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Fecal Colonization With Extended-spectrum Beta-lactamase–Producing *Enterobacteriaceae* and Risk Factors Among Healthy Individuals: A Systematic Review and Metaanalysis

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(See the Editorial Commentary by Turbett and Mansour on pages 319–21.)

Background. Gut colonization is a risk factor for infections with extended-spectrum beta-lactamase (ESBL)–producing organisms. We aimed to determine the ESBL class A reservoir among healthy individuals.

Methods. We searched PubMed and EMBASE (through 10 July 2015) looking for studies that contained data for fecal colonization with ESBL class A bacteria among healthy individuals for each World Health Organization–defined region. Distribution of isolates among cefotaximase (CTX-M), sulfhydryl variable, and temoneira enzymes and data on previous antibiotic use, international travel, previous hospitalization, and animal contacts were extracted.

Results. Sixty-six of 17 479 studies on 28 909 healthy individuals were included. The pooled prevalence of ESBL class A colonization was 14% (95% confidence interval [CI], 9, 20), with an increasing trend of 5.38% annually ($P = .003$). The pooled prevalence was higher in Asia and Africa (ranging from 46%, 95% CI, 29, 63 to 15%, 95% CI, 4, 31) and lower but still significant in central (3%, 95% CI, 1, 5), northern (4%, 95% CI, 2, 6), and southern Europe (6%, 95% CI, 1, 12) and the Americas (2%, 95% CI, 0, 5). CTX-Ms were the prevalent ESBL enzyme (69%). Antibiotic use for the prior 4 or 12 months was associated with a high colonization risk (risk ratio [RR] = 1.63; 95% CI, 1.19, 2.24 and RR = 1.58; 95% CI, 1.16, 2.16, respectively). International travel was also correlated with ESBL colonization [(RR = 4.06, (95% CI, 1.33, 12.41)].

Conclusions. The ESBL colonization rate among healthy individuals is significant worldwide. This should be taken into consideration in infection control and antibiotic management decisions.

Keywords. ESBL fecal colonization; community; healthy population; risk factors; metaanalysis.

Extended-spectrum beta-lactamases (ESBLs) are enzymes that mediate resistance to most beta-lactams. ESBL-producing *Enterobacteriaceae* (ESBL-PE) have recently emerged as a major public health threat [1–3]. They have been traditionally linked to hospitals, but community-acquired infections are becoming more common [4]. ESBL infections are associated with high mortality, prolonged length of hospital stay, and high cost [5–7]. Treatment options are limited, and patients often require treatment with carbapenems [8]. In countries including China and India, the consumption of last-resort antibiotics has almost doubled over the last decade [9].

Among the numerous enzymes associated with ESBL activity, ESBL class A (mainly represented by cefotaximase [CTX-M], temoneira [TEM], and sulfhydryl variable [SHV]) is most often detected [10–12]. CTX-Ms can diffuse easily due to their mobile genetic elements that mediate rapid dissemination [13–15]. These genes are also linked with transfer of other genes that confer resistance to beta-lactams, as well as other antibacterial agents such as quinolones [16, 17]. Although they represent a community-derived ESBL type, bacterial isolates that produce CTX-M enzymes have replaced those that produce TEM and SHV in hospitals [8, 18].

ESBL infections are associated with colonization [19–22] and, independent of the infection site, the digestive tract seems to be the main reservoir from which ESBLs are derived [19, 23, 24]. In this systematic review and metaanalysis, we estimate the prevalence of ESBL class A colonization among healthy patients and assess the factors that are associated with the colonization status.

METHODS

This systematic review and metaanalysis was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (Supplementary Table 1).

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Data Sources and Searches

We used the terms "ESBL" OR "(extended-spectrum beta-lactamase)" to search the PubMed and EMBASE databases for studies published from 31 October 1978 to 10 July 2015 and to identify studies that reported the prevalence of colonization with ESBL class A among healthy individuals. Two authors (S. K., T. K.) independently screened titles and abstracts to identify relevant studies. The search was supplemented by searching the reference lists of all eligible studies. Our analysis included published literature and abstracts from conference proceedings published in EMBASE.

Study Selection

Studies were considered eligible if they reported extractable data on the prevalence of ESBL fecal colonization among healthy individuals. Individuals were deemed healthy if they were characterized explicitly as such or reported as asymptomatic and were recruited from the community voluntarily for a research purpose without seeking medical advice for any health problem. Studies were included if the number of isolates per individual, sample, and/or collection time was clearly reported to avoid duplicate samples. Eligible studies clarified that the data were based on fecal samples or rectal swabs and reported the total number of positive ESBLs before proceeding to study a particular enzyme subpopulation (to avoid ESBL carriage underestimation). Studies of the same population performed at different time points were included only once, and we included the first-time data. In travel-related prospective studies, we used the pretravel sampling data as prevalence. A restriction for English and French literature was imposed.

Data Extraction and Quality Assessment

The primary outcomes were the prevalence of ESBL fecal colonization among healthy individuals and the dominant type of ESBL class A enzyme among them. The prevalence was calculated by dividing the number of healthy individuals with positive initial and confirmed screening results for ESBL by the total number of individuals who were screened. The dominant type of ESBL enzyme was calculated from the data provided by 28 studies, which provided extractable data among CTX-M, SHV, and TEM enzymes [25–52]. All enzymes were detected by polymerase chain reaction. As secondary outcomes, we estimated the impact of exposure to antibiotics, traveling abroad, previous hospitalization, and animal contacts. Two reviewers (S. K., T. K.) independently extracted data from eligible studies, and discrepancies were resolved by consensus.

The methodological quality of included studies was assessed by 2 reviewers (S. K., T. K.) who used the Newcastle–Ottawa scale checklist independently [53]. Each study could get up to 5 stars, and studies that were awarded ≥4 stars were considered to be of high quality (Supplementary Table 2).

Data Synthesis and Analysis

A random effects metaanalysis was carried out to calculate the combined prevalence and the 95% confidence intervals (CIs) using the approach of DerSimonian and Laird [54]. The variance of the raw proportions was stabilized using the Freeman–Tukey arcsine methodology [55], and no studies with 0% or 100% proportions were excluded from the metaanalysis [56, 57]. Studies were grouped according to World Health Organization (WHO) regions [58]. The τ-squared statistic was calculated as a measure of heterogeneity [59], and meta-regression analyses were implemented to perform subgrouping analysis and to account for potential sources of heterogeneity and confounding [60].

The effect of predefined covariates on ESBL prevalence was explored through univariate and multivariate random effects meta-regression using Knapp and Hartung modification. The covariates included in the meta-regression model are presented in Supplementary Table 3. Evidence for publication bias was sought using the Egger's regression test (ET) [61]. To model the time trends for ESBL colonization, an index year of each eligible study was determined and then the model coefficients were transformed to rates and plotted against this year along with the observed prevalence rates [62]. The effect of different factors on the risk of colonization was evaluated using random effects metaanalysis and reported as unadjusted risk ratio (RR) estimates and CIs (95% CI), with heterogeneity measured using the Cochran Q test. Statistical analysis was performed using Stata v13. Statistical significance was set at 0.05. For heterogeneity testing, $P_Q < .10$ was considered significant due to the low power of the Q test.

RESULTS

The database search yielded 17 479 studies (7118 from PubMed and 10 361 from EMBASE). The review process is shown in the PRISMA flowchart (Figure 1) All included studies were deemed of high quality; individual characteristics are presented in Supplementary Table 4 [25, 27–40, 41–51, 63–101].

Based on 28 909 individuals included in 66 studies, the pooled prevalence of fecal colonization with ESBL-PE was 14% (95% CI, 9, 20; $\tau^2 = 0.37$; ET = 1.93, $P_{ET} = .079$). Stratifying the studies per WHO-defined region, the pooled prevalence in the West Pacific was 46% (95% CI, 29,63; $\tau^2 = 0.37$), 22% in Southeast Asia (95% CI, 7,44; $\tau^2 = 0.67$), 22% in Africa (95% CI, 5,47; $\tau^2 = 0.27$), 15% in the eastern Mediterranean (95% CI, 4,31; $\tau^2 = 0.28$), 4% in Europe (95% CI, 2,5; $\tau^2 = 0.02$; ranging from 3% in central Europe [95% CI, 1,5] to 4% in northern Europe [95% CI, 2,6%] and 6% in southern Europe [95% CI, 1,12%]), and, finally, 2% in the Americas (95% CI, 0,5; $\tau^2 = 0.05$; Figures 2 and 3, Supplementary Table 5). In Supplementary Table 6, we present the distribution of study sample per antibiotic combination for initial or confirmatory ESBL screening, type of sample, age group, and the microbiological guidelines followed in each study. A time trend plot revealed a statistically significant worldwide increase in ESBL colonization prevalence among healthy individuals, with an annual

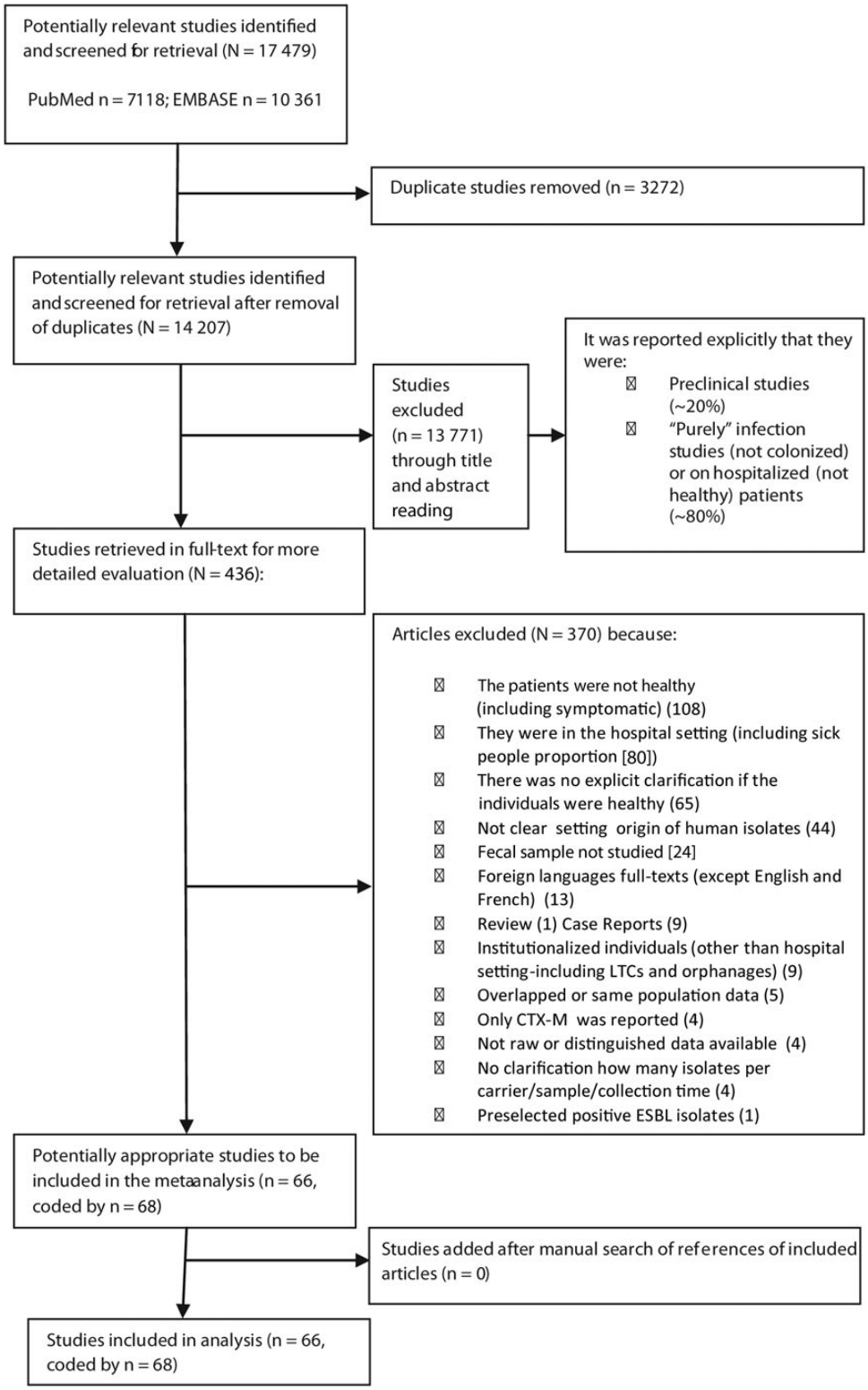

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of metaanalysis. Abbreviations: CTX-M, cefotaximase; ESBL, extended-spectrum beta-lactamase; LTC, long-term care.

increase rate of 5.38% ($P = .003$; $R^2 = 12.24$; Figure 4). Stratification per age group is shown in Supplementary Figures 1, 2 and Table 4.

Based on 6 studies, providing data on 1528 individuals and their antibiotic use within 12 months, individuals treated with antibiotics were significantly more likely to be colonized

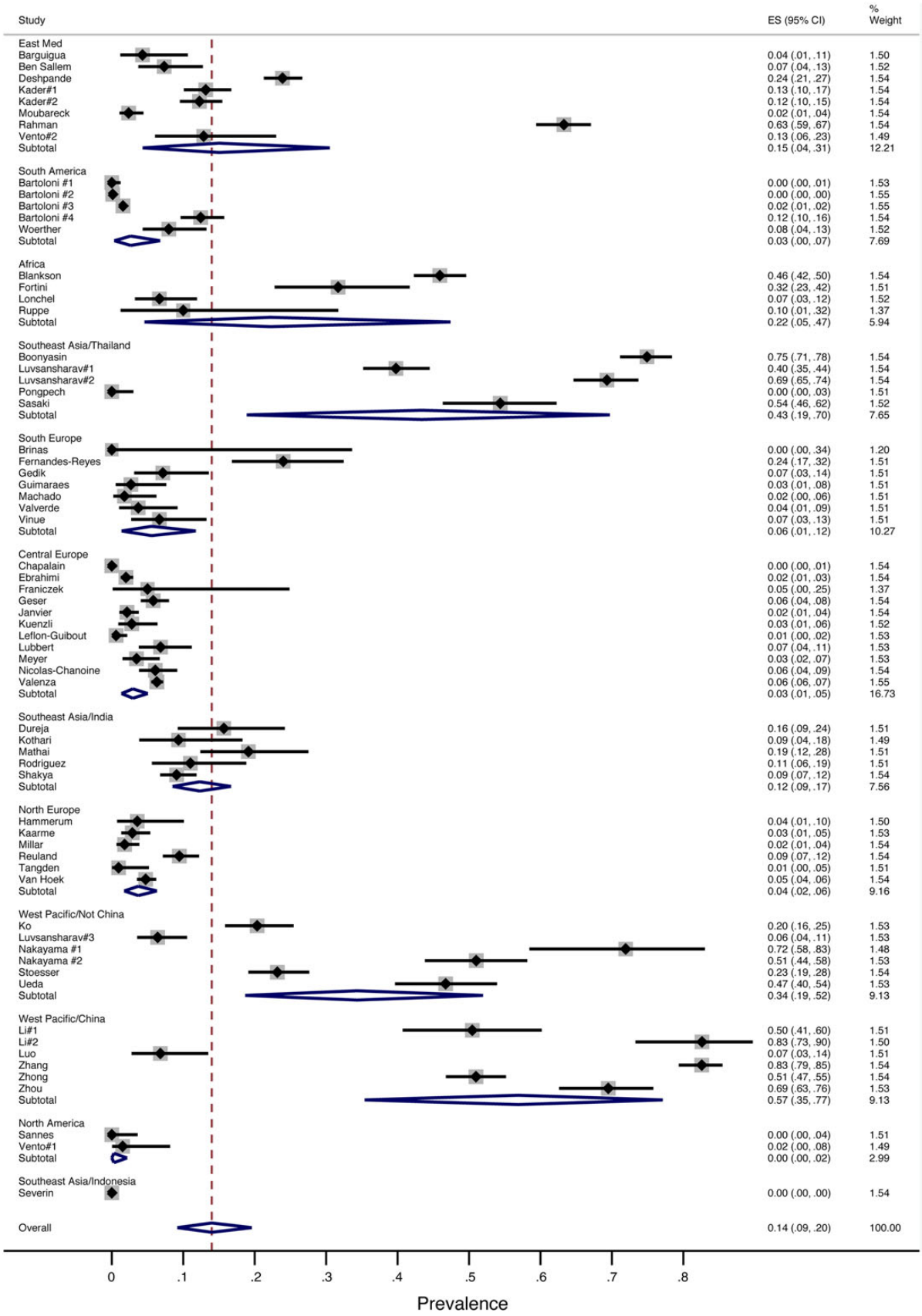

Figure 2. Forest plot of included studies stratified by World Health Organization regions and areas. Individuals and combined estimates of extended-spectrum beta-lactamase colonization. Abbreviations: CI, confidence interval; ES, effect size.

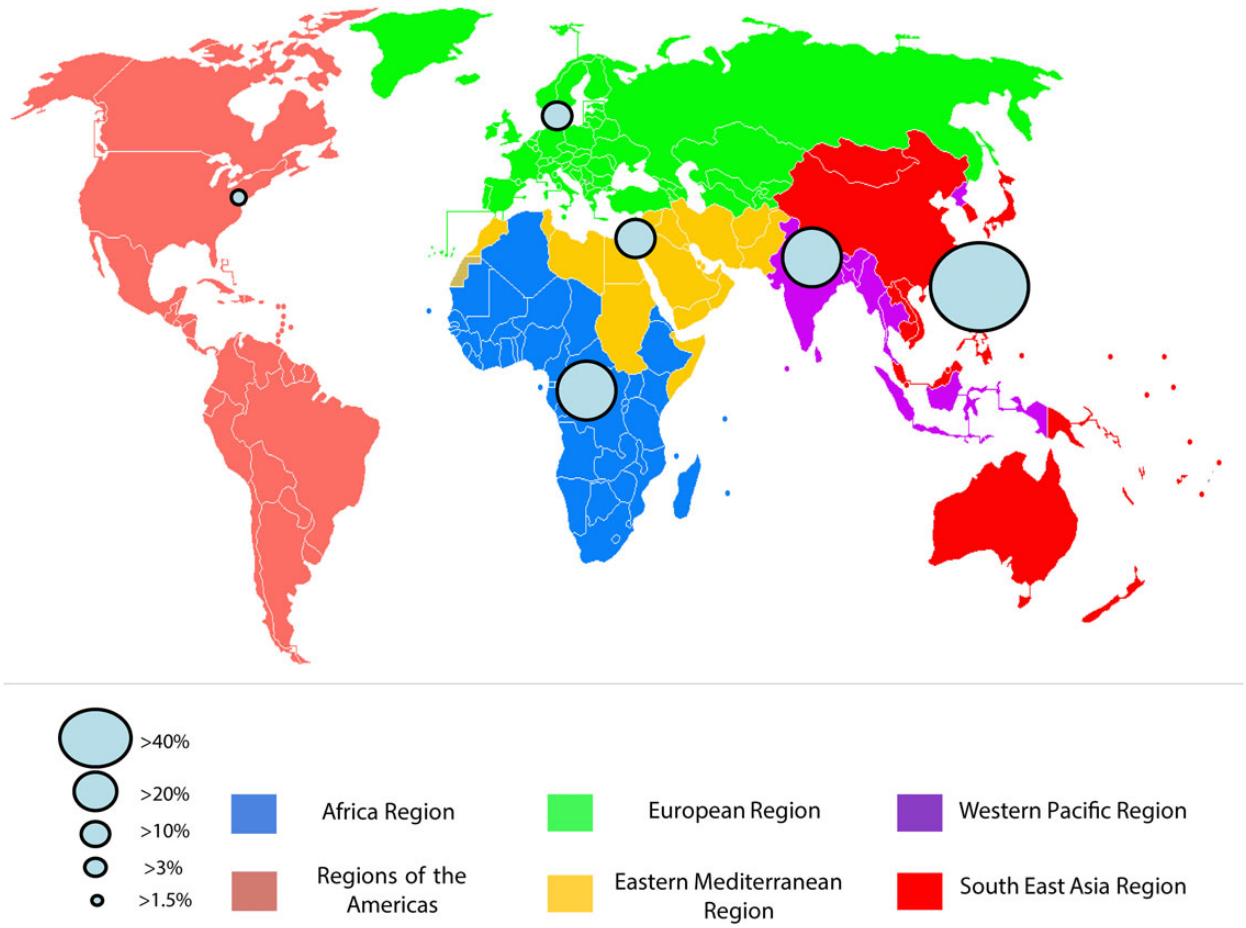

Figure 3. Pooled prevalence of fecal colonization with extended-spectrum beta-lactamase (ESBL)–producing organisms per World Health Organization region. Circle size represents the ESBL colonization rates.

with ESBL (RR = 1.58; 95% CI, 1.16,2.16; Q = 3.27, P_Q = .66; ET = −1.10, P_{ET} = .08; Figure 5, Supplementary Table 7) [27, 30, 42, 43, 74, 94]. Also, 5 of the studies reported antibiotic use during the previous 4 months for 1297 individuals, and these individuals were 63% more likely to be colonized with ESBL compared with those not treated with antibiotics (RR = 1.63; 95% CI, 1.19,2.24; Q = 2.32, P_Q = .68; ET = −0.95, P_{ET} = .20; Figure 5, Supplementary Table 7) [27, 30, 42, 43, 94]. Further data on the stratification per antimicrobial class were not provided in individual studies. Thus, no correlation between a specific antibiotic class and the risk of colonization could be made.

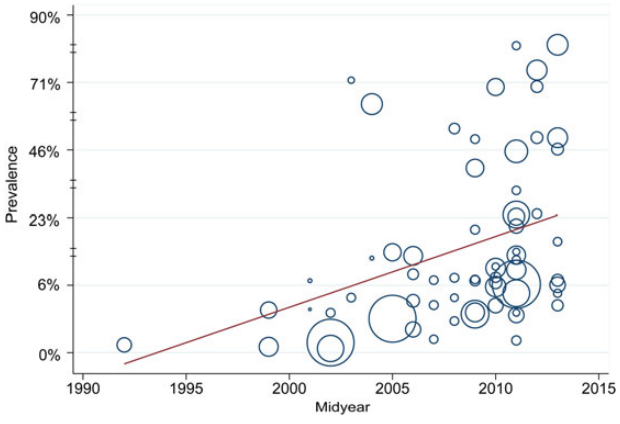

Figure 4. Extended-spectrum beta-lactamase class A colonization trends over time. Circles represent the estimates from each study, sized according to the precision of each estimate. The fitted regression line is depicted by study midyear. The estimated annual increase is 5.38%.

Based on 6 studies that provided data on 1887 individuals, those who traveled internationally were >4 times more likely to be colonized with ESBL (RR = 4.06; 95% CI, 1.33,12.41; Q = 50.96, P_Q = .00; ET = 0.68, P_{ET} = .90; Figure 6, Supplementary Table 7) [27, 36, 42, 74, 77, 79]. Regarding travel destination, based on 3 studies on 182 individuals, those who traveled to India were 240% more likely to be colonized with ESBL compared with those who traveled to any other destination (RR = 2.4; 95% CI, 1.26,4.58; Q = 18.44, P_Q = .00; ET = 5.32, P_{ET} = .28; Supplementary Table 7) [36, 77, 79]. Travel to Africa was tested as a potential high-risk destination but did not increase the risk for ESBL colonization (RR = 0.94; 95% CI, .14,6.17; Q = 13.44, P_Q = .00; ET = 0.71, P_{ET} = .88; Supplementary Table 8) [36, 74, 79].

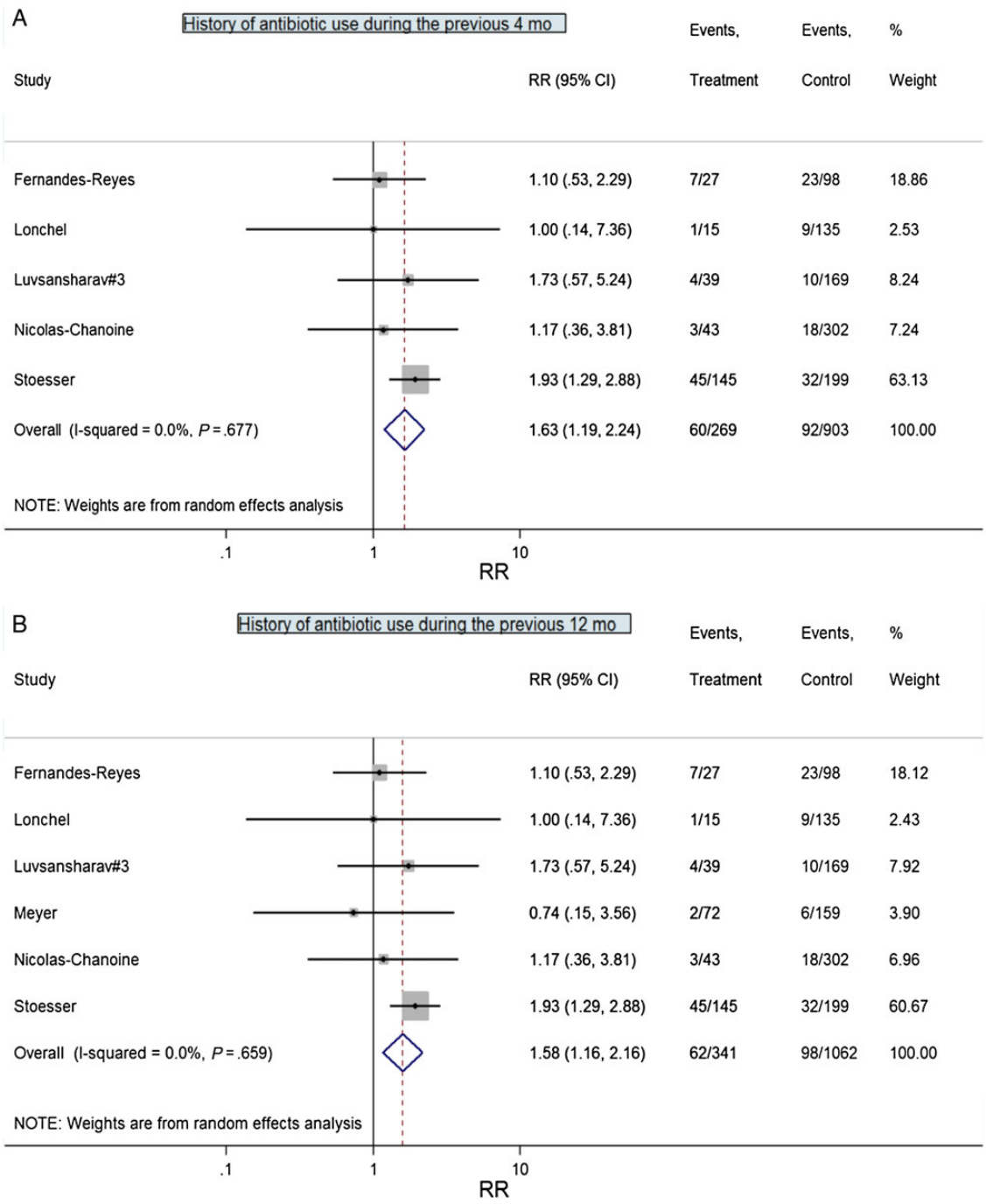

Figure 5. Forest plot of included studies. Relative risk (RR) estimates of antibiotic use history during the previous 4 months (*A*) and 12 months (*B*) among colonized and noncolonized individuals. Abbreviation: CI, confidence interval.

No significant association was found between colonization and either lifetime hospitalization (5 studies on 1379 individuals; RR = 1.18; 95% CI, .78,1.81; Q = 2.28, P_Q = .67; ET = 0.09, P_{ET} = .91) [27, 30, 42, 74, 94] or hospitalization within the previous year (4 studies on 1163 individuals; RR = 1.28; 95% CI, .82,2.03; Q = 1.44, P_Q = .70; ET = 0.30, P_{ET} = .70; Supplementary Table 7) [27, 30, 42, 74]. In addition, no significant association between animal contact and the risk of colonization was found based on 5 studies on 963 individuals (RR = 1.39; 95% CI, .89,2.18; Q = 4.73, P_Q = .32; ET = 1.74, P_{ET} = .14; Supplementary Table 7) [26, 39, 42, 43, 74].

In multivariate meta-regression analysis, among the preselected assessed factors/covariates (Supplementary Table 3), the prevalence of ESBL colonization was significantly affected

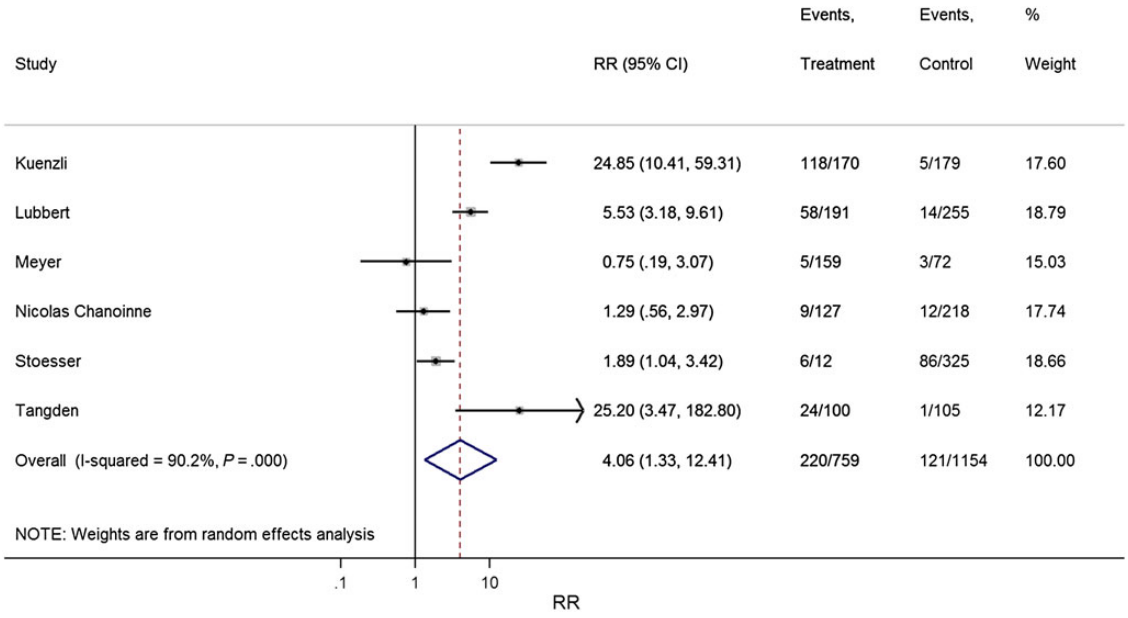

Figure 6. Forest plot of included studies. Relative risk (RR) estimates of history of international travel among colonized and noncolonized individuals. Abbreviation: CI, confidence interval.

by the geographical distribution, showing that the West Pacific and Southeast Asia demonstrated the strongest positive association with ESBL colonization rate. Predictably, the publication of new guidelines in 2010 was also a significant factor that affected our estimated prevalence. Overall, 49.80% (adjusted R-sq) of the between-study variance was found to be justified by the listed covariates.

A total of 59 of 66 studies provided data on the number of ESBL isolates, including carriers who were found with more than 1 isolate [21, 25, 27, 28, 30–40, 41–51, 63–71, 73–76, 79–89, 91–97, 99–102]. This pooled prevalence of ESBL colonization was 15% (95% CI, 9,21; $\tau^2 = 0.39$; ET = 1.92, $P_{ET} = .11$). Notably, 69% of isolates carried CTX-M enzymes, 21% TEM, and 10% SHV (Supplementary Table 9).

DISCUSSION

A significant and increasing burden of ESBL class A exists among healthy individuals worldwide. Overall, 14% of healthy healthy individuals are colonized with ESBL-PE. The colonization rates are increasing, with an annual rate of approximately 5%; rates are even higher in the West Pacific, Southeast Asia, Africa, and the eastern Mediterranean. Given the proven link between ESBL infections and fecal colonization [103], along with the morbidity and mortality related to ESBL infections [104], the high incidence rate should be taken into consideration when implementing infection control, stewardship measures, and antimicrobial selection.

Interestingly, prior antibiotic use within the past 4 or 12 months was linked to an increased possibility of colonization. The strength of this link is confirmed not only by the observation that the closer antimicrobial treatment was to screening, the greater was the risk for carriage but also from the lasting effect (up to 12 months) prior to screening. This is not surprising given the established causative correlation between antibiotic use and ESBLs [16] and identifies a demarcated high-risk population.

Previous studies have suggested that travel contributes to the acquisition of ESBL [18, 105]. The strong link found in our analysis may help explain the rising trend of ESBL worldwide, as travelers are moving from high-prevalence areas to lower-prevalence areas. The increased incidence in these different regions has been linked to a series of local features such as misuse of beta-lactams for empirical treatment of serious infections, poor-quality drinking water, and defective sewage disposal [106, 107].

No apparent association was found with animal contact. Livestock, wild animals, and rarely pets have been found to be colonized with ESBLs at low rates [108–110]. However, the increasing use of antibiotics in veterinary practices has raised the concern for probable exchange of ESBLs between humans and animals [111]. This may emerge as a risk factor for colonization later when the consequences of frequent antibiotic use in animals are more apparent.

We did not identify a statistically significant correlation between hospitalization and colonization status. According to studies that assessed risk factors exclusively in community individuals, hospitalization was not an independent risk factor [112, 113]. During the last decade, CTX-Ms have been commonly

detected, not only in the community but also in hospitals [8, 18, 114–117]. This implies that boundaries between hospitals and the community have become blurred in terms of ESBL spread and that influx and efflux from communities to hospitals and vice versa are frequently documented. Consequently, previous hospitalization may no longer be an important risk factor for ESBL colonization due to this perpetual, undirected flow of responsible enzymes, irrespective of the setting. However, studies focused on the immediate post-hospitalization period, which has been associated with increased ESBL acquisition, should be performed [114].

Regarding potential limitations of our study, we note that a fundamental change in screening guidelines, which took place in 2010 and was implemented by the Clinical and Laboratory Standards Institute and European Committee on Antimicrobial Susceptibility Testing. Many isolates that were previously stratified as sensitive have been categorized as intermediate or resistant since implementation of the guidelines [118–120]. Our prevalence data may have been affected by this change. However, even if we focus in studies conducted either before 2010 or after, the prevalence trend remains upward. Additionally, there is lack from data in North America that should be addressed. Moreover, we eliminated the possibility of publication bias by using Egger's *Q* test [61]. It was not found to be statistically significant in any estimation.

In conclusion, healthy individuals are an important reservoir for ESBLs and the colonization rate appears to be increasing over time. CTX-Ms are the predominant enzyme, and this worldwide distribution should be addressed as it relates to infection control and antimicrobial selection ramifications. Early interventions, including active surveillance followed by patient isolation and precautionary measures, may be considered, similar to approaches for the control of methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *enterococci* [121, 122]. Such measures could focus on individuals who received antibiotic treatment during the previous months or on international travelers, especially those who visited high-risk areas. Further research is warranted to determine the efficacy of these measures and the evaluation of decolonization strategies.

Supplementary Data

Supplementary materials are available at http://cid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

Author contributions. S. K., T. K., and E. M. accept full responsibility for the conduct of the study, had access to the data, and had control of the decision to publish.

Specific author contributions: S. K. and T. K. had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. S. K. conceptualized and designed the study; performed the literature search; participated in data collection, extraction, and interpretation; prepared tables and figures; performed the statistical analysis; wrote and drafted the initial manuscript; approved the final manuscript as submitted; and agreed to be accountable for all aspects of the work by ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved. T. K. conceptualized and designed the study; performed the literature search; participated in data collection, extraction, and interpretation; prepared tables and figures; performed the statistical analysis; wrote and drafted the manuscript; approved the final manuscript as submitted; and agreed to be accountable for all aspects of the work by ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved. M. A. participated in data interpretation, performed the statistical analysis, reviewed and revised the manuscript, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work by ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved. C. G. participated in data interpretation, performed the statistical analysis, reviewed and revised the manuscript, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work by ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved. E. M. conceptualized and designed the study, interpreted the data, reviewed and revised the manuscript, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work by ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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