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Variation of effect estimates in the analysis of mortality and length of hospital stay in patients with infections caused by bacteria-producing extended-spectrum beta-lactamases: a systematic review and meta-analysis

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ABSTRACT

Objective To assess the variation of effect estimates in the analysis of mortality and length of stay (LOS) in patients with infections caused by extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae*.

Design Systematic review and meta-analysis

Methods Literature search for clinical studies from 1 January 1960 to 1 October 2018 was conducted in PubMed. Primary outcomes were risk ratios (RRs) of all-cause and attributable mortality and weighted mean differences (WMDs) in LOS in patients with bloodstream infections (BSIs) and non-invasive infections. Any change in the effect estimates was assessed by grouping studies according to design, setting, economy-based country classification, reporting period, microbiological aetiology, infection type and adjustment for appropriateness of empirical treatment. The impact of ESBL production was calculated using random-effect meta-analysis and heterogeneity was evaluated by I^2 statistics and metaregression.

Results Eighty-four studies including 22 030 patients and 149 outcome measures were included in the meta-analysis. Most studies were retrospective cohorts from high-income countries, providing unadjusted estimates. ESBL production in patients with BSIs (56 studies) increased the RR for all-cause mortality by a factor of 1.70 (95% CI 1.52 to 1.90; p<0.001), attributable mortality (16 studies) by 1.75 (95% CI 1.448 to 2.108; p<0.001) and WMD in the intensive care unit by 3.07 days (95% CI 1.61 to 4.54; p<0.001). WMD in hospital LOS was significantly higher in BSIs (4.41 days; 95% CI 3.37 to 5.46; p<0.001) and non-invasive (2.19 days; 95% CI 1.56 to 2.81; p<0.001). Subgroup analyses showed variation of estimates by study design, population, strain and assessment of appropriateness of empiric treatment. High heterogeneity was observed in all analyses.

Conclusions Current evidence of the clinical burden of infections caused by ESBL-producing bacteria is highly heterogeneous and based mainly on unadjusted estimates derived from retrospective studies. Despite these limitations, ESBL production in strains causing BSIs seems associated with higher all-cause and attributable mortality and longer hospitalisation.

Strengths and limitations of this study

- Evidence of the impact of extended-spectrum beta-lactamase production on mortality and length of stay in strains causing bacteraemic and non-bacteraemic infections was collected systematically.
- Effect of multiple epidemiological and clinical variables was assessed in the calculation of estimates.
- Heterogeneity among studies was assessed.
- Only few studies had been performed in high-risk populations or low-income countries.

INTRODUCTION

Infections caused by extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* are responsible for high morbidity and mortality worldwide.[1–3] The 2018 WHO list of antibiotic-resistant pathogens identified mortality as the most important criteria to prioritise bacteria for research and development of new, effective antibiotics.[1] In this prioritisation exercise, ESBL-producing *Enterobacteriaceae* were designated a critical priority because of their high all-cause mortality and high prevalence globally in healthcare-associated and community-acquired infections. The incidence and attributable mortality of multidrug-resistant bacterial infections, including ESBL-producing *Enterobacteriaceae*, in European countries has been recently estimated using a modelling analysis.[4] In 2015, ESBL-producing *Escherichia coli* was responsible for almost 300 000 infections in Europe and

9000 attributable deaths, and ESBL-producing *Klebsiella pneumoniae* caused around 70 000 infections and more than 3500 deaths. The major limitation of this analysis is the sparseness of evidence on mortality due to ESBL-producing bacteria, which was limited largely to studies conducted in high-income countries (HICs).

Two systematic reviews have been performed to define the impact of ESBL production on mortality due to *Enterobacteriaceae*.[2 3] Both meta-analyses included studies targeting bloodstream infections (BSIs) and showed doubling all-cause mortality for ESBL-associated bacteraemia compared with non-ESBL *Enterobacteriaceae* bacteraemia. A major drawback of the analyses, highlighted by the authors, was the lack of control for confounding and limited adjustment for empiric therapy. No systematic review has been performed to assess attributable mortality and other indicators of clinical impact such as length of stay (LOS).

Because estimates of clinical burden drive policy design for antibiotic stewardship and infection control interventions, precise and current estimates are essential. The objective of this systematic review and meta-analysis was to assess the variation of effect estimates in the analysis of mortality and LOS in patients with infections due to ESBL-producing *Enterobacteriaceae*.

METHODS

Literature search strategy

The search was performed by two researchers (BPG and PS) in PubMed on 5 October 2018 using search terms (online supplementary table S1) relevant to the following combinations: (ESBL AND Escherichia coli AND mortality) OR (ESBL AND Klebsiella pneumoniae AND mortality) OR (ESBL AND Escherichia coli AND length of stay OR length of hospitalisation) OR (ESBL AND Klebsiella pneumoniae AND length of stay OR length of hospitalisation). Reference lists of retrieved articles were also searched.

Eligibility criteria

We included all clinical studies with a comparison group assessing all-cause mortality, attributable mortality and overall LOS and intensive care unit stay (ICU) LOS in hospitalised patients with ESBL infections. Studies published from 1 January 1960 to 1 October 2018 irrespective of the clinical setting and study design were included. No language restriction has been applied. Diagnostic studies, reviews, case reports, non-clinical studies and abstracts of conference presentations were not included.

Data extraction

Two reviewers (PS and BPG) independently assessed the eligibility of trials and extracted data. In case of disagreement, a third reviewer (DL) was consulted. Extracted data were collected in an electronic worksheet, using EpiInfo 7.1: authors, journal, country, year of publication, year of study, time of data collection, study design, comparison group, study setting, population, aetiology, type and site of infection, and raw data related to mortality and LOS/ICU-LOS. Countries were classified as high-income, middle-income or low-income using the World Bank Atlas method.[5] Adjusted effect estimates such as ORs or HRs and quality indicators such as reporting of antibiotic therapy, appropriateness of empirical treatment, resistance mechanisms and minimum inhibitory concentrations (MICs) were also extracted.

Mortality data were extracted as all-cause mortality or attributable mortality as defined in the studies. Where available, prespecified time periods for mortality assessment (ie, 14 days, 28 days, in hospital) were also extracted. LOS and ICU-LOS were extracted as days with mean and SD or median and IQR.

Data analysis

The primary outcomes for the clinical impact of ESBL infections were RRs of all-cause and attributable mortality and the weighted mean difference (WMD) in LOS and ICU-LOS in patients with ESBL infections compared with those in patients with non-ESBL infections and, where available, with uninfected patients. The impact of ESBL production on attributable and all-cause mortality was calculated with random-effect meta-analysis and expressed as RR with 95% CI. WMD in days with 95% CI was calculated to express the excess in LOS and ICU-LOS.

Variation of the effect estimate was assessed by grouping the studies according to the following study/outcome characteristics: mortality time assessment (7 vs 14 days), aetiology (*E. coli* vs *K. pneumoniae*), infection localisation, clinical setting (paediatric, oncology, ICU), economic country areas (HICs vs low-income and medium-income countries (LMICs)), study design, assessment of empiric therapy and year. Studies were classified according to the type of infections evaluated. Studies on BSIs were defined as those in which patients had positive blood cultures and were admitted to the hospitals with signs and symptoms of systemic inflammatory response and requiring therapy, similarly to the definition adopted by the most recent cohort studies on ESBL infections.[6] Non-invasive infections included non-bacteraemic patients with only localised signs and symptoms of infection (such as urinary tract infections (UTIs) or superficial surgical site infections).

Subgroup analysis was computed only if more than two studies were available for each group. Heterogeneity was evaluated by using I^2 statistics and metaregression. Overall significance testing was carried out using Wald tests adjusted using the Bonferroni correction. The unadjusted ORs were compared with the adjusted ORs to estimate the effect of adjustment. Reporting and publication bias was presented in funnel plots (online supplementary figures 1 and 2) and tested by Egger's test. Statistical analyses were performed using Stata V.15. Risk of bias was assessed independently by two authors (PS, DL) using the Newcastle-Ottawa Quality Assessment Scale for cohort studies.[7] Studies were classified as low, moderate or high quality according to Agency for Health Research and

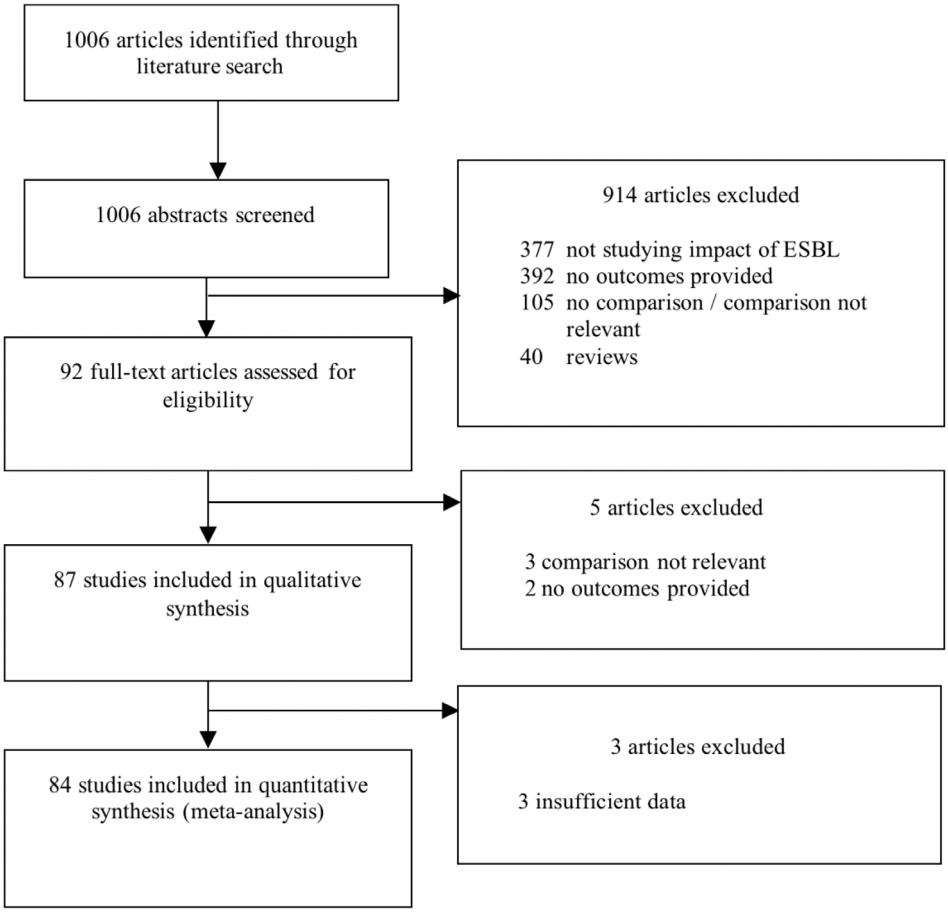

Figure 1 Literature search and study inclusion and exclusion. ESBL, extended-spectrum beta-lactamase.

Quality (AHRQ) standards (online supplementary table S2). All meta-analyses were performed in accordance with the Cochrane Collaboration recommendations[8] and reported according to the Preferred Reporting Items for Systematic Reviews andMeta-Analyses statement.[9]

The protocol is available online (https://im1-tuebingen.de/wp-content/uploads/2019/03/ClinicalImpactAMR_SR_studyprotocol_2018.pdf).

Patient and public involvement

There was no patient or public involvement in this systematic review of published literature.

RESULTS

Our literature search identified 1006 studies, and 92 (9.2%) met the eligibility criteria on the basis of abstract screening. Full-text screening excluded an additional 5 articles, providing an evidence base of 87 studies (figure 1).[10–96] The 87 studies included in the qualitative analysis were conducted between 1991 and 2017 in 25 countries, mainly in South Korea (14 studies), Thailand (7), USA (7), Taiwan (7) and Spain (7). Sixty (68.9%) studies were performed in HICs, 26 (29.9%) in LMICs and 1 included both HICs and LMICs.[56] About half (44, 50.6%) were retrospective cohort studies, 24 (27.6%) case cohort studies and 18 (20.7%) prospective cohort studies; 1 study had an interventional design.[57] The comparison group was patients with infections caused by gram-negative non-ESBL producers in 82 (94.3%) studies, non-infected patients in 2 (2.3%) and both control groups in 3 (3.5%). Most (57, 65.5%) studies included data from the entire hospital, while a few focused on specific settings, mainly ICUs (9, 10.3%) and paediatric wards (8, 9.2%). The most common ESBL-producing bacteria were *E. coli* (23, 26.4%) and *K. pneumoniae* (17, 19.5%). An overview of study characteristics is provided in online supplementary table 3.

Because data in 3 studies[22 61 87] were insufficient for quantitative analysis, 84 (96.6%) studies were included in the meta-analysis analysing data from 22 030 patients and 149 outcome measures. Fifty-seven studies analysed BSIs and 10 non-invasive infections. Study characteristics for all studies are provided in online supplementary table 4. Forty-nine (58.3%) studies were of high quality, 23 (27.3%) were of moderate quality and 12 (14.3%) were of low quality (online supplementary table S5).

All-cause mortality

All-cause mortality was reported in 81 studies including 21 942 patients (56 on BSIs and 7 on non-invasive infections). ESBL production in patients with BSIs increased all-cause mortality by a factor of 1.70 (95% CI 1.52 to

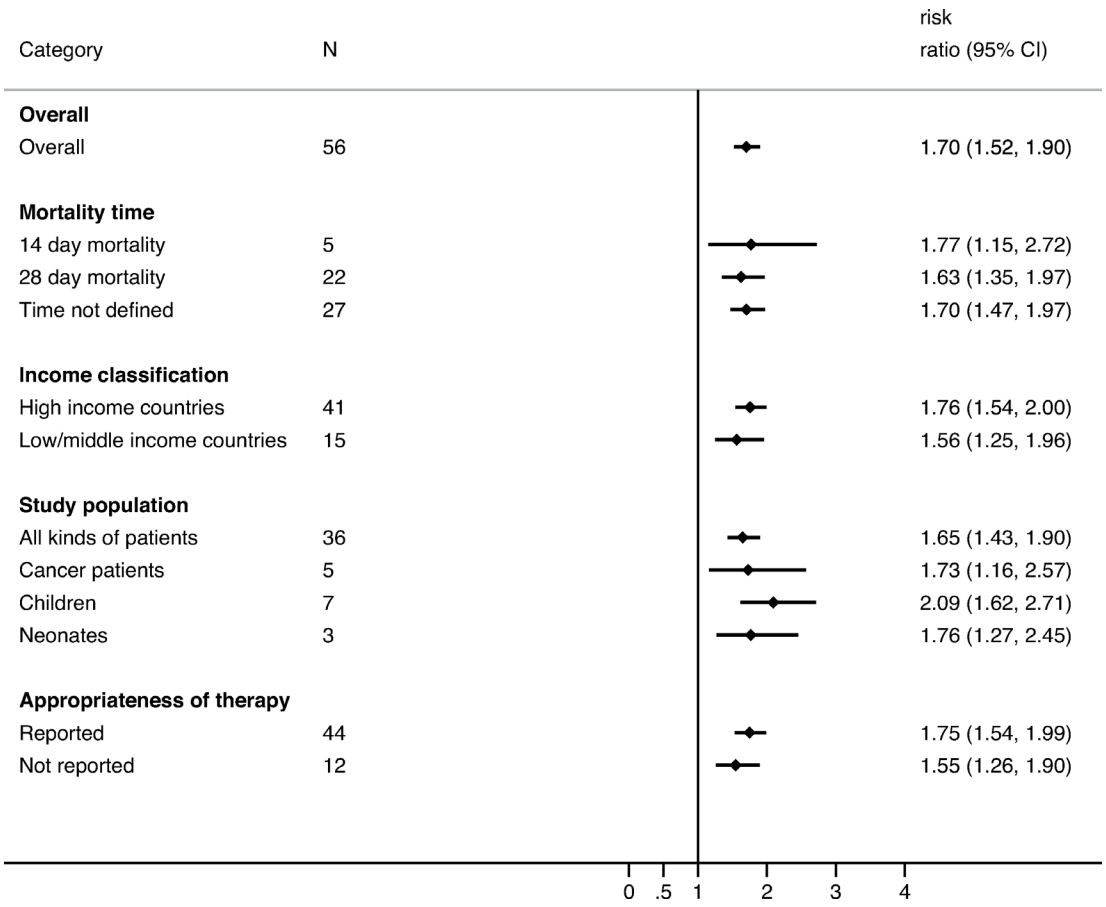

Figure 2 Pooled risk ratios for all-cause mortality in patients with extended-spectrum beta-lactamase (ESBL) bloodstream infections compared with patients with non-ESBL bloodstream infections—subgroups not included in attributable mortality.

1.90; p<0.001; I^2=45.3%; p<0.001) while studies including non-invasive reported an RR of 1.58 (95% CI 1.23 to 2.02; p<0.001; online supplementary figure 3). Among the patients with BSI, the RR increased over time from 1.56 (95% CI 1.15 to 2.11; p=0.004) in 1991–1999 to 1.74 (95% CI 1.50 to 2.01; p<0.001) in 2000–2009, and it was stable in 2010–2018 (1.72, 95% CI 1.39 to 2.13; p<0.001). The RR was higher in studies assessing appropriateness of empiric therapy (RR=1.75; 95% CI 1.54 to 1.99; p<0.001) than in those that did not (RR=1.55; 95% CI 1.26 to 1.90; p<0.001). The subgroup analysis by pathogen showed that ESBL production increased the RR in BSIs due to *E. coli* (RR=1.82; 95% CI 1.50 to 2.21; p<0.001) compared with those due to *K. pneumoniae* (RR=1.48; 95% CI 1.17 to 1.87; p=0.001). Stratification by population age showed a higher RR in paediatric population (RR=2.09; 95% CI 1.62 to 2.71; p<0.001). Effect estimates did not vary significantly by study country, mortality time assessment (14 vs 28 days), ESBL molecular resistance mechanisms, or study design (figure 2 and online supplementary figure 4). Adjusted estimates for inappropriate empirical antibiotic therapy were provided for 14 studies. The pooled unadjusted OR for all-cause mortality was 2.91 (95% CI 2.23 to 3.81; p<0.001, I^2=27.1%; p=0.164) and the pooled OR after adjusting for receipt of appropriate empirical treatment was 3.22 (95% CI 1.53 to 6.76; p=0.002; I^2=87.5%; p<0.001). The impact of ESBL production on LOS and mortality varied according to the infection type, with higher effect in intra-abdominal, respiratory and BSIs (online supplementary figures 5 and 6).

Attributable mortality

Attributable mortality was analysed in 16 studies including 2885 patients. All studies were performed in HICs. ESBL production in patients with BSIs increased the risk of attributable mortality by a factor of 1.75 (95% CI 1.45 to 2.11; p<0.001; I^2=0%; p<0.001). The RR increased over time from 1.53 (95% CI 1.10 to 2.12; p=0.011) in 1991–1999 to 1.91 (95% CI 1.43 to 2.54; p<0.001) in 2000–2009 (figure 3). Pathogen-specific RR for attributable mortality was 1.60 (95% CI 1.18 to 2.15; p=0.002) for *K. pneumoniae* and 1.76 (95% CI 1.33 to 2.34; p<0.001) when the gram-negative organisms were analysed all together without species differentiation. The subgroup analysis showed the RR was lower in case cohort studies (1.56; 95% CI 1.09 to 2.25; p=0.016) than in cohort studies (1.80; 95% CI 1.37 to 2.37; p<0.001).

Length of stay

LOS data were provided in 37 studies (17 on BSIs and 8 on non-invasive) analysing 38 outcome measures. The WMD of LOS in patients with BSIs was 4.41 days (95% CI 3.37

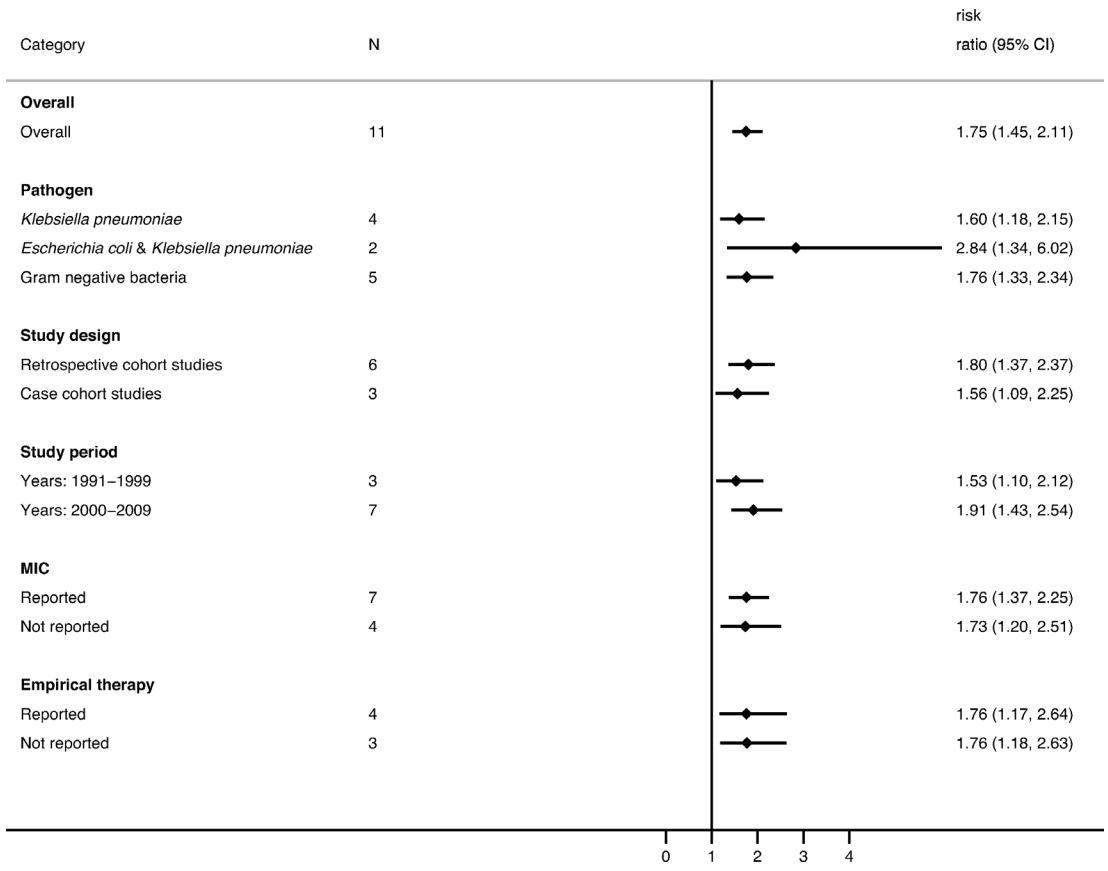

Figure 3 Pooled risk ratios for attributable mortality in patients with extended-spectrum beta-lactamase (ESBL) bloodstream infections compared with patients with non-ESBL bloodstream infections. MIC, minimum inhibitory concentration.

to 5.46; p<0.001) and decreased from 5.72 days (95% CI 2.69 to 8.75; p<0.001) in 1991–1999 to 4.22 days (95% CI 3.02 to 5.43; p<0.001) in 2000–2009 and was stable up to 2018 (4.30 days; 95% CI 1.38 to 7.22; p=0004). Higher WMD (p<0.001) was observed for BSIs due to *K. pneumoniae* (7.67 days; 4.63–10.71) than for those due to *E. coli* (6.07 days; 95% CI 3.71 to 8.43). Retrospective cohort studies reported higher (p<0.001) WMD (6.43 days; 95% CI 4.66 to 8.21; p<0.001) than case cohort studies (3.32 days; 95% CI 2.03 to 4.61). Studies in HICs showed higher WMD (4.56 days; 95% CI 3.43 to 5.70; p<0.001) than studies in LMICs (3.55 days; 95% CI 0.84 to 6.26; p=0.01) (figure 4).

Studies with non-invasive infections reported a WMD of 2.19 days (95% CI 1.56 to 2.81; p<0.001), which decreased from 7.66 (95% CI 5.83 to 9.46; p<0.001) in 2000–2009 to 1.44 (95% CI 0.77 to 2.10; p<0.001) in 2010–2018 (online supplementary figure 7).

The data on ICU-LOS were provided in seven studies and showed that BSIs caused by ESBL producers had a WMD of LOS of 3.07 days (95% CI 1.61 to 4.54; p<0.001).

Heterogeneity of the studied effect modifiers did not reach statistical significance when assessed by metaregression (online supplementary table S6). Sensitivity analysis based on the quality of studies revealed no notable difference in the effect estimates after exclusion of low-quality studies (data not shown). Egger's test and the funnel plots (online supplementary figures 1 and 2) showed evidence for small-study effects (p<0.001) and publication bias.

DISCUSSION

This systematic review shows that ESBL production has a significant impact on the most relevant patient-related clinical outcomes. In the subgroup analyses, all-cause mortality, attributable mortality and LOS both in hospital and in ICU were higher for patients with BSIs due to ESBL-producing *Enterobacteriaceae* than for patients with BSIs due to non-ESBL-producing strains. Non-invasive infections caused by ESBL-producing strains were associated with higher all-cause mortality and prolonged LOS. Within the limitation of the low number of studies evaluating specific patient populations, paediatric patient and patients with cancer seemed to suffer a higher impact of ESBL invasive infections than the overall population. Stratifying by pathogen type, the impact of ESBL production was higher for *E. coli* BSIs than for *K. pneumoniae* BSIs. No relevant differences in mortality analysis emerged with stratification by study design or country income level. Impact of ESBL infections on mortality became more evident in more recent studies. Studies reporting on appropriateness of empirical therapy, ESBL resistance mechanisms and MICs showed a higher clinical impact of ESBL infections than studies not assessing these

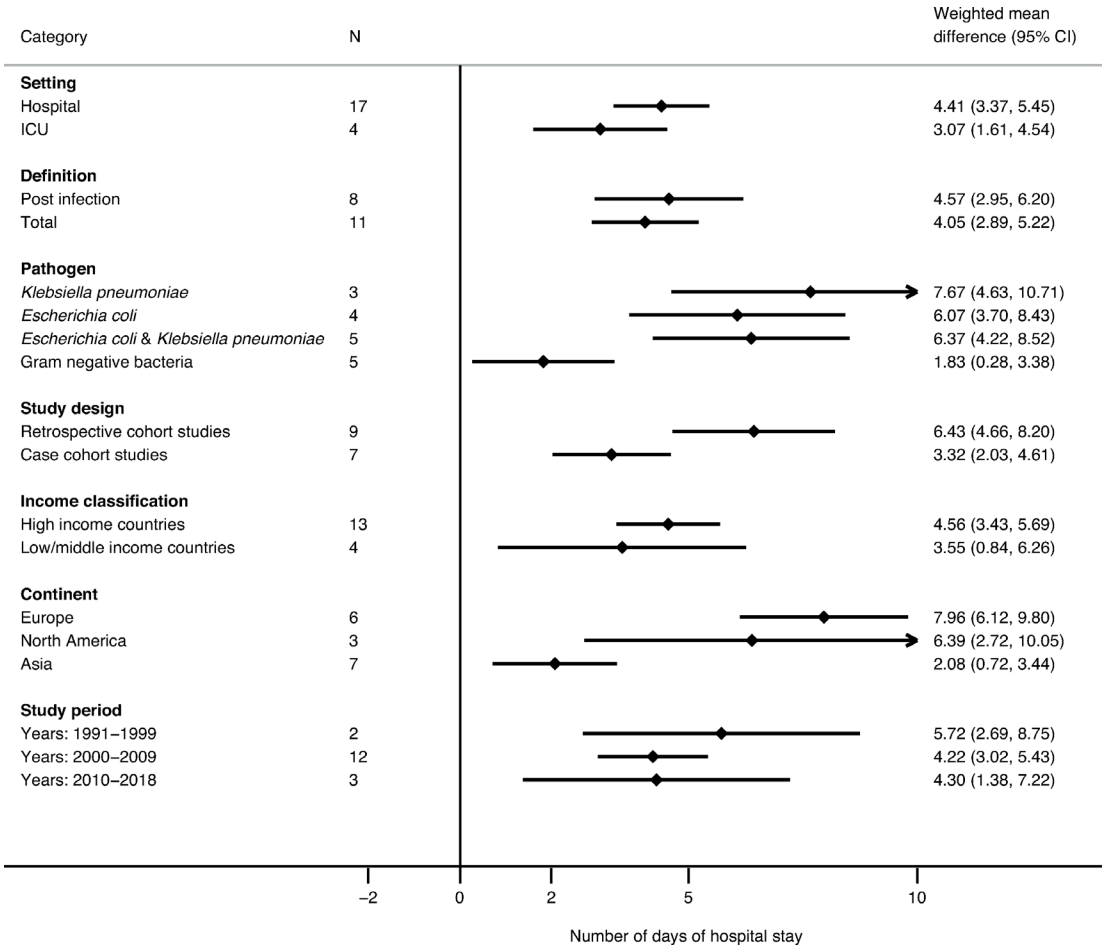

Figure 4 Weighted mean difference in the length of stay for patients with extended-spectrum beta-lactamase (ESBL) bloodstream infections compared with patients with non-ESBL bloodstream infections. ICU, intensive care unit.

variables. In particular, pooled ORs adjusted for inappropriate empirical treatment showed a remarkably higher OR for mortality in patients with ESBL infections.

Our findings confirm the results of previous systematic reviews. Schwaber *et al* performed a systematic review comparing mortality in ESBL BSIs and non-ESBL BSIs in studies published through 2003.[2] The authors show a pooled RR for all-cause mortality of 1.85 but, in contrast to our study, they combined *E. coli*, *Klebsiella* spp and *Proteus* spp in the analysis because of sample size limitations. Rottier *et al* analysed studies published through 2010 and adjusting results for inappropriate empirical treatment found an adjusted OR of 1.37.[3] Our study, adding more than 50 studies in 17 years to the Rottier systematic review, confirmed the clinical importance of ESBL production to all-cause mortality and for the first time assessed the role of ESBL production on attributable mortality. We addressed relevant effect modifiers through subgroup analyses and found that population, pathogen and assessment of empirical therapy all had an impact on estimates. Because we believe that appropriate empirical treatment plays a relevant role in invasive infections, we performed a secondary analysis by pooling only adjusted ORs and confirming the significant impact of antibiotic resistance as already shown in a previously published systematic review.[97] The lack of consideration of appropriateness of therapy in the studies evaluating mortality seems to underestimate the impact of ESBL production on mortality. However, studies assessing the impact of appropriate therapy did not provide homogeneous definition and could refer either to empirical or definite therapy or a single component irrespective of the dosage, making results difficult to interpret. Especially in infections with different sources and different clinical severity, the sole contribution of empirical therapy remains challenging to measure. For example, patients with UTI receiving inappropriate empirical antibiotic therapy can potentially show a favourable outcome, most probably due to the high concentration of antibiotic reached in the urinary tract.[98]

Community acquired ESBL infections emerged in the late 1990s and show an increasing trend.[99 100] Recent study shows that community onset ESBL infections are associated with lower mortality compared with healthcare-associated and hospital-acquired infections.[101] The place of acquisition could not be appropriately addressed in our meta-analysis due to the lack of data in included studies.

Our systematic review contributes to the discussion on the limitation of current evidence for the estimation of mortality due to antibiotic-resistant infections. The

impact of ESBL production on LOS in our study has shown that both BSIs and non-invasive infections lead to prolongation of hospitalisation.

Our study has some limitations. Although results of the meta-analyses were significant in all the subgroups, we could analyse only a limited number of studies providing information for subgroups such as haematological patients and low-income countries, making generalisability of results less certain for these specific patient populations. Only a few studies reported MIC data or specific ESBL molecular resistant phenotype (ie, AmpC). Moreover, publication bias was detected in both the main analyses (all-cause mortality and LOS), thus implying the possibility that results from small studies with non-significant results might have been conducted and not published, resulting in a possible overestimation of our results. The non-homogeneous reporting of some relevant data in published literature (eg, infection type, presence of bacteraemia, disease severity, underlying comorbidities and resistance mechanism) may also have affected the precision of the estimate. A limited number of patients with non-bacteraemic infections was included in our systematic review, thus limiting the generalisability of results to this patients' population. Moreover, patients with ESBL are intrinsically at higher risk of mortality and complications because they are often older, have more comorbidities or higher antibiotic exposure, and are at higher risk of receiving inappropriate empirical treatment.[102] Finally, due to resource constraints, we had to limit our search to PubMed database with the chance of missing relevant studies.

In summary, our systematic review emphasises the importance of suspicion and confirmation of ESBL production as soon as possible for invasive infections and demonstrates that ESBL production increases the risk of attributable mortality and LOS in both hospital and ICU for invasive and non-invasive infections. Patients with ESBL infections remain at higher risk of mortality and prolonged LOS even after adjustment for empirical inappropriate treatment. Control for other relevant effect modifiers is hindered by the sparseness of published data. Individual patient data network meta-analyses are needed to define differences in outcomes between severe intravascular infections and bacteraemia. Future studies addressing the clinical burden of drug-resistant infections must include ESBL production and should assess both the impact of molecular mechanisms of resistance and effect on specific patient populations such as haematological patients and those in LMIC.

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Contributors ET contributed to the study concept. BPG and PS performed data analysis. PS and AC extracted data and wrote the first draft of the manuscript. DL contributed to the first draft of the manuscript. EC and ET wrote the final version of the manuscript. CB reviewed the paper. All authors read, edited and approved the final manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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