resistant Enterobacterlaes	S, N	Mortality, LOS, Costs
Szilágyi 2009 [60]	Cohort-retrospective	Multicentre	Hungary	2005–2008	200	3GC-resistant *K. pneumoniae*	S	Mortality, Other
Thompson 2008 [61]	Case-control	Single centre	United Kingdom	1996–2006	Not reported	MRSA	N	Mortality
Tom 2014 [73]	Cohort-prospective	Multicentre	Global	2000–2008	5356	MRSA	S	Mortality
Trecarich 2019 [62]	Cohort-prospective	Multicentre	Italy	2016–2017	342	3GC-resistant *E. coli*	S	Mortality

(*continued on next page*)

Table 1 (*continued*)

Study	Reported design	Study sites	Country[a]	Study period	Overall study size[b]	Pathogen(s)	Comparison[c]	Reported outcomes
Trecarichi 2016 [63]	Cohort-prospective	Multicentre	Italy	2010–2014	278	Carbapenem-resistant *K. pneumoniae*	S	Mortality
Vergis 2001 [64]	Cohort-prospective	Multicentre	United States	1995–1997	398	VRE	S	Mortality, LOS, ICU admission, Recurrence
Vydra 2012 [71][d]	Cohort-prospective	Single centre	United States	2004–2008	752	VRE	S, N	Mortality
Weber 2019 [64]	Cohort-retrospective	Single centre	Germany	2007–2017	90	VRE	S	Mortality, ICU admission
Woudt 2018 [66][d]	Surveillance study	Multicentre	Netherlands	2008–2017	116 720	Carbapenem-resistant *P. aeruginosa*, MRSA, VRE, 3GC-resistant Enterobacterles	S	Recurrence
Wyllie 2006 [67]	Cohort-retrospective	Multicentre	United Kingdom	1997–2004	461	MRSA	S	Mortality

ICU, intensive care unit; LOS, length of (hospital) stay; MRSA, methicillin-resistant *S. aureus*; VRE, vancomycin-resistant Enterococci; 3GC, 3rd-generation cephalosporin.
[a] Studies including multiple countries only in Europe are recorded as 'European', studies that include sites outside Europe are recorded as 'Global'. All Global studies included at least one European site.
[b] The sample size refers to all patients included in the study and not to the specific pathogen-infection combinations.
[c] S—drug-susceptible infection comparator group, N—no infection comparator group.
[d] Not included in the meta-analysis (for specific reason for exclusion see Supplement 3).

Subgroup analyses

Only limited, stratified outcome data were found in the identified papers, relating to infection onset (community- or hospital-acquired), and age groups. The pooled estimate for crude, all-cause mortality compared with susceptible *S. aureus* BSI in studies including only hospital-acquired MRSA was OR 2.03 (95% CI 1.43−2.90, $I^2 = 63\%$, PrI 0.48−8.62, four studies) compared with OR 1.74 (95% CI 1.47−2.06, $I^2 = 12\%$, PrI 1.38−2.19, eight studies) for studies including both community- and hospital-acquired MRSA BSI. Estimate of community-acquired MRSA BSI mortality was only reported in one study [73]. There were not enough studies reporting specific age group mortality estimates for meta-analysis (one study each for children with VRE BSIs and elderly with MRSA BSI [71,74]).

Methodological aspects of included studies

Meta-analysis of adjusted estimates was only possible for excess mortality of VRE (five studies), MRSA, and 3GCR E. *coli* (four studies each) compared with susceptible BSI. For most pathogens, pooled estimates in combined analyses were slightly lower than in crude analyses except for 3GCR-resistant *K. pneumoniae* (Supplement 3, Table S10).

In studies assessing mortality, 45 of 48 applied multivariable analysis, of which 44.4% (20/45 studies) adjusted for antibiotic treatment inappropriateness. Subgroup meta-analysis could be performed for MRSA BSI mortality, by adjustment for inappropriate antibiotic treatment, yielding an OR of 1.75 (95% CI 1.45−2.10, ten studies, $I^2 = 56\%$) and 1.82 (95% CI 0.97−3.43, three studies, $I^2 = 61\%$) including and excluding inappropriateness, respectively (p 0.88 for subgroup differences).

Risk of bias assessment

Risk of bias assessment indicated an overall low quality of evidence, only 7 of 56 studies (12.5%) were judged as having low risk of bias (three MRSA studies, two 3GCR E. *coli,* one VRE, and one carbapenem-resistant *A. baumannii*, Supplement 3, Fig. S11). With regard to the critical elements of ROB; adjustment for confounding, 48 of 56 studies (86.7%) adjusted for confounders, and 43 of 48 studies (95.6%) clearly reported on adjustment methods. Seventeen studies properly addressed time from admission to infection onset (17/48, 35.4%), 20 of 48 studies (41.7%) included only time-fixed confounders measured before infection onset, and 32 of 48 studies (66.7%) adjusted for a minimum set of confounders. Most considered confounders were age, specific comorbidities, severity score, and antibiotic treatment appropriateness (Supplement 3, Table S11). In general, few studies had low risk of bias in domains assessing loss-to-follow-up (31/56 studies, 55.4%) and handling of missing data (21/56 studies, 37.5%). No publication bias was observed in Funnel plots for VRE, 3GCR E. *coli,* and MRSA BSI (Supplement 3, Figs S3D, S9C, and S10C, respectively). Adequacy of follow up was judged as low risk of bias, measuring either in-hospital mortality or specific day mortality, with post-discharge follow-up in 33 of 56 studies (58.9%).

Discussion

In this systematic review, we used a pathogen-infection-specific approach to study the clinical burden of AMR in the European setting to assess availability of data for prioritization and health technology assessment of AMR-prevention strategies, like vaccines or mAbs. We focused on six key drug-resistant pathogens and

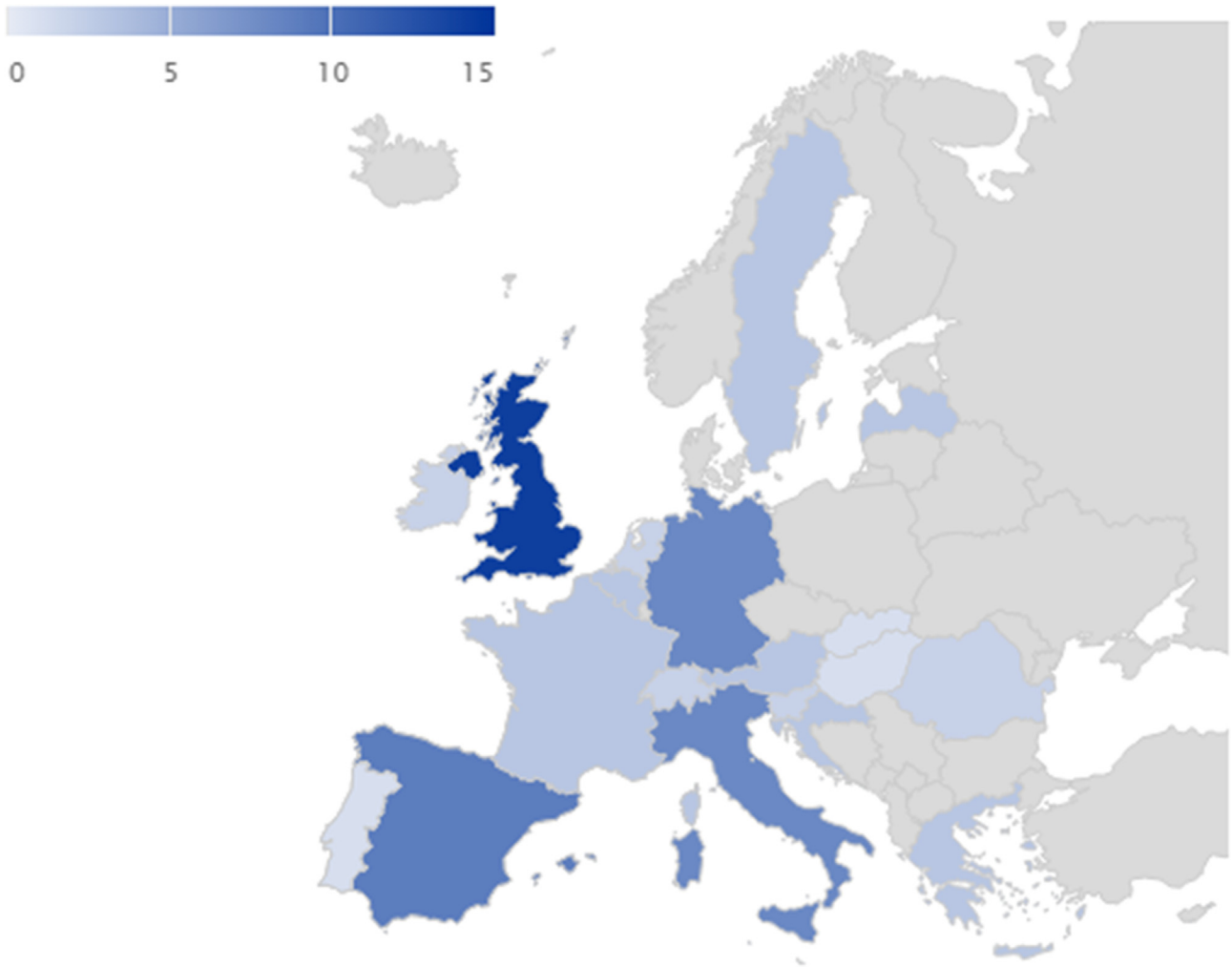

Fig. 2. Number of studies ($N = 31$) per European country that estimated the excess health risks associated with drug-resistant bloodstream infections for six critical pathogens and were included in the systematic review. Multinational studies were counted for each country. Non-European studies ($N = 25$).

reviewed studies reporting on excess health risks compared with drug-susceptible infections and/or uninfected patients. By applying the same criteria to evaluate the clinical impact of resistance for BSI by the different pathogens, we could provide a comprehensive overview of current evidence.

Pooled effect estimates indicated that drug-resistance was associated with an excess mortality risk for all assessed pathogens. The highest impact of resistance was observed for carbapenem-resistant *K. pneumoniae* BSIs, followed by carbapenem-resistant *A. baumannii*. These pathogens were also identified as priority pathogens in the recent study on the global burden of AMR, ranking them 3rd and 5th, respectively, for resistance associated deaths across all infection types [1]. European estimates from the same modelling study showed a similar ranking [2]. Of note, carbapenem-resistant *K. pneumoniae* was associated with the largest increase in resistance-attributable deaths from 2007 to 2015 in Europe [3]. On the other hand, the impact of carbapenem-resistant *P. aeruginosa* and 3GCR-resistant *K. pneumoniae* appeared marginal, as pooled estimates for crude mortality risk had CIs close to an OR of 1, which was reflected in estimates from the individual studies as well.

The focus of most published studies included in this review was on the excess mortality of drug-resistant versus drug-susceptible infections, but this provides only part of the picture of the burden of drug-resistant infections. To assess the burden of AMR, two different counterfactual scenarios can be applied: comparison of health outcomes of patients with drug-resistant infections versus those with drug-susceptible infections (replacement scenario) or compared with those with no infection (addition scenario) [75]. The excess health risk of drug-resistant infections compared with having no infection is especially important when assessing the potential cost-effectiveness of a bacterial vaccine, which prevents drug-resistant and drug-susceptible infections. Sufficient evidence to generate such estimates was detected only for BSIs because of VRE and MRSA. For other pathogens either one or no studies comparing outcomes to uninfected patients were found, precluding meta-analysis.

The scarcity of AMR burden data was evident in our review; many studies only included aggregated data for either a single infectious syndrome caused by various pathogens, or multiple infection types by the same pathogen, precluding collection of pathogen-infection-specific data. Over a period of more than 30 years, we only found a total of 31 European studies reporting on pathogen-specific excess health risks associated with drug-resistant BSIs. For MRSA, 3GCR E. *coli,* and *K. pneumonia*, a range of 3–13 European studies were available per each resistant pathogen, and we could provide pooled European estimates. For all other pathogens, we needed to combine European and non-

Please cite this article as: Hassoun-Kheir N et al., A systematic review on the excess health risk of antibiotic-resistant bloodstream infections for six key pathogens in Europe, Clinical Microbiology and Infection, https://doi.org/10.1016/j.cmi.2023.09.001

Table 2
Pooled estimates for crude OR of mortality associated with bloodstream infections, stratified by drug-resistant pathogen, comparator group, and mortality definition

Pathogen	Geographic studies' scope	No. studies	Deaths/Total in resistant (%)	Deaths/total in control (%)	OR	95% CI	95% Prediction intervals	I^2 (%)
Overall all-cause mortality compared with susceptible								
Carbapenem-resistant *A. baumannii*	HIC	4	138/329 (41.9%)	132/827 (16.0%)	2.63	1.34–5.17	0.14–49.76	78
Carbapenem-resistant *P. aeruginosa*	HIC	5	162/467 (34.7%)	295/1066 (27.7%)	1.31	1.03–1.68	0.87–1.99	21
Vancomycin-resistant *E. faecium*	HIC	9	417/1014 (41.1%)	289/1412 (20.5%)	2.46	1.96–3.09	1.48–4.11	27
Carbapenem-resistant *K. pneumoniae*	HIC	4	174/373 (46.6%)	114/511 (22.3%)	3.44	1.62–7.32	0.12–101.95	81
3GC-resistant *K. pneumoniae*[a]	Europe	3	70/245 (28.6%)	89/683 (13.0%)	1.95	1.02–3.74	NA	65
3GC-resistant *E. coli*	Europe	12	663/3167 (20.9%)	4549/30 466 (14.9%)	1.9	1.43–2.54	0.7–5.18	78
Methicillin-resistant *S. aureus*	Europe	13	715/2211 (32.3%)	1886/9177 (20.6%)	1.75	1.46–2.10	0.99–3.08	58
Overall infection-related mortality compared with susceptible								
Vancomycin-resistant *E. faecium*	HIC	4	152/450 (33.8%)	108/484 (22.3%)	2.28	1.45–3.60	0.43–12.17	52
Methicillin-resistant *S. aureus*	Europe	4	131/671 (19.5%)	88/834 (10.6%)	2.19	1.61–2.97	1.11–4.30	0
Overall all-cause mortality compared with uninfected								
VRE	HIC	4	169/470 (36.0%)	5184/97 280 (5.3%)	11.19	6.92–18.09	1.65–76.04	58
MRSA[b]	Europe	3	151/458 (33.0%)	10 291/605 523 (1.7%)	6.18	2.10–18.17	NA	94

HIC, high-income countries; MRSA, methicillin-resistant *S. aureus*; NA, not applicable; VRE, vancomycin-resistant Enterococci; 3GC, 3rd-generation cephalosporin.
[a] Fixed effects (Peto) model pooled estimate 2.16 (95% CI 1.45–3.23).
[b] Fixed effects (Peto) model pooled estimate 9.93 (95% CI 7.19–13.71).

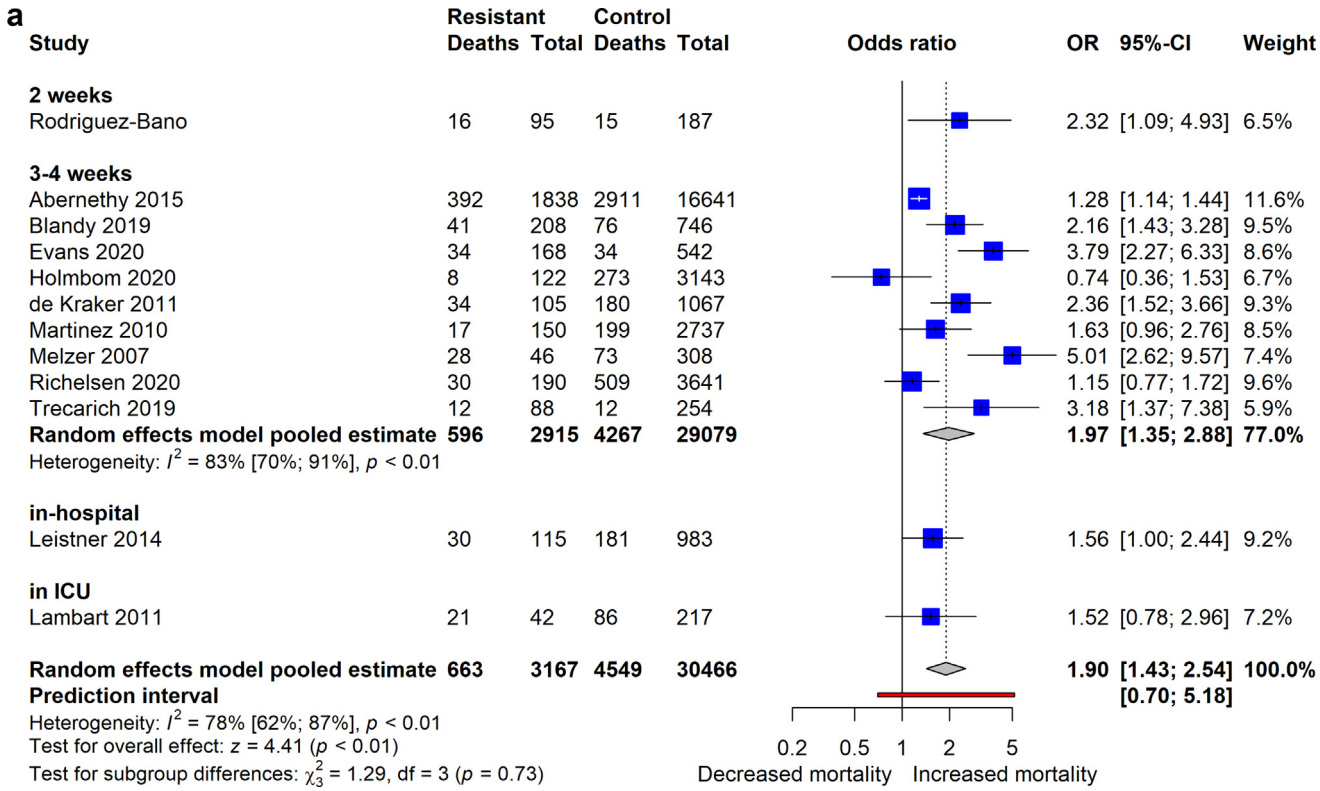

Fig. 3. (a) Forest plot of studies reporting overall, all-cause mortality of patients with bloodstream infection because of third-generation cephalosporin-resistant *E. coli* compared with susceptible *E. coli* bloodstream infection, reported as ORs based on crude data. Time refers to period between infection onset and mortality assessment. (b) Forest plot of studies reporting overall, all-cause mortality of patients with bloodstream infection because of methicillin-resistant *S. aureus* compared with methicillin susceptible *S. aureus* bloodstream infection, reported as ORs based on crude data. Time refers to period between infection onset and mortality assessment.

European data. For carbapenem-resistant *E. coli* BSI zero studies were identified, most probably because of the still, relatively low level of resistance. Furthermore, most of the reviewed literature focused on the tip of the iceberg and only reported mortality outcomes. Yet, from a patient-perspective, additional outcome types would be highly relevant. On the basis of the available data, we could only generate a pooled estimate for clinical failure/recurrence of infection associated with vancomycin resistance in *E. faecium* BSI. There was barely any stratified outcome data reported per risk group, including basic subdivisions like age/gender. Consequently, large uncertainties remain about the excess health risk of AMR per pathogen, infection type, or risk group.

High ROB was observed for most of the included studies; thus, we could not perform a subgroup analysis of high-quality studies as planned. However, we evaluated different analysis strategies by pooling only crude estimates, only adjusted estimates, and a combination of both. For most pathogens, the pooled estimates

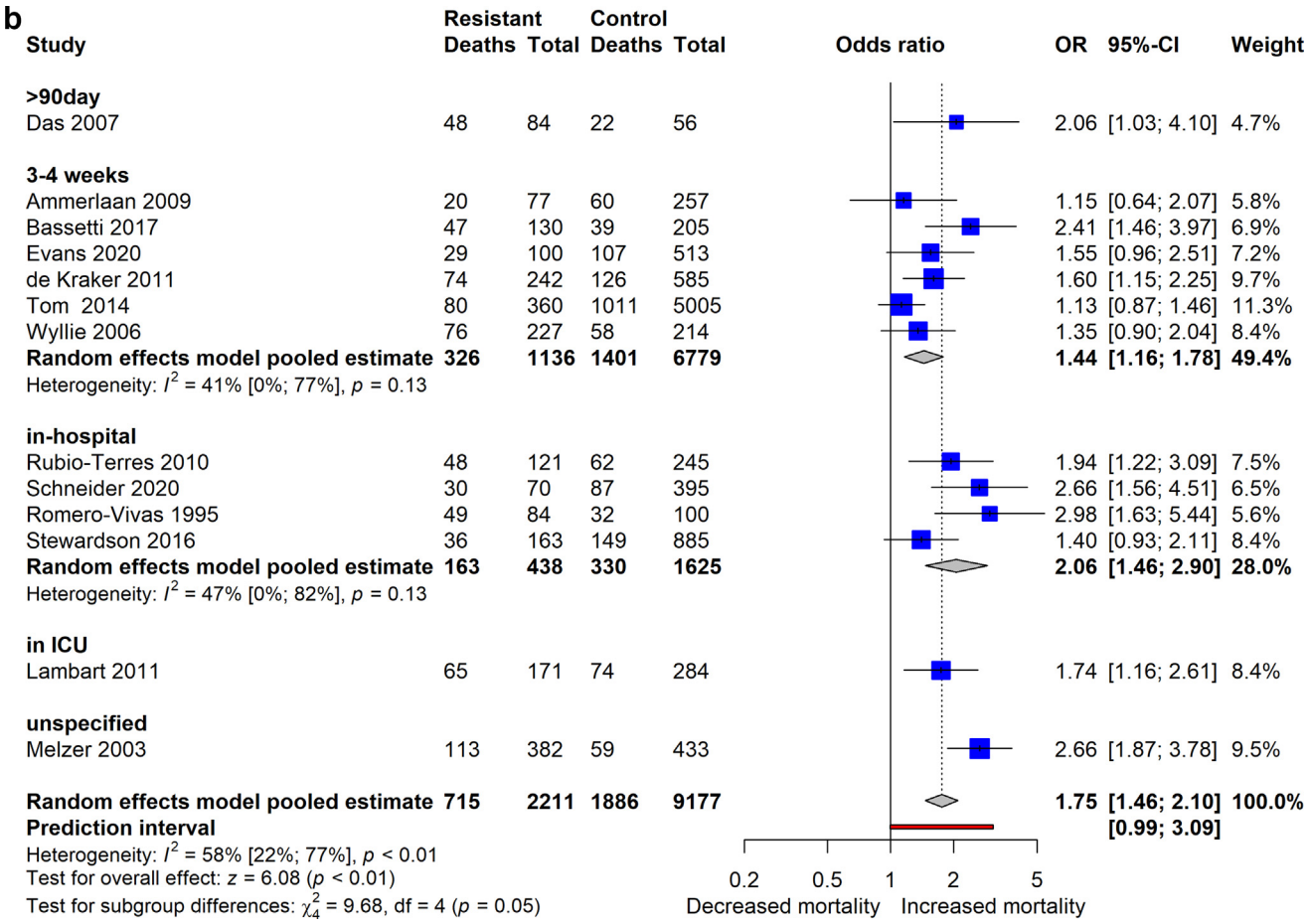

Fig. 3. *(continued).*

from the combined analyses were slightly lower than those from the crude analyses, but the direction of the effects remained the same. Immortal time bias and incomplete follow-up were frequently identified and could have biased the primary study estimates. Therefore, some uncertainty is expected in the pooled estimates. In addition, a large variability was observed in the study methodology and handling of confounding, which could have increased heterogeneity across studies. For example, antibiotic treatment appropriateness, on the pathway from drug-resistant infection to clinical outcomes, was adjusted for in a minority of the studies. However, we observed that adding treatment appropriateness to multivariable analysis only slightly changed pooled effect estimates for mortality following MRSA BSI.

There are some limitations of the current systematic review. European excess health risks were only available for MRSA, 3GCR-*K. pneumonia*, and *E. coli* BSI. For all other pathogens data from high-income countries had to be used, for which generalizability to the European setting may be limited, because of large variation in antibiotic stewardship, infection prevention practices, and health system structure in general [76]. A high degree of heterogeneity in the pathogen-specific, pooled estimates was evident, resulting in large prediction intervals. This is probably related to clinical and methodological diversity in the primary studies, including different infection-onsets, timing of mortality assessments, and analytical methods. Unfortunately, because of data scarcity, the options for subgroup analysis were limited. Sensitivity analysis pooling timepoint-specific mortality data, whenever available, did not give very different results.

Overall, we screened all publicly available evidence in the scientific literature from 1990 to 2022 for excess health risks associated with BSIs caused by six key drug-resistant pathogens in Europe. We extracted effect estimates, evaluated methodological approaches, and assessed heterogeneity and ROB. In parallel, a similar approach was used to evaluate the frequency of drug-resistant infections and the economic burden of these infections within PrIMAVeRa WP1. On the basis of data from 56 studies, we can conclude that drug-resistant BSIs are associated with an excess health risk, however, mortality varies widely per pathogen and comparator groups. Moreover, large knowledge gaps remain for AMR burden among risk groups, and for relevant health outcomes other than mortality, and a large part of the data comes from settings outside of Europe. With the current data availability, it will be challenging to guide the prioritisation and promote the development of potential vaccines and mAbs to reduce the burden of AMR in Europe.

Transparency declaration

VV, LA, JES, and AP are employees of GSK. VV, JES, and AP own GSK shares. JG is an employee of Janssen and owns stocks of Johnson & Johnson.

This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement no.

101034420 (Predicting the Impact of Monoclonal Antibodies & Vaccines on Antimicrobial Resistance [PrIMAVeRa]). This Joint Undertaking receives support from the European Union's Horizon 2020 Research and Innovation Programme and EFPIA.

This communication reflects the author's view and neither IMI nor the European Union, EFPIA, or any Associated Partners are responsible for any use that may be made of the information contained herein.

Data availability

The data used for the meta-analyses can be accessed via the Epi-NET website (https://epi-net.eu/primavera/).

Acknowledgements

We acknowledge the contributions of Toby Bonvoisin (University of Oxford) for the development of the European search filter, Eduardo Reyna-Villasmil and Jorly Mejia Montilla (Hospital Universitario Virgen Macarena, Seville) for their help at the first stages of the systematic review, and Johannes Eberhard Schmidt (GSK) for critically reviewing the REDCap data extraction form. The University Hospital of Verona for providing access to REDCap.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2023.09.001.

References

[1] Murray CJL, Ikuta KS, Sharara F, Swetschinski L, Robles Aguilar G, Gray A, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet 2022;399. https://doi.org/10.1016/s0140-6736(21)02724-0.

[2] European Antimicrobial Resistance Collaborators. The burden of bacterial antimicrobial resistance in the WHO European region in 2019: a cross-country systematic analysis. Lancet Public Health 2022;7:e897–913. https://doi.org/10.1016/s2468-2667(22)00225-0.

[3] Cassini A, Högberg LD, Plachouras D, Quattrocchi A, Hoxha A, Simonsen GS, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. Lancet Infect Dis 2019;19:56–66. https://doi.org/10.1016/s1473-3099(18)30605-4.

[4] Jansen KU, Knirsch C, Anderson AS. The role of vaccines in preventing bacterial antimicrobial resistance. Nat Med 2018;24:10–9. https://doi.org/10.1038/nm.4465.

[5] Zurawski DV, McLendon MK. Monoclonal antibodies as an antibacterial approach against bacterial pathogens. Antibiotics (Basel) 2020;9:155. https://doi.org/10.3390/antibiotics9040155.

[6] Frost I, Sati H, Garcia-Vello P, Hasso-Agopsowicz M, Lienhardt C, Gigante V, et al. The role of bacterial vaccines in the fight against antimicrobial resistance: an analysis of the preclinical and clinical development pipeline. Lancet Microbe 2023;4:e113–25. https://doi.org/10.1016/s2666-5247(22)00303-2.

[7] Frem JA, Doumat G, Kazma J, Gharamti A, Kanj SS, Abou Fayad AG, et al. Clinical predictors of mortality in patients with pseudomonas aeruginosa infection. PLOS ONE 2023;18:e0282276. https://doi.org/10.1371/journal.pone.0282276.

[8] Liu Q, Li X, Li W, Du X, He JQ, Tao C, et al. Influence of carbapenem resistance on mortality of patients with Pseudomonas aeruginosa infection: a meta-analysis. Sci Rep 2015;5:11715. https://doi.org/10.1038/srep11715.

[9] Lambert ML, Suetens C, Savey A, Palomar M, Hiesmayr M, Morales I, et al. Clinical outcomes of health-care-associated infections and antimicrobial resistance in patients admitted to European intensive-care units: a cohort study. Lancet Infect Dis 2011;11:30–8. https://doi.org/10.1016/s1473-3099(10)70258-9.

[10] Hassoun-Kheir N, Mejia Montilla J, Reyna-Villasmil E, Rodriguez-Baño J, Naylor N, Pouwels K, et al. A systematic review on the excess health risk of antibiotic-resistant infections in Europe 2022. https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=322586. [Accessed 6 May 2022].

[11] Cassini A, Plachouras D, Eckmanns T, Abu Sin M, Blank HP, Ducomble T, et al. Burden of six healthcare-associated infections on European population health: estimating incidence-based disability-adjusted life years through a population prevalence-based modelling study. PLOS Med 2016;13:e1002150. https://doi.org/10.1371/journal.pmed.1002150.

[12] Pezzani MD, Tornimbene B, Pessoa-Silva C, de Kraker M, Rizzardo S, Salerno ND, et al. Methodological quality of studies evaluating the burden of drug-resistant infections in humans due to the WHO Global Antimicrobial Resistance Surveillance System target bacteria. Clin Microbiol Infect 2021;27:687–96. https://doi.org/10.1016/j.cmi.2021.01.004.

[13] ECDC. Antimicrobial resistance in the EU/EEA (EARS-Net) – annual epidemiological report ECDC. 2019.

[14] Covidence. Covidence systematic review software, veritas health innovation Melbourne, Australia. www.covidence.org.

[15] Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: building an international community of software platform partners. J Biomed Inform 2019;95:103208. https://doi.org/10.1016/j.jbi.2019.103208.

[16] JBI. JBI Critical appraisal tools. South Australia; 2018: The University of Adelaide; 2022. https://jbi.global/critical-appraisal-tools. [Accessed 6 May 2022]

[17] Boutron I.P.M., Higgins J.P.T., Altman D.G., Lundh A., Hróbjartsson A. Chapter 7: considering bias and conflicts of interest among the included studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Cochrane, 2023. Available from www.training.cochrane.org/handbook. [Accessed 30 Jun -2023]

[18] Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 2011;343:d4002. https://doi.org/10.1136/bmj.d4002.

[19] McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): an R package and Shiny web app for visualizing risk-of-bias assessments. Res Synth Methods 2020;12:55–61. https://doi.org/10.1002/jrsm.1411.

[20] Abernethy JK, Johnson AP, Guy R, Hinton N, Sheridan EA, Hope RJ. Thirty day all-cause mortality in patients with *Escherichia coli* bacteraemia in England. Clin Microbiol Infect 2015;21. https://doi.org/10.1016/j.cmi.2015.01.001. 251.e1–8.

[21] Abu-Lybdeh O, Murik O, Oster Y, Assous MV, Mann T, Zeevi DA, et al. Vancomycin-resistant enterococcus bacteraemia in an endemic region: clinical features and genomic analysis: a 12-year cohort. J Hosp Infect 2022;121:105–13. https://doi.org/10.1016/j.jhin.2021.11.021.

[22] Ammerlaan H, Seifert H, Harbarth S, Brun-Buisson C, Torres A, Antonelli M, et al. Adequacy of antimicrobial treatment and outcome of *Staphylococcus aureus* bacteremia in 9 Western European countries. Clin Infect Dis 2009;49:997–1005. https://doi.org/10.1086/605555.

[23] Aviv T, Lazarovitch T, Katz D, Zaidenstein R, Dadon M, Daniel C, et al. The epidemiological impact and significance of carbapenem resistance in *Pseudomonas aeruginosa* bloodstream infections: a matched case-case-control analysis. Infect Control Hosp Epidemiol 2018;39:1262–5. https://doi.org/10.1017/ice.2018.181.

[24] Bassetti M, Peghin M, Trecarichi EM, Carnelutti A, Righi E, Del Giacomo P, et al. Characteristics of *Staphylococcus aureus* Bacteraemia and predictors of early and late mortality. PLOS ONE 2017;12:e0170236. https://doi.org/10.1371/journal.pone.0170236.

[25] Ben-David D, Kordevani R, Keller N, Tal I, Marzel A, Gal-Mor O, et al. Outcome of carbapenem resistant *Klebsiella pneumoniae* bloodstream infections. Clin Microbiol Infect 2012;18:54–60. https://doi.org/10.1111/j.1469-0691.2011.03478.x.

[26] Bhavnani SM, Drake JA, Forrest A, Deinhart JA, Jones RN, Biedenbach DJ, et al. A nationwide, multicenter, case-control study comparing risk factors, treatment, and outcome for vancomycin-resistant and -susceptible enterococcal bacteremia. Diagn Microbiol Infect Dis 2000;36:145–58. https://doi.org/10.1016/s0732-8893(99)00136-4.

[27] Blandy O, Honeyford K, Gharbi M, Thomas A, Ramzan F, Ellington MJ, et al. Factors that impact on the burden of *Escherichia coli* bacteraemia:

multivariable regression analysis of 2011–2015 data from West London. J Hosp Infect 2019;101:120–8. https://doi.org/10.1016/j.jhin.2018.10.024.
[28] Cheah AL, Peel T, Howden BP, Spelman D, Grayson ML, Nation RL, et al. Case-case-control study on factors associated with vanB vancomycin-resistant and vancomycin-susceptible enterococcal bacteraemia. BMC Infect Dis 2014;14:353. https://doi.org/10.1186/1471-2334-14-353.
[29] Contreras GA, Munita JM, Simar S, Luterbach C, Dinh AQ, Rydell K, et al. Contemporary clinical and molecular epidemiology of vancomycin-resistant enterococcal bacteremia: a prospective multicenter cohort study (VENOUS I). Open Forum Infect Dis 2022;9:ofab616. https://doi.org/10.1093/ofid/ofab616.
[30] Daikos GL, Petrikkos P, Psichogiou M, Kosmidis C, Vryonis E, Skoutelis A, et al. Prospective observational study of the impact of VIM-1 metallo-beta-lactamase on the outcome of patients with *Klebsiella pneumoniae* bloodstream infections. Antimicrob Agents Chemother 2009;53:1868–73. https://doi.org/10.1128/aac.00782-08.
[31] Das I, O'Connell N, Lambert P. Epidemiology, clinical and laboratory characteristics of *Staphylococcus aureus* bacteraemia in a university hospital in UK. J Hosp Infect 2007;65:117–23. https://doi.org/10.1016/j.jhin.2006.09.022.
[32] de Kraker ME, Wolkewitz M, Davey PG, Koller W, Berger J, Nagler J, et al. Clinical impact of antimicrobial resistance in European hospitals: excess mortality and length of hospital stay related to methicillin-resistant *Staphylococcus aureus* bloodstream infections. Antimicrob Agents Chemother 2011;55:1598–605. https://doi.org/10.1128/aac.01157-10.
[33] de Kraker ME, Wolkewitz M, Davey PG, Koller W, Berger J, Nagler J, et al. Burden of antimicrobial resistance in European hospitals: excess mortality and length of hospital stay associated with bloodstream infections due to *Escherichia coli* resistant to third-generation cephalosporins. J Antimicrob Chemother 2011;66:398–407. https://doi.org/10.1093/jac/dkq412.
[34] Evans RN, Pike K, Rogers CA, Reynolds R, Stoddart M, Howe R, et al. Modifiable healthcare factors affecting 28-day survival in bloodstream infection: a prospective cohort study. BMC Infect Dis 2020;20:545. https://doi.org/10.1186/s12879-020-05262-6.
[35] Holmbom M, Möller V, Nilsson LE, Giske CG, Rashid MU, Fredrikson M, et al. Low incidence of antibiotic-resistant bacteria in south-east Sweden: an epidemiologic study on 9268 cases of bloodstream infection. PLOS ONE 2020;15:e0230501. https://doi.org/10.1371/journal.pone.0230501.
[36] Huang ST, Chiang MC, Kuo SC, Lee YT, Chiang TH, Yang SP, et al. Risk factors and clinical outcomes of patients with carbapenem-resistant *Acinetobacter baumannii* bacteremia. J Microbiol Immunol Infect 2012;45:356–62. https://doi.org/10.1016/j.jmii.2011.12.009.
[37] Hussein K, Raz-Pasteur A, Finkelstein R, Neuberger A, Shachor-Meyouhas Y, Oren I, et al. Impact of carbapenem resistance on the outcome of patients' hospital-acquired bacteraemia caused by *Klebsiella pneumoniae*. J Hosp Infect 2013;83:307–13. https://doi.org/10.1016/j.jhin.2012.10.012.
[38] Johnstone J, Chen C, Rosella L, Adomako K, Policarpio ME, Lam F, et al. Patient- and hospital-level predictors of vancomycin-resistant Enterococcus (VRE) bacteremia in Ontario, Canada. Am J Infect Control 2018;46:1266–71. https://doi.org/10.1016/j.ajic.2018.05.003.
[39] Joo EJ, Kang CI, Ha YE, Kang SJ, Park SY, Chung DR, et al. Risk factors for mortality in patients with *Pseudomonas aeruginosa* bacteremia: clinical impact of antimicrobial resistance on outcome. Microb Drug Resist 2011;17:305–12. https://doi.org/10.1089/mdr.2010.0170.
[40] Kang JS, Moon C, Mun SJ, Lee JE, Lee SO, Lee S, et al. Antimicrobial susceptibility trends and risk factors for antimicrobial resistance in *Pseudomonas aeruginosa* bacteremia: 12-year experience in a tertiary hospital in Korea. J Korean Med Sci 2021;36:e273. https://doi.org/10.3346/jkms.2021.36.e273.
[41] Kim D, Yoon EJ, Hong JS, Lee H, Shin KS, Shin JH, et al. Impact of vanA-positive *Enterococcus faecium* exhibiting diverse susceptibility phenotypes to glycopeptides on 30-day mortality of patients with a bloodstream infection. Antimicrob Agents Chemother 2020 Jun 23;64(7). https://doi.org/10.1128/AAC.02180-19. e02180-19.
[42] Kim YJ, Kim SI, Hong KW, Kim YR, Park YJ, Kang MW. Risk factors for mortality in patients with carbapenem-resistant *Acinetobacter baumannii* bacteremia: impact of appropriate antimicrobial therapy. J Korean Med Sci 2012;27:471–5. https://doi.org/10.3346/jkms.2012.27.5.471.
[43] Kim YJ, Jun YH, Kim YR, Park KG, Park YJ, Kang JY, et al. Risk factors for mortality in patients with *Pseudomonas aeruginosa* bacteremia; retrospective study of impact of combination antimicrobial therapy. BMC Infect Dis 2014;14:161. https://doi.org/10.1186/1471-2334-14-161.
[44] Kwon KT, Oh WS, Song JH, Chang HH, Jung SI, Kim SW, et al. Impact of imipenem resistance on mortality in patients with Acinetobacter bacteraemia. J Antimicrob Chemother 2007;59:525–30. https://doi.org/10.1093/jac/dkl499.
[45] Lautenbach E, Bilker WB, Brennan PJ. Enterococcal bacteremia: risk factors for vancomycin resistance and predictors of mortality. Infect Control Hosp Epidemiol 1999;20:318–23. https://doi.org/10.1086/501624.
[46] Leistner R, Sakellariou C, Gürntke S, Kola A, Steinmetz I, Kohler C, et al. Mortality and molecular epidemiology associated with extended-spectrum β-lactamase production in *Escherichia coli* from bloodstream infection. Infect Drug Resist 2014;7:57–62. https://doi.org/10.2147/idr.S56984.
[47] Martínez JA, Cobos-Trigueros N, Soriano A, Almela M, Ortega M, Marco F, et al. Influence of empiric therapy with a beta-lactam alone or combined with an aminoglycoside on prognosis of bacteremia due to gram-negative microorganisms. Antimicrob Agents Chemother 2010;54:3590–6. https://doi.org/10.1128/aac.00115-10.
[48] Melzer M, Eykyn SJ, Gransden WR, Chinn S. Is methicillin-resistant *Staphylococcus aureus* more virulent than methicillin-susceptible S. aureus? A comparative cohort study of British patients with nosocomial infection and bacteremia. Clin Infect Dis 2003;37:1453–60. https://doi.org/10.1086/379321.
[49] Melzer M, Petersen I. Mortality following bacteraemic infection caused by extended spectrum beta-lactamase (ESBL) producing *E. coli* compared to non-ESBL producing E. coli. J Infect 2007;55:254–9. https://doi.org/10.1016/j.jinf.2007.04.007.
[50] Nambiar K, Seifert H, Rieg S, Kern WV, Scarborough M, Gordon NC, et al. Survival following *Staphylococcus aureus* bloodstream infection: a prospective multinational cohort study assessing the impact of place of care. J Infect 2018;77:516–25. https://doi.org/10.1016/j.jinf.2018.08.015.
[51] Peña C, Suarez C, Gozalo M, Murillas J, Almirante B, Pomar V, et al. Prospective multicenter study of the impact of carbapenem resistance on mortality in *Pseudomonas aeruginosa* bloodstream infections. Antimicrob Agents Chemother 2012;56:1265–72. https://doi.org/10.1128/aac.05991-11.
[52] Pogue JM, Zhou Y, Kanakamedala H, Cai B. Burden of illness in carbapenem-resistant *Acinetobacter baumannii* infections in US hospitals between 2014 and 2019. BMC Infect Dis 2022;22:36. https://doi.org/10.1186/s12879-021-07024-4.
[53] Richelsen R, Smit J, Schønheyder HC, Laxsen Anru P, Gutiérrez-Gutiérrez B, Rodríguez-Bāno J, et al. Outcome of community-onset ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* bacteraemia and urinary tract infection: a population-based cohort study in Denmark. J Antimicrob Chemother 2020;75:3656–64. https://doi.org/10.1093/jac/dkaa361.
[54] Rodríguez-Baño J, Picón E, Gijón P, Hernández JR, Ruíz M, Peña C, et al. Community-onset bacteremia due to extended-spectrum beta-lactamase-producing *Escherichia coli*: risk factors and prognosis. Clin Infect Dis 2010;50:40–8. https://doi.org/10.1086/649537.
[55] Rubio-Terrés C, Garau J, Grau S, Martinez-Martinez L. Cast of Resistance Study group. Cost of bacteraemia caused by methicillin-resistant vs. methicillin-susceptible *Staphylococcus aureus* in Spain: a retrospective cohort study. Clin Microbiol Infect 2010;16:722–8. https://doi.org/10.1111/j.1469-0691.2009.02902.x.
[56] Schneider SM, Schaeg M, Gärtner BC, Berger FK, Becker SL. Do written diagnosis-treatment recommendations on microbiological test reports improve the management of *Staphylococcus aureus* bacteremia? A single-center, retrospective, observational study. Diagn Microbiol Infect Dis 2020;98:115170. https://doi.org/10.1016/j.diagmicrobio.2020.115170.
[57] Shay DK, Maloney SA, Montecalvo M, Banerjee S, Wormser GP, Arduino MJ, et al. Epidemiology and mortality risk of vancomycin-resistant enterococcal bloodstream infections. J Infect Dis 1995;172:993–1000. https://doi.org/10.1093/infdis/172.4.993.
[58] Sheng WH, Liao CH, Lauderdale TL, Ko WC, Chen YS, Liu JW, et al. A multicenter study of risk factors and outcome of hospitalized patients with infections due to carbapenem-resistant *Acinetobacter baumannii*. Int J Infect Dis 2010;14:e764–9. https://doi.org/10.1016/j.ijid.2010.02.2254.
[59] Smolyakov R, Borer A, Riesenberg K, Schlaeffer F, Alkan M, Porath A, et al. Nosocomial multi-drug resistant *Acinetobacter baumannii* bloodstream infection: risk factors and outcome with ampicillin-sulbactam treatment. J Hosp Infect 2003;54:32–8. https://doi.org/10.1016/s0195-6701(03)00046-x.
[60] Szilágyi E, Füzi M, Böröcz K, Kurcz A, Tóth A, Nagy K. Risk factors and outcomes for bloodstream infections with extended-spectrum beta -lactamase-producing *Klebsiella pneumoniae*; Findings of the nosocomial surveillance system in Hungary. Acta Microbiol Immunol Hung 2009;56:251–62. https://doi.org/10.1556/AMicr.56.2009.3.5.
[61] Thompson DS, Workman R, Strutt M. Contribution of acquired meticillin-resistant *Staphylococcus aureus* bacteraemia to overall mortality in a general intensive care unit. J Hosp Infect 2008;70:223–7. https://doi.org/10.1016/j.jhin.2008.07.004.
[62] Trecarichi EM, Giuliano G, Cattaneo C, Ballanti S, Criscuolo M, Candoni A, et al. Bloodstream infections caused by *Escherichia coli* in onco-haematological patients: risk factors and mortality in an Italian prospective survey. PLOS ONE 2019;14:e0224465. https://doi.org/10.1371/journal.pone.0224465.
[63] Trecarichi EM, Pagano L, Martino B, Candoni A, Di Blasi R, Nadali G, et al. Bloodstream infections caused by *Klebsiella pneumoniae* in onco-hematological patients: clinical impact of carbapenem resistance in a multicentre prospective survey. Am J Hematol 2016;91:1076–81. https://doi.org/10.1002/ajh.24489.
[64] Vergis EN, Hayden MK, Chow JW, Snydman DR, Zervos MJ, Linden PK, et al. Determinants of vancomycin resistance and mortality rates in enterococcal bacteremia. A prospective multicenter study. Ann Intern Med 2001;135:484–92. https://doi.org/10.7326/0003-4819-135-7-200110020-00007.
[65] Weber S, Hogardt M, Reinheimer C, Wichelhaus TA, Kempf VAJ, Kessel J, et al. Bloodstream infections with vancomycin-resistant enterococci are associated with a decreased survival in patients with hematological diseases. Ann Hematol 2019;98:763–73. https://doi.org/10.1007/s00277-019-03607-z.
[66] Woudt SHS, de Greeff SC, Schoffelen AF, Vlek ALM, Bonten MJM. Antibiotic resistance and the risk of recurrent bacteremia. Clin Infect Dis 2018;66:1651–7. https://doi.org/10.1093/cid/cix1076.
[67] Wyllie DH, Crook DW, Peto TE. Mortality after *Staphylococcus aureus* bacteraemia in two hospitals in Oxfordshire, 1997-2003: cohort study. BMJ 2006;333:281. https://doi.org/10.1136/bmj.38834.421713.2F.

Please cite this article as: Hassoun-Kheir N et al., A systematic review on the excess health risk of antibiotic-resistant bloodstream infections for six key pathogens in Europe, Clinical Microbiology and Infection, https://doi.org/10.1016/j.cmi.2023.09.001

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[68] Butler AM, Olsen MA, Merz LR, Guth RM, Woeltje KF, Camins BC, et al. Attributable costs of enterococcal bloodstream infections in a nonsurgical hospital cohort. Infect Control Hosp Epidemiol 2010;31:28–35. https://doi.org/10.1086/649020.

[69] Lee XJ, Stewardson AJ, Worth LJ, Graves N, Wozniak TM. Attributable length of stay, mortality risk, and costs of bacterial health care-associated infections in Australia: a retrospective case-cohort study. Clin Infect Dis 2021;72:e506–14. https://doi.org/10.1093/cid/ciaa1228.

[70] Stewardson AJ, Allignol A, Beyersmann J, Graves N, Schumacher M, Meyer R, et al. The health and economic burden of bloodstream infections caused by antimicrobial-susceptible and non-susceptible *Enterobacteriaceae* and *Staphylococcus aureus* in European hospitals, 2010 and 2011: a multicentre retrospective cohort study. Euro Surveill 2016;21:30319. https://doi.org/10.2807/1560-7917.Es.2016.21.33.30319.

[71] Vydra J, Shanley RM, George I, Ustun C, Smith AR, Weisdorf DJ, et al. Enterococcal bacteremia is associated with increased risk of mortality in recipients of allogeneic hematopoietic stem cell transplantation. Clin Infect Dis 2012;55:764–70. https://doi.org/10.1093/cid/cis550.

[72] Balkhair A, Al-Muharrmi Z, Al'Adawi B, Al Busaidi I, Taher HB, Al-Siyabi T, et al. Prevalence and 30-day all-cause mortality of carbapenem-and colistin-resistant bacteraemia caused by *Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*: description of a decade-long trend. Int J Infect Dis 2019;85:10–5. https://doi.org/10.1016/j.ijid.2019.05.004.

[73] Tom S, Galbraith JC, Valiquette L, Jacobsson G, Collignon P, Schønheyder HC, et al. Case fatality ratio and mortality rate trends of community-onset *Staphylococcus aureus* bacteraemia. Clin Microbiol Infect 2014;20:O630–2. https://doi.org/10.1111/1469-0691.12564.

[74] Romero-Vivas J, Rubio M, Fernandez C, Picazo JJ. Mortality associated with nosocomial bacteremia due to methicillin-resistant *Staphylococcus aureus*. Clin Infect Dis 1995;21:1417–23. https://doi.org/10.1093/clinids/21.6.1417.

[75] de Kraker MEA, Lipsitch M. Burden of antimicrobial resistance: compared to what? Epidemiol Rev 2022;43:53–64. https://doi.org/10.1093/epirev/mxab001.

[76] Hansen S, Schwab F, Zingg W, Gastmeier P. PROHIBIT study group. Process and outcome indicators for infection control and prevention in European acute care hospitals in 2011 to 2012 – results of the PROHIBIT study. Euro Surveill 2018;23:1700513. https://doi.org/10.2807/1560-7917.Es.2018.23.21.1700513.

Please cite this article as: Hassoun-Kheir N et al., A systematic review on the excess health risk of antibiotic-resistant bloodstream infections for six key pathogens in Europe, Clinical Microbiology and Infection, https://doi.org/10.1016/j.cmi.2023.09.001