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The prevalence and risk of mortality associated with antimicrobial resistance within nosocomial settings—a global systematic review and meta-analysis of over 20,000 patients

The prevalence and risk of mortality associated with antimicrobial resistance within nosocomial settings—a global systematic review and meta-analysis of over 20,000 patients

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Summary

Background Bacterial antimicrobial resistance (AMR) is a leading cause of death globally. However, there has been no data synthesis on whether it influences mortality within hospital settings. We conducted a systematic review and meta-analysis to quantify the prevalence and risk of mortality associated in hospitalised patients with AMR, compared to patients with infections not classified as AMR.

Methods Databases (MEDLINE, EMBASE, and Cochrane library) were searched from inception up to 14th April 2025 for studies that reported the prevalence of AMR in patients who acquired infections in hospitals and mortality (PROSPERO CRD42023420609). We calculated pooled prevalence estimates of AMR as well as unadjusted and adjusted estimates of the effect of AMR on mortality using a random-effects model. Study quality was assessed using the Joanna Briggs Quality Appraisal Tool, risk of bias using DOI plots and LFK index and certainty of evidence of mortality using GRADE criteria.

Findings We identified 34 studies (20,658 patients with resistant organisms) from 18 countries–namely the USA, China, the UK, Canada, Israel, Japan, Malaysia, Korea, Brazil, and Singapore. Of these, 33 were observational studies whilst two studies (one observational study and one purely modelling study) mechanistically modelled risk of mortality in relation to transmission. No studies were conducted in the African subcontinent, the Middle-East, Russia, and India. The prevalence of AMR was high in patients in hospital (pooled prevalence: 36.5%, 95% CI: 29%–44%, I^2 = 99%) and associated with higher mortality (unadjusted pooled risk ratio [RR]: 1.64, 95% CI: 1.37–1.97, I^2 = 96.22%, τ^2 = 0.20; adjusted pooled RR: 1.58, 95% CI: 1.33–1.87, I^2 = 85.9%, τ^2 = 0.13) compared to non-AMR organisms.
Sensitivity analyses showed particularly elevated risks for in-hospital mortality and for AMR-associated bacteraemia. Study quality was generally rated to be high, but there was evidence of publication bias in estimates of both prevalence and mortality. Overall certainty of evidence of mortality was graded to be low.

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Interpretation AMR is highly prevalent within hospital settings globally and associated with increased in-hospital mortality. Crucially, no data was identified from the India subcontinent, African subcontinent, the Middle East, and Russia, and only two studies used mechanistic modelling to explore how transmission of AMR affects mortality. Further research is required, particularly in underrepresented regions to inform interventions aimed at reducing both AMR transmission and its related mortality within hospital settings.

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Keywords: Antimicrobial resistance; Bacterial; Mortality; Global; Modelling studies

Research in context

Evidence before this study

Bacterial antimicrobial resistance (AMR) has been projected to cause up to 10 million deaths annually by 2050. Existing evidence links AMR to increased mortality in community settings, however the mechanisms underlying this association remain incompletely understood. In hospital settings, it is unclear whether AMR confers direct prognostic significance for patients.

Added value of this study

This systematic review and meta-analysis pools evidence to compare the impact of AMR and no AMR organisms on mortality in hospitalised patients who are infected with resistant organisms. Our study suggests that there is a high prevalence of AMR within hospital settings, with over one-third of culture-positive organisms classified as resistant. Compared to infections without AMR, AMR infections were associated with a higher risk of mortality (adjusted pooled RR: 1.58, 95% CI: 1.33–1.87, I^2 = 85.9%, τ^2 = 0.13); a trend that persisted in sensitivity analyses assessing mortality within the same hospital admission with a diagnosis of AMR. We also found no studies that examined the risk of mortality among hospitalised patients in the Indian subcontinent, African subcontinent, the Middle East, and Russia.

Implications of all the available evidence

AMR is prevalent within hospital environments across the world and associated with increased in-hospital mortality. In addition to the substantial public health implications regarding transmission and diminishing treatment options, AMR exerts an acute negative impact on patient outcomes. Robust interventions are urgently required to mitigate both the immediate and long-term consequences of AMR.

Introduction

Bacterial antimicrobial resistance (AMR) is a leading cause of death globally.[1] The prevalence of AMR is rising[2] and has been exacerbated by the COVID-19 pandemic.[3–5] A review on antimicrobial resistance commissioned by the UK Government in 2014 projected that AMR could cause 10 million deaths per year by 2050.[6]

AMR is of particular importance within nosocomial settings.[7] Hospitals represent high-risk environments for acquisition of AMR, due to their substantial numbers of patients with various bacterial infections and heavy antibiotic use.[8,9] Additional factors, such as increased virulence of certain organisms,[10,11] decreased effectiveness of empirical antibiotic therapy,[12] increased antibiotic toxicity or improper dosing,[13,14] increased need for surgery,[15] recurrent hospitalisations,[16] and ageing population with comorbidities[17] may also affect clinical outcomes in these patients.

One recent study using statistical predictive models from a global systematic review estimated that 4.71 million deaths were associated with bacterial AMR, including 1.14 million deaths attributable to bacterial AMR in 2021.[18] However, these estimates were derived from community settings, leaving open the question of whether such deaths stemmed directly from resistant infections or indirectly from factors such as inadequate access to inappropriate antibiotics. Consequently, data regarding the clinical significance of mortality directly attributable to AMR in hospitalised patients—namely, the importance of AMR in contributing to mortality compared to having a similar, infection that is not classified to be AMR—remains unclear.

In this study, we synthesise global estimates of the prevalence of AMR in hospital-based studies and assess how AMR relates to mortality in hospitalised populations, compared to non-AMR infections. Our findings will help elucidate the acute impact of AMR on patient outcomes within these settings and inform priorities for public health intervention.

Methods

We conducted this review in accordance with the Preferred Reporting Items in Systematic Reviews and Meta-Analyses guidelines (PRISMA) and prospectively

registered our review on PROSPERO (CRD42023420609). Ethical approval and informed consent of participants were not required for this work as no new data was collected.

Data sources and searches

A comprehensive search strategy was developed by an academic librarian (PD). The databases MEDLINE, Embase, PROSPERO, and the Cochrane Library were searched from inception to April 14th 2025, for relevant articles (search strategies provided in Supplementary Materials 1).

Eligibility criteria

We included studies that reported original clinical data on patients hospitalised and tested positive for organisms that had AMR (for example, methicillin or vancomycin-resistant *Staphylococcus aureus* extended-spectrum β-lactamase producing *Enterobacteriaceae* or multi-drug-resistant bacteria). Eligible studies must compare mortality outcomes between drug-resistant and non-AMR infections (or colonisation) and report mortality data in both groups. We also included studies that incorporated mechanistic modelling of AMR in hospital settings, provided that they used original clinical data (e.g., to derive model parameters). This was to help understand whether existing transmission models of AMR considered the impact of transmission on acute mortality.

Studies were excluded if they were correspondence pieces, studies on tuberculosis, studies in children and neonates. We also excluded studies that included special populations, such as those who were immunocompromised, or studies which exclusively investigated one source of infection, or did not record mortality from AMR infections. These exclusions ensured that studies extracted were broadly representative of general hospital populations, while maintaining comparability for meta-analysis. This would also allow us to present a prevalence statistic that was representative of the proportion of culture positive infections in hospitals that were resistant, compared to classification as not resistant. We allowed studies of bacteraemia only if they investigated AMR and non-AMR infections to mortality.

The main exposure of interest was AMR (compared to patients with organism not classified to have AMR), as defined by the study. This was usually defined by resistance profiles as per the Clinical and Laboratory Standards Institute (CLSI) or European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria, however, if neither were used, the criteria or definition was obtained from the methodology and collated accordingly.

Study selection

Three reviewers (NG, DK, and LS) independently screened the titles, abstracts and full texts. DK and LS each screened 50% of the titles, abstracts, and full texts, while NG independently screened all records in full. Thus, each article was screened by two reviewers. Any disagreements were resolved by discussion with an adjudicator, DP, when necessary.

Data extraction

One reviewer (NG) completed 100% of data extraction from each eligible article, all of which were independently checked by additional reviewers (LS, DK, and DP). Disagreements were resolved with group discussion. EndNote and Rayyan software were used to manage references, deduplication, and for screening.[19,20] Data were extracted using a predesigned excel sheet and based on study design, study setting, country of study, carrier or infection state, type of infection with organism involved, standardised criteria for sensitivity and resistance and mortality reported.

Quality assessment

Quality assessment of the articles was divided between LS and DK, while NG independently assessed all 34 papers using the Joanna Briggs Institute Critical Appraisal (JBI) tools for observational studies. The tool consisted of an 11-point scale for cohort studies, a 10-point scale for case-controlled studies and an 8-point scale for cross-sectional studies. Each primary study was assigned two points if they satisfied the criteria used in the relevant tool; one if partially satisfied, and zero if not satisfied. Any disagreements were resolved through discussion with DP. Each article was independently evaluated by two different authors.

A quality appraisal score was calculated by using the numerator and denominator relevant for each study. The mechanistic modelling aspect of studies was not graded using any tools, but the mechanistic models and findings of the models are collated. Publication bias was assessed visually using DOI plots and formally with the LFK test for primary analyses including at least 10 studies substantiated with a trim-and-fill sensitivity analysis to explore the impact of this bias. We also used Egger's and Begg's test to assess publication bias.

GRADE criteria

We assessed overall certainty in the pooled adjusted estimates using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach for prognosis. For GRADE we focused on the pooled adjusted analyses relating to mortality, since collection of mortality was necessary within our inclusion criteria. The overall certainty estimates were categorised into one of four levels: high, moderate, low, very low. In keeping with GRADE guidance for prognostic studies, observational studies start as high certainty evidence.

Certainty was rated down based on the following criteria:

1. Risk of bias: rated down if most studies were moderate or high risk of bias.
2. Imprecision: rated down if confidence intervals were wide, relative to the clinical decision threshold (i.e., would the outcome differ depending on whether the upper or lower boundary of the confidence interval represented the truth).
3. Inconsistency: rated down if there was wide variation in point estimates for mortality, or if there was publication bias.
4. Indirectness: rated down if most studies did not provide definitions for AMR.

Statistical analysis

We first synthesised data on the prevalence of AMR in each study, as well as the risk of mortality in those with bacteria that had AMR and did not have AMR. Raw counts were used for unadjusted data to calculate risk ratio (RR) and 95% confidence intervals (Cis).

We then synthesised mortality data adjusted for key confounders as defined by the individual studies such as age, co-morbidities, gender, APACHE score etc.; this included extraction of adjusted risk ratios (RR). Adjusted OR were converted to adjusted RR using the conversion method as recommended by the Cochrane Handbook.[21] For mortality we extracted adjusted hazard ratios (HR) with 95% CI where possible and assumed adjusted RR to approximate an adjusted HR. For studies with adjusted RRs, we recorded the confounders that the study had adjusted for. For both adjusted and unadjusted comparisons, data were extracted for analyses which used patients' non-AMR bacterial organisms (classified to not have AMR) as the reference group.

We performed sensitivity analyses by study design, continent, hospital settings, site of infection, type of infection, and mortality (short term: up to 30 days, long term: 30–90 days, and in-hospital mortality); this was only performed if an intended sensitivity analysis had five or more studies. We also conducted a leave-one-out analysis to demonstrate the robustness in our study findings.

For all outcomes and data types, we synthesised data (prevalence, unadjusted RR and adjusted RR/HR) using the DerSimonian and Laird random-effects model. I^2 was used to assess heterogeneity. All meta-analysis were conducted using STATA version 17.[22] We used the statistical packages *metan* and *meta* in STATA to generate forest plots and pooled estimates. p values < 0.05 were considered to be statistically significant. The data and the analysis code can be released upon reasonable request.

Role of funding sources

The funders had no role in the study design, data collection and analysis, decision to publish or preparation of the manuscript. All authors had access to the data and critically reviewed and approved the manuscript as submitted.

Results

Study selection

We identified a total of 2630 articles in the database search of published literature, as shown in Fig. 1. After removal of 52 duplicate records, we screened 2578 titles were screened for eligibility, after which 2336 were excluded. We then screened abstracts in the remaining 242 articles; 166 were excluded, leaving 76 articles for full text assessment. We subsequently excluded another 42 articles after full text assessment, leaving 34 articles (33 observational studies, of which one includes a mathematical model and another mathematical modelling study with original clinical data). These articles included a total of 39,282 patients among whom 20,658 patients grew an organism in sample cultures which was used for data extraction and analysis.

Characteristics of included studies

Characteristics of 33 observational studies are shown in Table 1.[23–40,41–56] All were conducted before the COVID-19 pandemic. The geographical distribution of these studies is shown in Fig. 2. Many studies were conducted in China, the United States, Canada, Brazil, and Europe. We identified no studies from Russia, the African subcontinent, the Indian subcontinent or the Middle-East, despite these regions being recognised for high rates of community AMR. Of the observational studies 24 were cohort studies,[23–27,29,30,33,34,36–38,40,41,43–46,48,50,51,53–55] and 9 were case-control.[28,31,32,35,42,47,49,52,56] Three studies focused exclusively on AMR in patients managed in general hospital wards,[33,47,55] 7 studies examined patients from intensive care units (ICU)[23,25,38,40,46,50,54] and the remaining 23[24,26–32,34–37,41–45,48,49,51–53,56] studies included patients from both wards and ICUs. All studies recruited patients from acute care hospitals, although one study[54] also included community hospitals. 23 reported in-hospital mortality, 4 recorded short-term mortality (<30 days), and 6 had long term mortality (30–90 days). None of the included studies reported the interval from hospital admission to obtaining a positive blood culture result. Overall, the studies were rated as high quality. Details of the quality assessment are shown within our Supplementary Materials.

Two of the included studies[39,53] incorporated mathematical modelling within their analysis, as shown in Table 2; one study was a cohort study[53] of MRSA that used hazard ratios generated from original clinical data, within a multistate model with seven states that intrinsically incorporated the acquisition (or no acquisition) of hospital acquired MRSA and MSS. The other, published in 1989,[39] did not describe in detail the characteristics of the data they used, but instead, focused on the mathematical modelling that described the relation between antibiotic use and propagation of

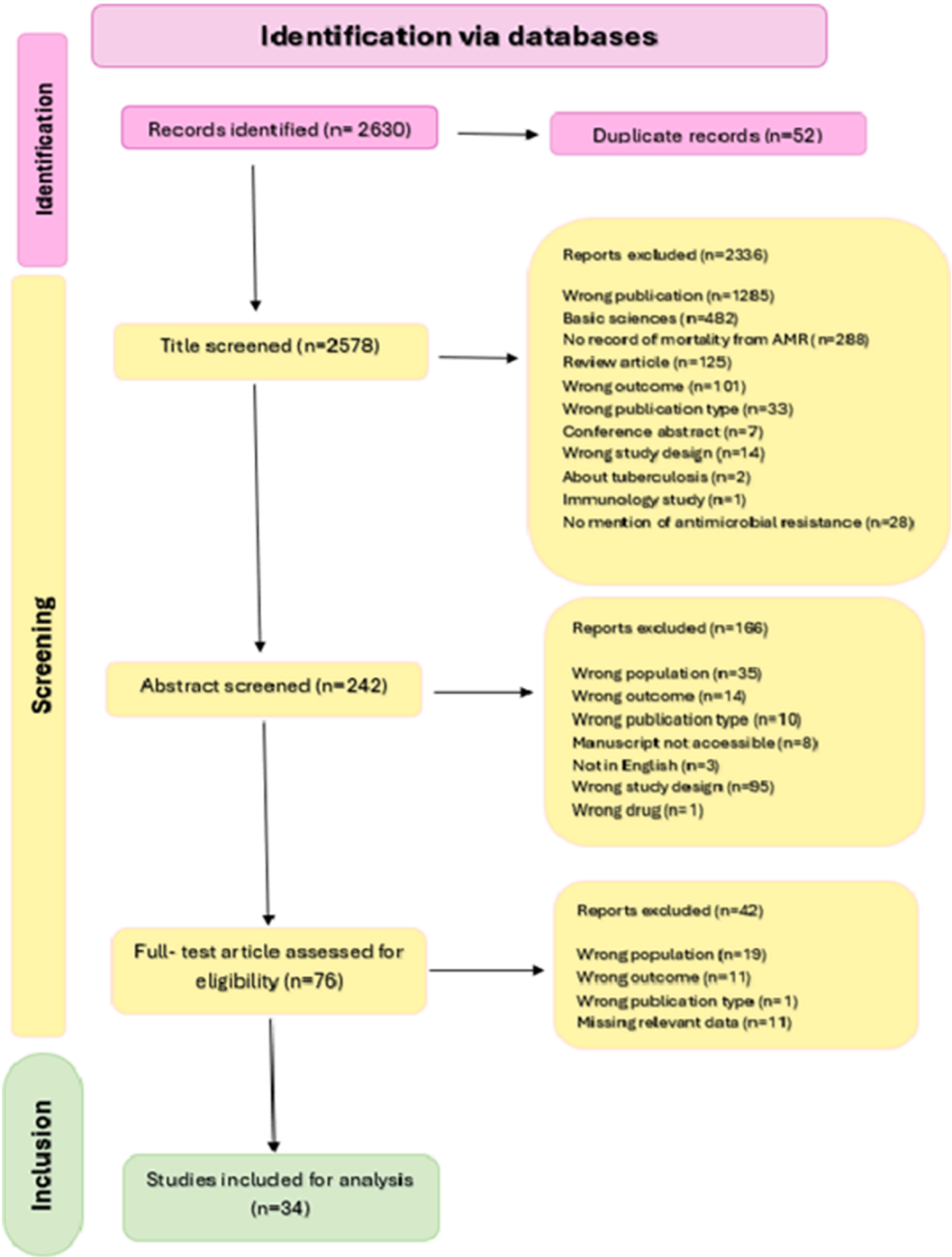

Fig. 1: PRISMA flowchart of studies identified for analysis.

antibiotic resistant hospital acquired gram-negative infections. The modelling studies were synthesised narratively due to a lack of research available and were not included in the meta-analysis and neither modelling studies identified AMR as an important associate of mortality and neither modelling studies identified AMR as an important associate of mortality.

Definitions of AMR used across the studies are summarised in Table 3. Variation in AMR definitions was substantial. Two studies had no description of how AMR was defined; 12 studies made non-specific reference to guidelines (CLSI, ESCMID, and Global Burden of Diseases studies); four studies used the standardised international definition[57]: microorganisms resistant to

Study	Country	Study design	Setting	Date published	Population description	Criteria for positive culture	Time from admission to positive culture	Population size (N)	Organism	Site of Infection	Factors adjusted for when examining mortality	Mortality definitions	Study score (%)
Al-Sunaidar	Malaysia	Cohort	ICU	2022	Tertiary hospital	Positive culture after admission to ICU but before antibiotics	Not specified	228	Combination of organisms	Various sites	Age; gender; ethnicity; time and type of surgery; infection site; MDRO; GCS on day 1	In hospital death	100
Bar	US	Cohort	Ward + ICU	2006	Tertiary hospital	Positive culture retrospectively with mono-organism (enterococcus BSI)	Not specified	50	Enterococci	Various sites	Age; gender; LOS; ICU stay; Antibiotics use; CVC line; vancomycin resistance; TPN; IMV; Comorbidities	7 day mortality	100
Blanco	US	Cohort	ICU	2018	Tertiary hospital	Positive blood culture taken retrospectively with time to ICU admission	Not specified	7925	*A. baumannii*	Bacteraemia	Age; Comorbidities; Antibiotics use	In-hospital death	79
Cao	China	Cohort	Ward + ICU	2004	Tertiary hospital	Inpatient positive cultures identified retrospectively	Not specified	112	*P. aeroginosa*	Various sites	Age; gender; ICU admission; comorbidities; APACHE II score; IMV; Antibiotic use; resistance; infection with multiple organisms	In-hospital death	100
Esterly	US	Cohort	Ward + ICU	2011	Tertiary hospital	Patients with one positive blood culture identified retrospectively which also included those who have been on treatment for more than 2 days	Not specified	79	*A. baumannii*	Bacteraemia	N/A	In-hospital death	100
Fortun	Spain	Case-control	Ward + ICU	2002	Tertiary hospital	Patients with positive blood cultures identified retrospectively	Not specified	49	Enterococci (*E. faecium*)	Bacteraemia	Age; APACHE II score; parenteral nutrition; urinary catheter; comorbidities; AREF bacteraemia	In-hospital death	100
Gasink	US	Cohort	Ward + ICU	2006	Tertiary hospital	Patients with positive blood cultures identified retrospectively; new event if positive blood culture after 30 days of admission	Not specified	847	*P. aeroginosa*	Various sites	N/A	In-hospital death	86
Guillamet	US	Cohort	Ward + ICU	2016	Tertiary hospital	Patients with radiological diagnosis of pneumonia with a positive blood culture identified retrospectively	Not specified	1031	Combination of organisms	Pneumonia	*P. aeroginosa* bacteraemia; Antibiotics use; immunosuppression; Septic shock	In-hospital death	100
Harthug	Norway	Case-control	Ward + ICU	2000	Tertiary hospital	Patients with positive culture identified prospectively which was matched with a control patient	Not specified	246	Enterococci	N/A	N/A	In-hospital death	83
Hattori	Japan	Cohort	Ward + ICU	2018	Tertiary hospital	Patients with positive blood cultures identified retrospectively with HAI classified as positive blood culture within two days of admission. CAI were all other samples	Not specified	2105	Combination of organisms	Bacteraemia	Age; hospital acquired infection; SOFA score; comorbidities; BSI secondary to certain organisms; surgery before and after BSI; MDR pathogens; type of infection	30 day mortality	100

(Table 1 continues on next page)

Study	Country	Study design	Setting	Date published	Population description	Criteria for positive culture	Time from admission to positive culture	Population size (N)	Organism	Site of Infection	Factors adjusted for when examining mortality	Mortality definitions	Study score (%)
(Continued from previous page)													
Hautemaniere	France	Cohort	Ward	2009	Tertiary hospital	Prospectively identified with positive rectal swabs during their hospital stay, those that were positive at admission were excluded	Not specified	226	Enterococci	Colonisation of various sites	GRE status; Comorbidities	In-hospital death	100
Jamulitrat	Thailand	Cohort	Ward + ICU	2009	Tertiary hospital	Patients with positive blood cultures was identified retrospectively	Not specified	198	*A. baumannii*	Various sites	N/A	In-hospital death	92
Jia	China	Case-control	Ward + ICU	2015	Tertiary hospital	Patients who were admitted for more than 48 h with positive blood culture was identified retrospectively	Not specified	88	Enterococci	Various sites	Age; gender; colonisation; invasive procedure 4 weeks prior; Antibiotics use 3 months; Comorbidities; surgical unit admission	In-hospital death	100
Kim	Korea	Cohort	Ward + ICU	2012	Tertiary hospital	Patients with positive blood cultures were identified retrospectively	Not specified	102	Combination of organisms	Various sites	MDR bacteria; hospital acquired infection; Antibiotic use; ICU; Platelets; Neutrophils	28 day mortality	79
Kritsotakis	Greece	Cohort	Ward + ICU	2017	Tertiary hospital	Patients with positive cultures identified prospectively in the acute care ward. Same day discharge were excluded	Not specified	8247	Combination of organisms	Various sites	N/A	30 day mortality	93
Lambert	Europe	Cohort	ICU	2011	Tertiary hospital	Patients with positive cultures 2 days after admission into ICU were identified prospectively	Not specified	4986	Combination of organisms	Pneumonia	Age; gender; SAPS score II; type of admission; days with CVC and intubation; Antibiotics use; trauma; impaired immunity	In-hospital death	93
Levin	Israel and Canada	Cohort	ICU	2010	Tertiary hospital	Patients with positive cultures 2 days after admission into ICU were identified prospectively	Not specified	423	Combination of organisms	Various sites	N/A	N/A	86
MacKinnon	Canada	Cohort	Ward + ICU	2021	Tertiary hospital	Patients with positive blood cultures either within 48 h of admission or 48 h before discharge identified prospectively	Not specified	1080	*E. coli*	Bacteraemia	Age; Comorbidities; site of infection; setting of onset	30 day mortality	100
Meng	China	Case-control	Ward + ICU	2017	Tertiary hospital	Patients with positive cultures identified retrospectively after 48 h of admission	Not specified	147	*E. coli*	Various sites	N/A	In-hospital death	92
Pena	Spain	Cohort	Ward + ICU	2008	Tertiary hospital	Patients with positive blood cultures identified retrospectively	Not specified	200	*E. coli*	Various sites	N/A	30 day mortality	79
Persoon	Netherlands	Cohort	Ward + ICU	2020	Tertiary hospital	Patients with positive blood cultures identified retrospectively	Not specified	249	*P. aeroginosa*	Bacteraemia	Age; Gender; Antibiotic use; ICU; resistant strain; hospital acquisition	28 day mortality	100

(Table 1 continues on next page)

Study	Country	Study design	Setting	Date published	Population description	Criteria for positive culture	Time from admission to positive culture	Population size (N)	Organism	Site of Infection	Factors adjusted for when examining mortality	Mortality definitions	Study score (%)
(Continued from previous page)													
Podha	Thailand	Cohort	Ward + ICU	2019	Tertiary hospital	Patients with positive cultures after 2 days of admission identified retrospectively	Not specified	523	Combination of organisms	Various sites	Gender; Admitted ward; Comorbidities; type of organism; resistant pathogen; site of infection number of hospital episodes	In-hospital death	93
Quillici	Brazil	Cohort	ICU	2020	Tertiary hospital	Patients admitted for more than 48 h with positive blood cultures identified retrospectively	Not specified	270	*Enterobacteriaceae*	Bacteraemia	Age; Co-morbidities; Admission unit; Septic shock; IMV; MDR pathogen; haemodialysis	30 day mortality	93
Sakka	Greece	Case-control	Ward	2008	Tertiary hospital	Patients with positive rectal swabs were identified prospectively where 3 samples were taken over 5 days	Not specified	159	Enterococci	Colonisation of various sites	Age; Malignancy; Co-morbidities; longer hospitalisation; invasive device in-situ; prolonged antibiotics use; VRE colonisation	In-hospital death	100
Schwaber	Israel	Case-control	Ward + ICU	2008	Tertiary hospital	Patients with positive cultures identified retrospectively	Not specified	104	*K. pneumoniae*	Various sites	Gender; comorbidities; poor functional status; CVC line; Urinary catheter; ICU stay; IMV use; Antibiotic use; isolation of resistant organism	In-hospital death	100
Shi	China	Cohort	Ward + ICU	2022	Tertiary hospital	Patients admitted for more than 24 h with positive blood cultures that were identified retrospectively	Not specified	1018	Combination of organisms	Bacteraemia	Age; Co-morbidities; CVC line; MDR strain; NF bacteria; use of carbapenams and tigecycline; use of catheter (urinary)	In-hospital death	93
Shilo	Israel	Case-control	Ward + ICU	2013	Tertiary hospital	Patients with positive cultures identified retrospectively	Not specified	262	*K. pneumoniae*	Bacteraemia	N/A	In-hospital death	86
Tabah	Global	Cohort	ICU	2012	Tertiary hospital	Patients with positive blood cultures identified prospectively	Not specified	1156	Combination of organisms	Various sites	Age; gender; comorbidities; SOFA score; organism resistance; antibiotic use; source of infection	28 day mortality	100
Teo	Singapore	Cohort	Ward + ICU	2012	Tertiary hospital	Patients with positive cultures identified retrospectively	Not specified	58	*Enterobacteriaceae*	Various sites	Age; gender; comorbidities; APACHEII score; previous hospital admission; ICU stay; immunosuppression use; Antibiotic use; ERE infection	In-hospital death	100
Wang	China	Case-control	Ward + ICU	2018	Tertiary hospital	Patients admitted for 48 h with positive cultures were identified retrospectively	Not specified	96	*K. pneumoniae*	Various sites	Age; gender; Co-morbidities; ICU stay; Antibiotic use; site of infection; Steroid use; previous surgery; 6 month re-admission	In-hospital death	100

(Table 1 continues on next page)

Study	Country	Study design	Setting	Date published	Population description	Criteria for positive culture	Time from admission to positive culture	Population size (N)	Organism	Site of Infection	Factors adjusted for when examining mortality	Mortality definitions	Study score (%)
(Continued from previous page)													
Wolkewitz	UK	Cohort	Ward + ICU	2011	Tertiary hospital	Patients who were admitted for more than 48 h with positive blood culture was identified retrospectively	Not specified	3132	*S. aureus*	Bacteraemia	Age; gender; comorbidities; hospitalisation	90 day mortality	93
Zahar	France	Cohort	ICU	2011	Tertiary hospital and community hospital	Positive cultures identified prospectively, before 48 h classified as community acquired and more than 48 h as hospital acquired	Not specified	3588	Combination of organisms	Various sites	Severity of infection; comorbidities; Antibiotic use	In-hospital death	100
Zavascki	South Brazil	Cohort	Ward	2006	Tertiary hospital	Patients with positive cultures identified prospectively	Not specified	298	*P. aeroginosa*	Bacteraemia	MBL production; Age; Charlson score; Severe sepsis; Antibiotic use	In-hospital death	93

Table 1: Summary of manuscripts analysed.

at least one antimicrobial agent in three or more different antimicrobial categories; and the remaining described definition of AMR in more detail, including methods, equipment and thresholds of resistance and interpretation used specific to the microorganism.

Pooled prevalence

Altogether, we found a total of 20,658 patients (53% of patients included in studies) had reported antimicrobial sensitivities. Fig. 3a shows the pooled prevalence of AMR within these patients. Overall pooled prevalence was 36.5% (95% CI: 29.1%–44.2%, $I^2 = 99\%$); but varied widely across different studies. Sensitivity analyses revealed no statistical differences in pooled AMR prevalence by study design (cohort vs case-control), infection site (bacteraemia vs mixed sites), treatment setting (ICU only vs all settings), or continent of study (Asia, Europe, North America) as shown in Fig. 3b.

Mortality

Fig. 4a shows adjusted and unadjusted relative risk of mortality across all studies, and the overall mortality estimate, within both adjusted and unadjusted analyses. Overall, we found that AMR was associated with an increased risk of mortality, compared to having non-AMR infections (pooled unadjusted RR: 1.64, 95% CI: 1.37–1.97, $I^2 = 96.22\%$, $\tau^2 = 0.20$, vs pooled adjusted RR: 1.58, 95% CI: 1.33–1.87, $I^2 = 85.9\%$, $\tau^2 = 0.13$). Most studies found an increased risk of mortality.

Fig. 4b shows overall adjusted and unadjusted mortality estimates in the sensitivity analyses, separated by study design, different definitions of mortality (death within hospital and death after 30 days), site of infection, settings of care and continent. Estimates of mortality was higher in AMR compared to non-AMR infections in both case-control and cohort designs (adjusted RR in case control: 1.66, 95% CI: 1.01–2.72; and cohort: 1.57, 95% CI: 1.33–1.86) as well as in studies of death within the same hospital admission as when the AMR was detected (adjusted RR: 1.71, 95% CI: 1.40–2.07). Furthermore, mortality was higher in studies of bacteraemia only (adjusted RR: 1.37, 95% CI: 1.20–1.55), as well as intensive care settings, and across studies conducted in Asia, Europe and North America. The heterogeneity between studies was particularly low in sensitivity analyses involving studies of bacteraemia, and studies conducted in Europe and North America.

Supplementary Materials 2 shows a leave-one-out sensitivity analysis to assess the robustness of the pooled estimate. The analysis demonstrated that the exclusion of any one study did not substantially alter the overall effect size, with the pooled estimates ranging narrowly between 1.29 and 1.33. All iterations remained statistically significant, reiterating the association between AMR and increased mortality in hospitalised patients.

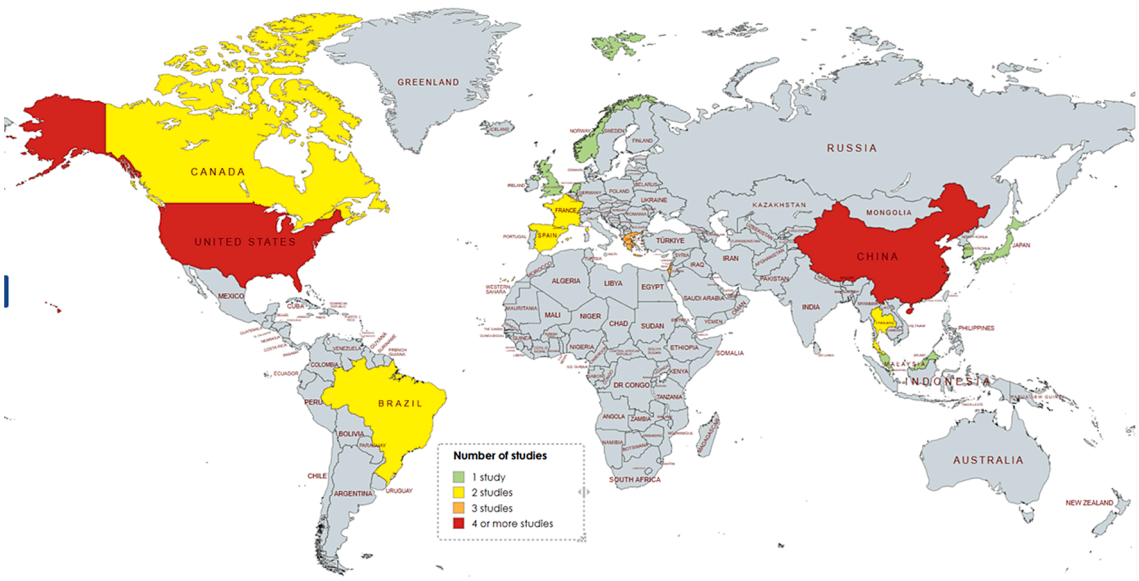

Fig. 2: World map demonstrating where studies analysed were conducted.

Risk of bias assessment

For prevalence estimates of AMR, there was clear asymmetry in DOI plots and LFK index (8.42), indicating publication bias in the main analysis along with a trim-and-fill analysis (as shown in Supplementary Materials 3). As precision increases, for most studies the standardised estimate starts decreasing (after a precision estimate of 0) and the Z-score increases. The trim-and-fill sensitivity analysis suggested the presence of four potentially missing studies indicative of small or non-significant studies that may not have been published. The pooled effect size from the observed data was 0.776 (95% CI: 0.766–0.786), while the adjusted effect size after imputing the missing studies was slightly reduced to 0.758 (95% CI: 0.749–0.768). Despite this adjustment, the overall effect remained statistically significant, suggesting that AMR is consistently associated with increased mortality in hospitalised patients and supports the robustness of the findings. For estimates of mortality, there was also evidence of publication bias within the main analysis as shown by asymmetry from the funnel plot with an Egger's test p value result for 0.003. In contrast, Begg's rank correlation test did not identify significant bias (p value: 0.411), which likely is attributable to the lower statistical power of Begg's test in meta-analyses with a limited number of studies.

Manuscript author	Publication date	Main study aim	Mechanistic model used	Main finding
Garber	1989	To investigate the relation between antibiotic use and the propagation of antibiotic-resistant hospital-acquired infections due to gram-negative bacteria in hospitalised patients.	The model incorporates the effects of an individual's antibiotic use and other characteristics, as well as the effects of total antibiotic use in a population on the risk of acquiring bacterial infection in hospital. Patients are assumed to move from one health infection state to another with a daily probability that is a logistic function of several explanatory variables; the underlying stochastic process is assumed to have first-order Markov property, conditional on the set of explanatory variables.	AMR was not significantly associated with mortality; but there were strong associations between hospital outcomes and age, underlying disease and antibiotic consumption, with those receiving more antibiotics generally less likely to die.
Wolkewitz	2011	To study the impact of in-hospital bacteraemia caused by MRSA compared to MSSA, on mortality within 90 days after admission.	A multistate model with seven states were used; where patients were assumed to go from hospital admission to death, with acquisition (or no acquisition) of hospital acquired MSSA/MRSA, followed by discharge or remaining in hospital, as key mediators. Hazard ratios for each state were obtained using various Cox regression models.	Length of stay affected the study of bacteraemia caused by *S. aureus* in hospital; infected patients had already stayed a few days in hospital before the infection occurred, and once they were infected, hospital stays were considerably increased. Mortality differences secondary to MRSA or MSSA were not statistically significant.

Table 2: **Summary of manuscripts that employed mechanistic modelling.**

Authors	Organisms investigated	Definitions of resistance
Al-Sunaider et al. Blanco et al. Podha et al. Quillici et al.	Combination of organisms *A. baumanii* Combination of organisms Gram negative bacilli	Microorganisms resistant to at least one antimicrobial agent in three or more different antimicrobial categories
Guillamet et al. Hattori et al. Meng et al. Pena et al. Schwaber et al. Cao et al. Gasink et al. Esterly et al. Wang et al. Zavascki et al.	Combination of organisms Combination of organisms *E. coli* *E. coli* *K. pneumoniae* *P. aeruginosa* *P. aeruginosa* *A. baumanii* *K. pneumoniae* *P. aeruginosa*	Disk diffusion method according to guidelines established by CLSI
Bar et al.	*Enterococcus* spp.	Minimum inhibitory concentrations using E-test. Vancomycin resistance defined as an MIC $\geq$32 µg/mL
Fortun et al. Hautemaniere et al. Sakka et al.	*Enterococcus* spp. *Enterococcus* spp. *Enterococcus* spp.	Agar dilution method according to NCCLS guidelines. Ampicillin resistance defined as MICs > 16 mg/L. *E. faecium* isolates with glycopeptide resistance were examined for the presence of resistance genes using PCR. Isolates with vancomycin MICs of 4–16 mg/L were classified as intermediate; $\geq$32 mg/L as VRE
Harthug et al.	*Enterococcus faecium*	Agar diffusion method, using paper discs and PDM antibiotic sensitivity medium. Ampicillin resistance and vancomycin resistance according to recommendations by The Norwegian Working Group on Antibiotics. Gentamicin resistance examined by E-test. MIC of ampicillin, vancomycin, and teicoplanin were determined by E-test. Isolates with vancomycin MIC > 2 mg/L were analysed for the presence of *vanA*, *vanB*, and *vanC* resistance genes by PCR
Jamulitrat et al. Kritsotakis et al.	*A. baumanii* Combination of organism	*In-vitro* resistance or intermediately susceptible to an antibiotic Assessed based on antibiotic susceptibility data
Jia et al.	*Enterococcus* spp.	In-vitro susceptibilities were identified using VITEK Compact AST-GP67 card; all non-susceptible results for Linezolid were confirmed manually by standard broth microdilution method as per CLSI; Enterococcal isolates with linezolid MIC >4 µg/mL were classified as nonsusceptible
Kim et al.	Combination of organisms	Undefined; used definition from global burden of disease study
Lambert et al.	Combination of organisms	*A. baumannii* Resistance to Ceftazidime *P. aeruginosa* Resistance to Ceftazidime *E. coli* Resistance to third-generation cephalosporin *MRSA* Resistance to Oxacillin For other gram-negative organisms, intermediately sensitive strains were reported as resistant
Levin et al.	Combination of organisms	Resistance to any one or more of the following: Third-generation cephalosporins (Ceftazidime only for *P. aeruginosa*) Fluoroquinolones Carbapenem antibiotics
MacKinnon et al.	*E. coli*	Resistance to third-generation cephalosporins. National study in Canada; breakpoint used in Calgary, Sherbrooke, and the Western interior used CLSI; Canberra, Finland, and Skaraborg used EUCAST guidelines. Antimicrobial susceptibility test was broth microdilution for all regions apart from Skaraborg, which used disk diffusion
Persoon et al.	*P. aeruginosa*	PCR for detection of *bla* gene in all isolates with MIC $\geq$8 mg/L or disk diffusion <17 mm for imipenem and MIC > 2 mg/L for tobramycin, or for isolates with intermediate or resistant susceptibility results for imipenem in combination with a highly resistant microorganism profile (resistance in three or more of the following: aminoglycosides, fluoroquinolones, ceftazidime, piperacillin, carbapenems), as per the Dutch Working Party on Infection Prevention. Antibiotic susceptibility was performed on VITEK2. Antibiotic susceptibility interpreted using EUCAST criteria
Shi et al.	Combination of organisms	MDR defined according to European Centre for Disease Prevention and Control criteria; *Enterobacteriales* and non-fermenting bacterial isolates resistant to ceftazidime or cefotaxime were considered ESBL producers. Carbapenem-resistant strains were defined as isolates intermediate resistant to one or more carbapenems using the CLSI breakpoints; but not all isolates were tested against all carbapenems
Tabah et al.	Combination of organisms	MDR, XDR, and PDR according to ESCMID guidelines
Teo et al.	*Enterobactereaceae*	Antimicrobial susceptibility testing was performed with VITEK2; carbapenem MIC confirmed with E-test according to EUCAST breakpoints. Presence of carbapenemase production also investigated phenotypically using diagnostic meropenem tablets of the KPC/Metallo-β-lactamase confirmation kit. Characterisation of β-lactamase genes was performed by PCR assays targeting serine carbapenemases and OXA-type carbapenemases
Wolkewitz et al. Zahar et al.	*S. aureus* Combination of organisms	No description of how MRSA was defined No description of AMR definition

Table 3: **Definitions of antimicrobial resistance used in manuscripts.**

GRADE assessment

Within our main analysis of pooled adjusted risk estimates for mortality, we found risk of bias to be serious; imprecision to be serious (adjusted confidence intervals of effect to be wide); inconsistency of results to be not serious and indirectness (definitions of AMR between studies) to also be serious. As such, our overall certainty of evidence for the effect of mortality from AMR compared to sensitive organisms to be low.

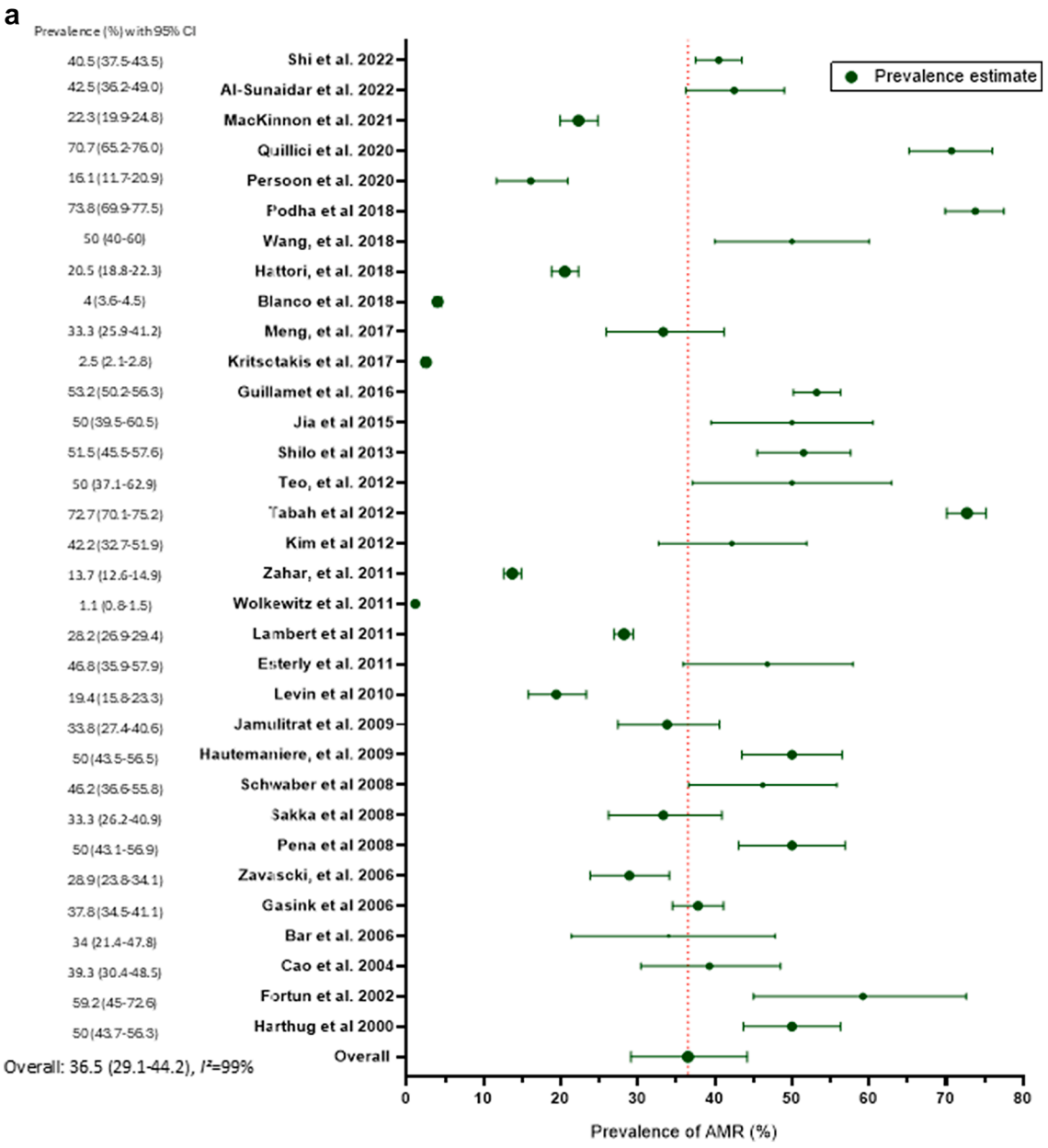

Fig. 3: a: Forest plot showing prevalence estimates of antimicrobial resistance, as well as overall synthesised prevalence estimates of antimicrobial resistance. b: Forest plot showing prevalence estimates of antimicrobial resistance by type of study, infection site, hospital setting and continent.

Discussion

Bacterial AMR remains a critical threat to global health, associated with increased mortality and longer hospital stays,[58,59] which is more pronounced in low-income and middle-income countries (LMICs).[60,61] In this systematic review and meta-analysis, we present a global synthesis of studies specifically investigating the risk of mortality in hospitalised patients infected with resistant organisms compared with those infected with non-AMR organisms. Our data indicate a notably high pooled prevalence of AMR (circa 37%) and a significantly worse prognosis (adjusted risk ratio of death: 1.58, 94% CI: 1.33–1.87) in patients with AMR compared with those who have non-AMR organisms, especially those with bacteraemia, and in cohorts where death occurred in the same hospital admission as AMR identification. These findings suggest a more direct relationship between AMR and mortality, than previously hypothesised, as demonstrated by the lack of mechanistic modelling models of AMR that specifically looked at whether AMR contributes to in-hospital mortality.

Importantly, we also identified large gaps in the available evidence, with a distinct lack of studies on

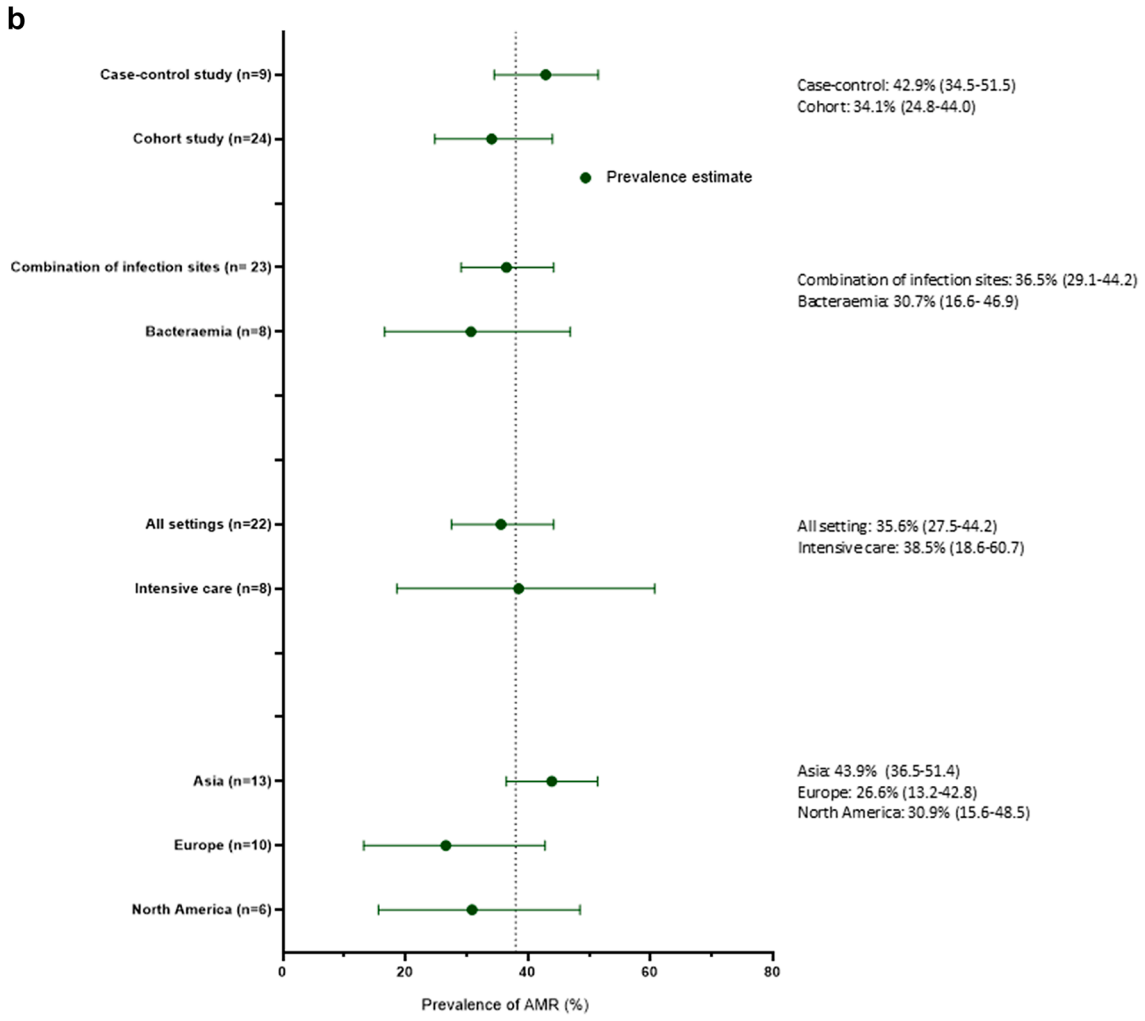

Fig. 3: Continued.

AMR and mortality from parts of the world where community prevalence of AMR is reported to be high—namely, sub-Saharan Africa, Russia, the Middle-East, and India. The absence of data from these regions contrasts with the reported burden in the Global Burden of Disease 2021[18] AMR collaborators study,[18] which highlighted that some of the highest rates of AMR-attributable deaths occur in these regions. Within the African sub-continent, inappropriate use of antimicrobials in hospitals is widely reported and exacerbated by high rates of HIV, TB and malaria, coupled with variable diagnostic resources.[62] Furthermore, lack of equipment and funding models of diagnostics lead to empirical antibiotic use without culture and susceptibility testing.[63] These factors may explain the lack of data in the African subcontinent seen in our work. Similarly, a very high prevalence of antibiotic use is seen in Pakistan and other South Asian countries.[64,65] Increased use of point-prevalence surveys of AMR in these countries, however, may mean that such data will become increasingly available in the future.[66] Crucially, these surveys should now also aim to incorporate in-hospital mortality with AMR use, based on our studies' findings.[18]

We found that 36.5% of reported infections in hospitals were resistant organisms. Whilst this might partly be explained by community acquisition of AMR, hospitals themselves are also a focal point for AMR transmission, given their vulnerable patient populations.[67,68] Most studies in our analysis adjusted for disease severity and prior antibiotic use when estimating mortality risk, but few accounted for whether the AMR organisms were acquired in the hospital[32,36,44,45] or the community.[54] It is this gap that might also explain why only two studies used mathematical models to link infection transmission within hospitals to mortality. Future studies must characterise the site of AMR acquisition and incorporate transmission modelling to clarify these associations.

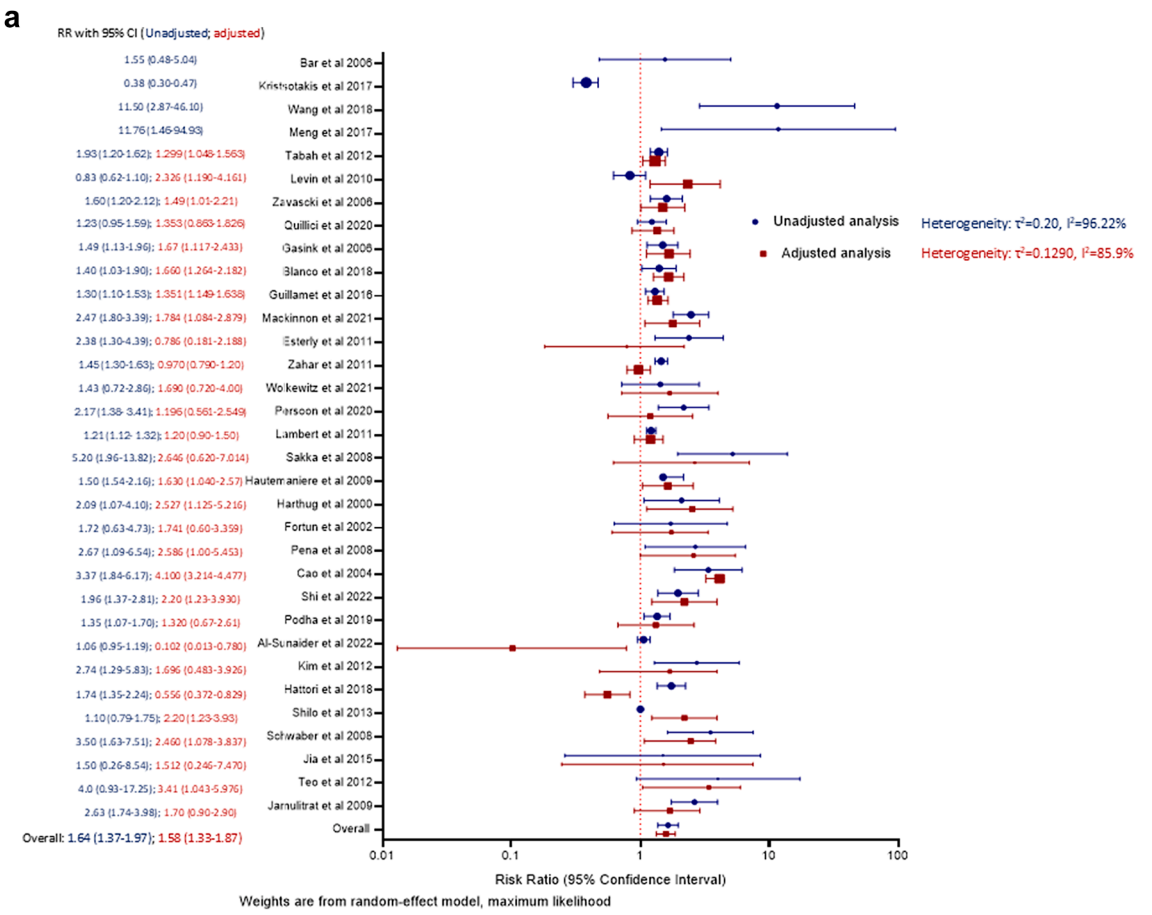

Fig. 4: a: Forest plot showing synthesised unadjusted and adjusted risk ratios for mortality in relation to study participants with antimicrobial resistant organisms, compared to the same antibiotic sensitive organisms across studies. b: Forest plot showing synthesised unadjusted and adjusted risk ratios for mortality in relation to study participants with antimicrobial resistant organisms, compared to the same antibiotic sensitive organisms across studies, by type of study, mortality within hospital or after 30 days, infection site, study setting (including intensive care) and continent.

Previous work on AMR has largely emphasised the role of excessive antibiotic use driving resistance.[2,60,69–72] Our work highlights the direct clinical relevance of AMR for individual patients, showing a strong association with in-hospital mortality even when key founders such as age and disease severity are adjusted for.[73,74] Our findings agree with another systematic review, by Ciapponi and colleagues, review of literature from 2000 to 2022 focussing on studies from Latin America who found a higher risk of death in patients observed to have multi-drug resistant organisms compared to those infected with other pathogens (adjusted odds ratio: 1.93, 85% CI: 1.58–2.37), with higher risk of death observed in those who did not receive appropriate empirical treatment (odds ratio 2.27, 95% CI: 1.44–3.56).[75] Greater awareness of the risks of AMR directly on mortality may influence clinical behaviour[76–78]—if clinicians understood that AMR is directly linked to poorer outcomes in hospitalised patients, they may be more inclined to improve antibiotic stewardship,[76–78] including more prudent antibiotic prescribing[71,72,79] and enhanced infection-control measures.[79]

Several plausible biological and clinical factors could cloud the link that we have shown between AMR and increased mortality risk. Older hospitalised patients are more likely to have multiple long-term conditions; although many studies adjusted this crudely, residual confounding from age-related changes, such as frailty of the patient[80–82]; accumulation of antibiotic use in older individuals through multiple hospital admissions[82]; changes in gut flora across lifetimes in older individuals,[83] immunosenescence[81,82,84] and a lower tolerance for the use of effective antibiotics[85] against resistant bacteria cannot be excluded. Such factors are beyond the scope of this work to disentangle but may be important factors to consider in future prospective studies.

Our study had limitations. Variations across papers in relation to populations, setting, treatment context as well as differences within reporting definitions of AMR

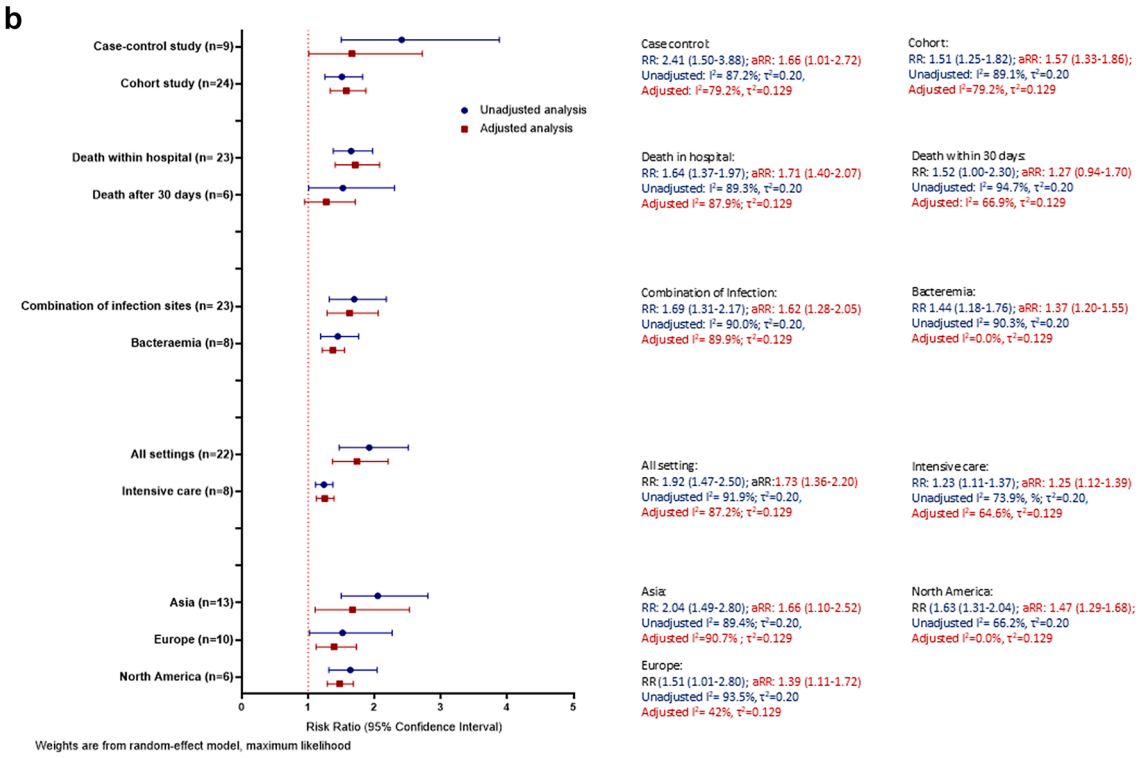

Fig. 4: Continued.

and outcomes meant that there was a high degree of heterogeneity.[86,87] However, this does not preclude pooling of data and is consistent with other meta-analyses on infection in diverse populations.[18,60,75,88–91] We attempted to explore heterogeneity through sensitivity analyses of different sub-populations. The analyses provide an important visualisation of the data available and highlight the need to improve data collection and analyses on this topic, including greater standardisation in adjusted analyses. We found clear evidence of publication bias. Most studies included in this work were retrospective observational studies; less than half of individuals in the included studies had organisms in which sensitivities were reported and consequently, we may have underestimated the prevalence of AMR, but it is unclear as to why this is. The observational nature of studies that we examined also means that the evidence generated for a direct association with AMR and mortality in hospital is circumstantial and prone to competing risks bias; however, our work provides early evidence of such a relationship that could motivate researchers to design better, prospective observational studies that examine for this relationship in greater detail. Furthermore, all studies included in this review were performed prior to the COVID-19 pandemic; the epidemiology of AMR within hospitals may have changed significantly since (although our search up to 2025 showed no recent studies investigating this issue). However, our work provides an important summary of existing epidemiology prior to a pandemic. Ideally, we would prefer to have performed this data synthesis by bacterial species, resistance by antibiotic class and separate colonisation from infection; however, the high heterogeneity in definitions of AMR and lack of data on specific species and colonisation prevented us from performing this analysis Furthermore, resistance patterns naturally change over time according to selective pressure. Yet, our aim of focussing on data representative of hospital cohorts, rather than infection from a specific site, was to provide a general summary of the effect on mortality, which has previously never been achieved. Finally, our analyses are reliant on robust estimates of unadjusted and adjusted ratios generated by the original studies themselves; in studies where, adjusted results were very different to unadjusted results for mortality, we contacted study authors to ensure that the results were interpreted correctly. The overall low certainty of evidence from our data synthesis suggests the need for better designed studies investigating this issue; that are adequately powered, with the right denominator (sensitive organism) and granular definitions of AMR.

In conclusion, the prevalence of AMR in hospitalised patients with infections is high, and AMR independently confers worse outcomes, including death within hospital. Early identification of patients with

AMR and the development of rapid diagnostic methods could improve clinical decision making and patient care. Our findings emphasise both the public health urgency of controlling AMR and the direct mortality risk it poses to infected individuals. This is of particular global health relevance, if countries are going to meet the new United Nations General Assembly goals for the use of Access antibiotics (vs Watch and Reserve antibiotics) as well as generally seek to reduce AMR.[92] Addressing these challenges will require a coordinated global effort, expanded surveillance in underrepresented regions and effective stewardship strategies to mitigate further escalation of AMR in the future.

Contributors

NAG: investigation, data curation, methodology, formal analysis, visualisation, writing–original draft. DP: conceptualisation, investigation, methodology, supervision, visualisation, validation, writing–original draft. LS: methodology, data curation, writing–review and editing. RFB: methodology, writing–review and editing. PI: writing–review and editing. PD: data curation. AAO: writing–review and editing. DPK: methodology, data curation, writing–review and editing. CAM: formal analysis, validation, writing–review and editing. JN: formal analysis, validation, writing–review and editing. IC: funding acquisition, writing–review and editing. SLC: methodology, writing–review and editing. LBN: supervision, funding acquisition, writing–review and editing. MP: conceptualisation, project administration, supervision, funding acquisition, writing–review and editing.

Data sharing statement

All data collated is publicly available from existing work in the literature. Form request of spreadsheets and analysis is available upon reasonable request.

Editor note

The Lancet Group takes a neutral position with respect to territorial claims in published maps and institutional affiliations.

Declaration of interests

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103384.

References

1 Kim C, Holm M, Frost I, Hasso-Agopsowicz M, Abbas K. Global and regional burden of attributable and associated bacterial antimicrobial resistance avertable by vaccination: modelling study. *BMJ Glob Health*. 2023;8(7):e011341.
2 Browne AJ, Chipeta MG, Haines-Woodhouse G, et al. Global antibiotic consumption and usage in humans, 2000-18: a spatial modelling study. *Lancet Planet Health*. 2021;5(12):e893–e904.
3 Langford BJ, Soucy JR, Leung V, et al. Antibiotic resistance associated with the COVID-19 pandemic: a systematic review and meta-analysis. *Clin Microbiol Infect*. 2023;29(3):302–309.
4 Despotovic A, Milosevic B, Cirkovic A, et al. The impact of COVID-19 on the profile of hospital-acquired infections in adult intensive care units. *Antibiotics (Basel)*. 2021;10(10):1146.
5 Abdelaziz Abdelmoneim S, Mohamed Ghazy R, Anwar Sultan E, Hassaan MA, Anwar Mahgoub M. Antimicrobial resistance burden pre and post-COVID-19 pandemic with mapping the multidrug resistance in Egypt: a comparative cross-sectional study. *Sci Rep*. 2024;14(1):7176.
6 O'Neill J. Tackling drug resistant infections globally: final report and recommendations. Review on antimicrobial resistance. 2016. https://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf.
7 Serra-Burriel M, Keys M, Campillo-Artero C, et al. Impact of multidrug resistant bacteria on economic and clinical outcomes of healthcare-associated infections in adults: systematic review and meta-analysis. *PLoS One*. 2020;15(1):e0227139.
8 Salamzade R, Manson AL, Walker BJ, et al. Inter-species geographic signatures for tracing horizontal gene transfer and long-term persistence of carbapenem resistance. *Genome Med*. 2022;14(1):37.
9 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(11):e897–e913.
10 Baba T, Takeuchi F, Kuroda M, et al. Genome and virulence determinants of high virulence community-acquired MRSA. *Lancet*. 2002;359(9320):1819–1827.
11 Cosgrove SE, Sakoulas G, Perencevich EN, Schwaber MJ, Karchmer AW, Carmeli Y. Comparison of mortality associated with methicillin-resistant and methicillin-susceptible Staphylococcus aureus bacteremia: a meta-analysis. *Clin Infect Dis*. 2003;36(1):53–59.
12 Gentry CA, Rodvold KA, Novak RM, Hershow RC, Naderer OJ. Retrospective evaluation of therapies for Staphylococcus aureus endocarditis. *Pharmacotherapy*. 1997;17(5):990–997.
13 Levin AS, Barone AA, Penco J, et al. Intravenous colistin as therapy for nosocomial infections caused by multidrug-resistant Pseudomonas aeruginosa and Acinetobacter baumannii. *Clin Infect Dis*. 1999;28(5):1008–1011.
14 Lodise TP, McKinnon PS, Swiderski L, Rybak MJ. Outcomes analysis of delayed antibiotic treatment for hospital-acquired Staphylococcus aureus bacteremia. *Clin Infect Dis*. 2003;36(11):1418–1423.
15 Linden PK, Pasculle AW, Manez R, et al. Differences in outcomes for patients with bacteremia due to vancomycin-resistant Enterococcus faecium or vancomycin-susceptible E. faecium. *Clin Infect Dis*. 1996;22(4):663–670.
16 Cocker D, Birgand G, Zhu N, et al. Healthcare as a driver, reservoir and amplifier of antimicrobial resistance: opportunities for interventions. *Nat Rev Microbiol*. 2024;22(10):636–649.
17 Li X, Tang Y, Deng X, et al. Modified frailty index effectively predicts adverse outcomes in sepsis patients in the intensive care unit. *Intensive Crit Care Nurs*. 2024;84:103749.
18 GBD 2021 Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance 1990-2021: a systematic analysis with forecasts to 2050. *Lancet*. 2024;404(10459):1199–1226.
19 Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. *Syst Rev*. 2016;5:210.
20 Team TE. *EndNote*. Philadelphia, PA: Clarivate; 2013.
21 Higgins JPT, Thomas J, Chandler J, et al. Cochrane handbook for systematic reviews of interventions. Cochrane. 2024. https://www.cochrane.org/authors/handbooks-and-manuals/handbook.
22 StataCorp. *Stata Statistical Software: Release 17*. College Station, Texas: StataCorp LLC; 2022.
23 Al-Sunaidar KA, Aziz NA, Hassan Y, Jamshed S, Sekar M. Association of multidrug resistance bacteria and clinical outcomes of adult patients with sepsis in the intensive care unit. *Trop Med Infect Dis*. 2022;7(11):365.
24 Bar K, Wisplinghoff H, Wenzel RP, Bearman GM, Edmond MB. Systemic inflammatory response syndrome in adult patients with nosocomial bloodstream infections due to enterococci. *BMC Infect Dis*. 2006;6:145.

25 Blanco N, Harris AD, Rock C, et al. Risk factors and outcomes associated with multidrug-resistant *Acinetobacter baumannii* upon Intensive care unit admission. *Antimicrob Agents Chemother*. 2018;62(1):e01631-17.
26 Cao B, Wang H, Sun H, Zhu Y, Chen M. Risk factors and clinical outcomes of nosocomial multi-drug resistant Pseudomonas aeruginosa infections. *J Hosp Infect*. 2004;57(2):112–118.
27 Esterly JS, Griffith M, Qi C, Malczynski M, Postelnick MJ, Scheetz MH. Impact of carbapenem resistance and receipt of active antimicrobial therapy on clinical outcomes of Acinetobacter baumannii bloodstream infections. *Antimicrob Agents Chemother*. 2011;55(10):4844–4849.
28 Fortun J, Coque TM, Martin-Davila P, et al. Risk factors associated with ampicillin resistance in patients with bacteraemia caused by Enterococcus faecium. *J Antimicrob Chemother*. 2002;50(6):1003–1009.
29 Gasink LB, Fishman NO, Weiner MG, Nachamkin I, Bilker WB, Lautenbach E. Fluoroquinolone-resistant Pseudomonas aeruginosa: assessment of risk factors and clinical impact. *Am J Med*. 2006;119(6):526.e19–526.e25.
30 Guillamet CV, Vazquez R, Noe J, Micek ST, Kollef MH. A cohort study of bacteremic pneumonia: the importance of antibiotic resistance and appropriate initial therapy? *Medicine (Baltimore)*. 2016;95(35):e4708.
31 Harthug S, Eide GE, Langeland N. Nosocomial outbreak of ampicillin resistant Enterococcus faecium: risk factors for infection and fatal outcome. *J Hosp Infect*. 2000;45(2):135–144.
32 Hattori H, Maeda M, Nagatomo Y, et al. Epidemiology and risk factors for mortality in bloodstream infections: a single-center retrospective study in Japan. *Am J Infect Control*. 2018;46(12):e75–e79.
33 Hautemaniere A, Hunter PR, Diguio N, Albuisson E, Hartemann P. A prospective study of the impact of colonization following hospital admission by glycopeptide-resistant Enterococci on mortality during a hospital outbreak. *Am J Infect Control*. 2009;37(9):746–752.
34 Jamulitrat S, Arunpan P, Phainuphong P. Attributable mortality of imipenem-resistant nosocomial Acinetobacter baumannii bloodstream infection. *J Med Assoc Thai*. 2009;92(3):413–419.
35 Jia X, Ma W, Xu X, Yang S, Zhang L. Retrospective analysis of hospital-acquired linezolid-nonsusceptible enterococci infection in Chongqing, China, 2011-2014. *Am J Infect Control*. 2015;43(12):e101–e106.
36 Kim HW, Ku S, Jeong SJ, et al. Delta neutrophil index: could it predict mortality in patients with bacteraemia? *Scand J Infect Dis*. 2012;44(7):475–480.
37 Kritsotakis EI, Kontopidou F, Astrinaki E, Roumbelaki M, Ioannidou E, Gikas A. Prevalence, incidence burden, and clinical impact of healthcare-associated infections and antimicrobial resistance: a national prevalent cohort study in acute care hospitals in Greece. *Infect Drug Resist*. 2017;10:317–328.
38 Lambert ML, Suetens C, Savey A, et al. Clinical outcomes of healthcare-associated infections and antimicrobial resistance in patients admitted to European intensive-care units: a cohort study. *Lancet Infect Dis*. 2011;11(1):30–38.
39 Garber AM. A discrete-time model of the acquisition of antibiotic-resistant infections in hospitalized patients. *Biometrics*. 1989;45(3):797–816.
40 Levin PD, Simor AE, Moses AE, Sprung CL. End-of-life treatment and bacterial antibiotic resistance: a potential association. *Chest*. 2010;138(3):588–594.
41 MacKinnon MC, McEwen SA, Pearl DL, et al. Mortality in Escherichia coli bloodstream infections: a multinational population-based cohort study. *BMC Infect Dis*. 2021;21(1):606.
42 Meng X, Liu S, Duan J, et al. Risk factors and medical costs for healthcare-associated carbapenem-resistant Escherichia coli infection among hospitalized patients in a Chinese teaching hospital. *BMC Infect Dis*. 2017;17(1):82.
43 Pena C, Gudiol C, Calatayud L, et al. Infections due to *Escherichia coli* producing extended-spectrum beta-lactamase among hospitalised patients: factors influencing mortality. *J Hosp Infect*. 2008;68(2):116–122.
44 Persoon MC, Voor In't Holt AF, Wielders CCH, Gommers D, Vos MC, Severin JA. Mortality associated with carbapenem-susceptible and Verona Integron-encoded Metallo-beta-lactamase-positive Pseudomonas aeruginosa bacteremia. *Antimicrob Resist Infect Control*. 2020;9(1):25.
45 Phodha T, Riewpaiboon A, Malathum K, Coyte PC. Annual relative increased in inpatient mortality from antimicrobial resistant nosocomial infections in Thailand. *Epidemiol Infect*. 2019;147:e133.
46 Quillici MCB, Resende DS, Goncalves IR, et al. Gram-negative bacilli bacteremia: a 7 year retrospective study in a referral Brazilian tertiary-care teaching hospital. *J Med Microbiol*. 2021;70(1). https://doi.org/10.1099/jmm.0.001277.
47 Sakka V, Tsiodras S, Galani L, et al. Risk factors and predictors of mortality in patients colonised with vancomycin-resistant enterococci. *Clin Microbiol Infect*. 2008;14(1):14–21.
48 Shi N, Kang J, Wang S, et al. Bacteriological profile and antimicrobial susceptibility patterns of gram-negative bloodstream infection and risk factors associated with mortality and drug resistance: a retrospective study from Shanxi, China. *Infect Drug Resist*. 2022;15:3561–3578.
49 Shilo S, Assous MV, Lachish T, et al. Risk factors for bacteriuria with carbapenem-resistant Klebsiella pneumoniae and its impact on mortality: a case-control study. *Infection*. 2013;41(2):503–509.
50 Tabah A, Koulenti D, Laupland K, et al. Characteristics and determinants of outcome of hospital-acquired bloodstream infections in intensive care units: the EUROBACT International Cohort Study. *Intensive Care Med*. 2012;38(12):1930–1945.
51 Teo J, Cai Y, Tang S, et al. Risk factors, molecular epidemiology and outcomes of ertapenem-resistant, carbapenem-susceptible *Enterobacteriaceae:* a case-case-control study. *PLoS One*. 2012;7(3):e34254.
52 Wang Z, Qin RR, Huang L, Sun LY. Risk factors for carbapenem-resistant *Klebsiella pneumoniae* infection and mortality of *Klebsiella pneumoniae* infection. *Chin Med J*. 2018;131(1):56–62.
53 Wolkewitz M, Frank U, Philips G, Schumacher M, Davey P, Group BS. Mortality associated with in-hospital bacteraemia caused by Staphylococcus aureus: a multistate analysis with follow-up beyond hospital discharge. *J Antimicrob Chemother*. 2011;66(2):381–386.
54 Zahar JR, Timsit JF, Garrouste-Orgeas M, et al. Outcomes in severe sepsis and patients with septic shock: pathogen species and infection sites are not associated with mortality. *Crit Care Med*. 2011;39(8):1886–1895.
55 Zavascki AP, Barth AL, Goncalves AL, et al. The influence of metallo-beta-lactamase production on mortality in nosocomial Pseudomonas aeruginosa infections. *J Antimicrob Chemother*. 2006;58(2):387–392.
56 Schwaber MJ, Klarfeld-Lidji S, Navon-Venezia S, Schwartz D, Leavitt A, Carmeli Y. Predictors of carbapenem-resistant Klebsiella pneumoniae acquisition among hospitalized adults and effect of acquisition on mortality. *Antimicrob Agents Chemother*. 2008;52(3):1028–1033.
57 Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect*. 2012;18(3):268–281.
58 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(10):e506–e514.
59 Nelson RE, Hyun D, Jezek A, Samore MH. Mortality, length of stay, and healthcare costs associated with multidrug-resistant bacterial infections among elderly hospitalized patients in the United States. *Clin Infect Dis*. 2022;74(6):1070–1080.
60 Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet*. 2022;399(10325):629–655.
61 Ikhimiukor OO, Odih EE, Donado-Godoy P, Okeke IN. A bottom-up view of antimicrobial resistance transmission in developing countries. *Nat Microbiol*. 2022;7(6):757–765.
62 Afriyie DK, Sefah IA, Sneddon J, et al. Antimicrobial point prevalence surveys in two Ghanaian hospitals: opportunities for antimicrobial stewardship. *JAC Antimicrob Resist*. 2020;2(1):dlaa001.
63 Vounba P, Loul S, Tamadea LF, Siawaya JFD. Microbiology laboratories involved in disease and antimicrobial resistance surveillance: strengths and challenges of the central African states. *Afr J Lab Med*. 2022;11(1):1570.
64 Mustafa ZU, Salman M, Khan AH, Harun SN, Meyer JC, Godman B. Antimicrobial use among hospitalized neonates and children; findings and implications from a comprehensive point prevalence survey among general tertiary hospitals in Pakistan. *Infect Drug Resist*. 2024;17:5411–5428.

65 Otaigbe II, Elikwu CJ. Drivers of inappropriate antibiotic use in low- and middle-income countries. *JAC Antimicrob Resist*. 2023;5(3):dlad062.
66 Saleem Z, Godman B, Cook A, et al. Ongoing efforts to improve antimicrobial utilization in hospitals among African countries and implications for the future. *Antibiotics (Basel)*. 2022;11(12):1824.
67 Almagor J, Temkin E, Benenson I, Fallach N, Carmeli Y, DRIVE-AB Consortium. The impact of antibiotic use on transmission of resistant bacteria in hospitals: insights from an agent-based model. *PLoS One*. 2018;13(5):e0197111.
68 Mboowa G, Sserwadda I, Bulafu D, et al. Transmission dynamics of antimicrobial resistance at a national referral hospital in Uganda. *Am J Trop Med Hyg*. 2021;105(2):498–506.
69 Sulis G, Gandra S. Access to antibiotics: not a problem in some LMICs. *Lancet Glob Health*. 2021;9(5):e561–e562.
70 McNulty C, Read B, Quigley A, Verlander NQ, Lecky DM. What the public in England know about antibiotic use and resistance in 2020: a face-to-face questionnaire survey. *BMJ Open*. 2022;12(4):e055464.
71 Carpenter L, Miller S, Flynn E, et al. Exposure to doxycycline increases risk of carrying a broad range of enteric antimicrobial resistance determinants in an elderly cohort. *J Infect*. 2024;89(4):106243.
72 Waterlow NR, Cooper BS, Robotham JV, Knight GM. Antimicrobial resistance prevalence in bloodstream infection in 29 European countries by age and sex: an observational study. *PLoS Med*. 2024;21(3):e1004301.
73 Bai AD, Lo CKL, Komorowski AS, et al. Staphylococcus aureus bacteraemia mortality: a systematic review and meta-analysis. *Clin Microbiol Infect*. 2022;28(8):1076–1084.
74 Eichel VM, Last K, Bruhwasser C, et al. Epidemiology and outcomes of vancomycin-resistant enterococcus infections: a systematic review and meta-analysis. *J Hosp Infect*. 2023;141:119–128.
75 Ciapponi A, Bardach A, Sandoval MM, et al. Systematic review and meta-analysis of deaths attributable to antimicrobial resistance, Latin America. *Emerg Infect Dis*. 2023;29(11):2335–2344.
76 Krockow EM, Harvey EJ, Ashiru-Oredope D. Addressing long-term and repeat antibiotic prescriptions in primary care: considerations for a behavioural approach. *BMJ Qual Saf*. 2022;31(11):782–786.
77 Smieszek T, Pouwels KB, Dolk FCK, et al. Potential for reducing inappropriate antibiotic prescribing in English primary care. *J Antimicrob Chemother*. 2018;73(suppl_2):ii36–ii43.
78 Van Staa T, Li Y, Gold N, et al. Comparing antibiotic prescribing between clinicians in UK primary care: an analysis in a cohort study of eight different measures of antibiotic prescribing. *BMJ Qual Saf*. 2022;31(11):831–838.
79 Saito N, Tsuchiya J, Itoga M, et al. Multiple blood culture sampling, proper antimicrobial choice, and adequate dose in definitive therapy supported by the antimicrobial stewardship team could decrease 30-day sepsis mortality rates. *Infect Drug Resist*. 2024;17:207–219.
80 Le Maguet P, Roquilly A, Lasocki S, et al. Prevalence and impact of frailty on mortality in elderly ICU patients: a prospective, multicenter, observational study. *Intensive Care Med*. 2014;40(5):674–682.
81 Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet*. 2013;381(9868):752–762.
82 Theodorakis N, Feretzakis G, Hitas C, et al. Antibiotic resistance in the elderly: mechanisms, risk factors, and solutions. *Microorganisms*. 2024;12(10):1978.
83 O'Sullivan O, Coakley M, Lakshminarayanan B, et al. Alterations in intestinal microbiota of elderly Irish subjects post-antibiotic therapy. *J Antimicrob Chemother*. 2013;68(1):214–221.
84 Sahin E, Depinho RA. Linking functional decline of telomeres, mitochondria and stem cells during ageing. *Nature*. 2010;464(7288):520–528.
85 Faulkner CM, Cox HL, Williamson JC. Unique aspects of antimicrobial use in older adults. *Clin Infect Dis*. 2005;40(7):997–1004.
86 Sze S, Pan D, Nevill CR, et al. Ethnicity and clinical outcomes in COVID-19: a systematic review and meta-analysis. *EClinicalMedicine*. 2020;29:100630.
87 Irizar P, Pan D, Kapadia D, et al. Ethnic inequalities in COVID-19 infection, hospitalisation, intensive care admission, and death: a global systematic review and meta-analysis of over 200 million study participants. *EClinicalMedicine*. 2023;57:101877.
88 Bernabe KJ, Langendorf C, Ford N, Ronat JB, Murphy RA. Antimicrobial resistance in West Africa: a systematic review and meta-analysis. *Int J Antimicrob Agents*. 2017;50(5):629–639.
89 Chukwudile B, Pan D, Silva L, et al. Antimicrobial resistance among migrants in Europe: a systematic review and meta-analysis - update from 2017 to 2023. *EClinicalMedicine*. 2024;75:102801.
90 Nellums LB, Thompson H, Holmes A, et al. Antimicrobial resistance among migrants in Europe: a systematic review and meta-analysis. *Lancet Infect Dis*. 2018;18(7):796–811.
91 Founou RC, Founou LL, Essack SY. Clinical and economic impact of antibiotic resistance in developing countries: a systematic review and meta-analysis. *PLoS One*. 2017;12(12):e0189621.
92 Funiciello E, Lorenzetti G, Cook A, et al. Identifying AWaRe indicators for appropriate antibiotic use: a narrative review. *J Antimicrob Chemother*. 2024;79(12):3063–3077.