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Global prevalence of human intestinal carriage of ESBL-producing *E. coli* during and after the COVID-19 pandemic

Rita W.Y. Ng [1,2], **Liuyue Yang**[1], **Sai Hung Lau**[1], **Peter Hawkey**[3] **and Margaret Ip** [1,2]*

[1]*Department of Microbiology, Faculty of Medicine, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, N.T., Hong Kong, China;* [2]*S. H. Ho Research Centre for Infectious Diseases, The Chinese University of Hong Kong, China;* [3]*Institute of Microbiology and Infection, University of Birmingham, UK*

*Corresponding author. E-mail: margaretip@cuhk.edu.hk

Background: There is a pressing need for global surveillance of ESBL-producing *Escherichia coli* due to its health impacts, travel and increased antibiotic use during the COVID-19 pandemic. This systematic review and meta-analysis aimed to summarize evidence investigating the global prevalence of ESBL *E. coli*.

Methods: Four databases, including Embase, MEDLINE, PubMed and Web of Science, were searched for quantitative studies that reported prevalence data of faecal carriage of ESBL-producing *E. coli* published between 23 April 2021 and 22 April 2024. Meta-analysis was performed using the inverse variance heterogeneity model.

Results: Of the 25 studies (13 901 unique participants) included for final analysis, the overall pooled prevalence of ESBL *E. coli* was 25.4% (95% CI, 19.7%–31.2%). The pooled prevalences of ESBL *E. coli* in healthy individuals in community settings and inpatients in healthcare settings were 23.4% (95% CI, 14.7%–32.2%) and 27.7% (95% CI, 18.8%–36.7%), respectively. Nearly one-third of the included studies (32%) were from the Western Pacific Region. There was a significant between-group difference for studies with different WHO regions and healthcare contact.

Conclusions: The pooled prevalence of ESBL *E. coli* remains high and there was a significant between-group difference for different WHO regions, with the highest being in Asian regions. Standardized surveillance of antimicrobial resistance and antibiotic stewardship especially in these regions are needed to enhance the control of this global emergency.

Introduction

Infections caused by ESBL-producing Enterobacterales are of great concern, particularly since these organisms have been increasingly implicated in both community-acquired extraintestinal infections[1] and hospital-acquired infection.[2] The WHO has updated the Bacterial Priority Pathogens List in 2024 to include third-generation cephalosporin-resistant Enterobacterales as one of the Critical Group bacterial pathogens.[3] Infections caused by ESBL-producing Enterobacterales account for higher morbidity and mortality rates compared with those due to less resistant organisms.[4] Although hospital outbreaks of ESBL-producing bacteria due to contamination of common facilities such as toilets occurs,[5] a recent molecular epidemiology study showed that the infections in hospitalized patients are primarily acquired from community colonization.[6]

Given this healthcare and infection control emergency, the focus of this meta-analysis is the global prevalence of human intestinal carriage of ESBL-producing *Escherichia coli*. Intestinal carriage of ESBLs *E. coli* often precedes systemic infection, and treatment will involve antibiotics such as carbapenems as the bacteria are resistant to previously used broad-spectrum antibiotics. There is a pressing need for global surveillance of ESBLs because of their health impacts, the frequency of international travel and a much high prevalence of ESBL-producing bacteria in the developing regions of the world.[7] A previous study found the rate of human intestinal ESBL *E. coli* carriage in both community and healthcare settings worldwide was 21.1% in patients in healthcare settings and 17.6% in healthy individuals in the community during the period from 2020 to 2021.[8] The intestinal carriage of ESBL *E. coli* is usually asymptomatic and persistent;[9] however, previous study has shown the association of faecal

carriage with ESBL *E. coli* infections.[10] The higher rates of human faecal ESBL *E. coli* carriage in hospital settings compared with the community may be attributable to the use of antibiotics.[11] Furthermore, antibiotic-mediated dysbiosis in the gut and loss of colonization resistance could facilitate the transmission of ESBL *E. coli* in the hospital setting via patients and the environment. The veterinary use of antibiotics is also a major driver of carriage of ESBL-producing organisms in the community. A study found that there were many commonly shared ESBL genes, including $bla_{CTX-M-14}$, $bla_{CTX-M-27}$, $bla_{CTX-M-55}$ and $bla_{CTX-M-65}$, in human faeces and urine samples, food-producing animals and retail meat in China,[12] suggesting horizontal spread of the organism. ESBL *E. coli* is the indicator organism used by the WHO for global monitoring under the One Health approach to combat antimicrobial resistance (AMR).[13] In the post-COVID-19 era, there has been an increase in the incidence density of resistant Gram-negative organisms including ESBL Enterobacterales.[14] The high level of antibiotic prescriptions during the COVID-19 pandemic, despite the low proportion of patients with confirmed bacterial infection, is likely to have had an effect on ESBL rates.[15] Although many studies have reviewed the prevalence of human intestinal carriage of ESBL-producing *E. coli* in different settings, no systematic review or meta-analysis, to our knowledge, has determined the global prevalence of human intestinal carriage of ESBL-producing *E. coli* following the COVID-19 pandemic. The aim of this meta-analysis, therefore, was to determine the global prevalence of human intestinal carriage of ESBL-producing *E. coli*.

Methods

This meta-analysis was developed as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[16] reporting guidelines. The study was registered in the PROSPERO International Prospective Register of Systematic Reviews (CRD42024548720).[17]

Data sources

A comprehensive literature search for publications published between 23 April 2021 and 22 April 2024 was completed in Embase, MEDLINE, PubMed and Web of Science. Search terms were related to organism name, resistance type, type of faecal specimen and origin of ESBL-producing organism, and can be found in Appendix S1 (available as Supplementary data at *JAC-AMR* Online). Grey literature was searched via Google Scholar using the search terms and the reference list of included articles.

Study selection

Studies included in the meta-analysis were observational studies and prospective studies reporting the prevalence of ESBL *E. coli*. Studies were included if they included patients (healthcare settings) or healthy individuals (community setting) of all ages. Study subjects were classified into four categories by the duration of contact with a healthcare setting at the time of stool sampling: (i) healthy individuals (in the community); (ii) admitted ≤48 h; (iii) admitted <72 h; (iv) admitted with time of screening unspecified; and (v) living in nursing care facilities. Studies were included if the double-disc synergy test (DDST) was used to confirm ESBL production, or the presence of ESBL genes was determined by PCR. We included original articles written in English and excluded case series, case-control studies, conference abstracts, theses and reviews. Studies that reported prevalence of faecal ESBL *E. coli* among patients with recurrent urinary tract infection were excluded. We also excluded studies of ESBL *E. coli* carriage in returning travellers from countries with a high

prevalence or among household contacts of colonized individuals, those involved with non-human study subjects or non-faecal samples, and studies that included microorganisms without species identification.

Data extraction

After removing duplicates, titles and abstracts were screened, followed by full-text screening. Screening was completed by two independent reviewers (R.W.Y.N. and S.H.L.), with discrepancies resolved via discussion among the review authors. A data extraction template was developed, and the following information was extracted for each study: authors, year of publication, country, WHO area, study design, sample size, study setting, type of healthcare contact, total number of individuals with stool sample screening performed, number of ESBL *E. coli*–positive individuals among those screened and method of ESBL detection in stool sample. Included studies were assessed for internal validity and bias risk using the critical appraisal tool, the Joanna Briggs Institute (JBI) Appraisal Checklist for reporting prevalence data.[18] The JBI tool is found in Appendix S2. The research team decided that good-quality studies needed to score ≥70% (score of ≥7 of 9), moderate-quality studies needed to score 50% to <70% (score of 5 or 6 of 9), and poor-quality studies scored <50% (score of ≤4 of 9). These quality assessment threshold scores have been used in past reviews.[19] Quality assessment was completed on all included studies by two independent reviewers (R.W.Y.N. and S.H.L.). Any disputes relating to quality assessment between the reviewers were resolved by discussion with the senior supervisor (M.I.).

Statistical analysis

Data analysis involved determining an overall pooled prevalence of ESBL *E. coli* in healthcare and community settings from 25 included studies.[20–44] All included studies were either cohort or cross-sectional studies. Subgroup analysis was completed for the general population and reviewed ESBL prevalence by WHO regions (African Region, Region of Americas, South-East Asian Region, European Region, Eastern Mediterranean Region, Western Pacific Region), study design, study settings (community setting or healthcare settings) and ESBL confirmation method. A meta-analysis could be completed only if there were two or more studies included in the subgroup. Significance testing between the subgroups was completed via the 95%CIs. A random-effects meta-analysis was chosen for meta-analysis. Statistical heterogeneity between the studies was evaluated using the I^2 statistic and Cochran Q test. Heterogeneity was considered an issue if the I^2 statistic was >40% and/or the Q statistic was significant at two-sided $P=0.01$.[45] The Egger test was used to assess publication bias. Library 'meta', 'metasens ' and 'ggplot2' for the R environment were used for data analysis.

Results

A total of 25 studies met the inclusion criteria and were therefore included in the meta-analysis. The details of these studies are listed in Table 1. Figure 1 shows the PRISMA flow diagram.

The meta-analysis included non-duplicate stool samples from 9164 healthy individuals (13 articles in community settings) and 4737 inpatients (12 articles in healthcare settings). There was a total of 13 901 stool samples, with 2238 stools with ESBL-producing *E. coli* isolated across these studies. Five studies were conducted during the COVID-19 pandemic in 2021, with 20 (80%) being published after the year 2022. The 25 studies were from 20 countries and six WHO regions. Three of the included studies reported ESBL prevalence in the general population, whereas the remaining studies focused on special patient groups, including paediatric patients (10 studies) and pregnant women (3 studies). Nearly one-third of

the included studies (32%) were from the Western Pacific Region (including China, Taiwan, Cambodia, Japan and Laos), six (24%) were from the African Region (including Benin, Ethiopia, Kenya, Zambia, Tanzania and Nigeria), five (20%) were from the Eastern Mediterranean Region (including Iran, Lebanon and Pakistan), three (12%) were from the European Region (including Germany, Norway and Switzerland), two (0.08%) were from the South-East Asian Region (Indonesia and Nepal) and one (0.04%) was from the Region of the Americas (Brazil). Table 1 gives study-specific country detail. Six (24%) studies used both the double-disc synergy test (DDST) and PCR as the confirmation method of ESBL detection, whereas 14 (56%) studies used DDST only and 5 (20%) studies used PCR only.

Quality assessment of the included studies

The JBI quality checklist[18] determined that all 25 studies were of good quality (100%). No studies were excluded from the main meta-analysis based on the JBI score. The quality assessment scores for each study are in Table 1.

Meta-analysis base case results

The pooled prevalence of human intestinal carriage of ESBL-producing *E. coli* in healthcare settings and community settings was determined. Figure 2 shows that the overall pooled prevalence of ESBL *E. coli* in healthcare and community settings was 25.4% (95% CI, 19.7%–31.2%, $I^2 = 99\%$). Publication bias as reported in Figure S1 showed major asymmetry [Luis Furuya-Kanamori (LFK) index = 7.12].

Subgroup analyses were completed in which WHO region, study design, study settings (community and healthcare settings), ESBL confirmation method and type of healthcare contact (healthy individuals in the community, admitted to hospital with admission time unspecified, admitted £48 h, admitted <72 h, long-term care facilities) were reported separately. Figure 3 shows a significant between-group difference for studies with different WHO regions ($P < 0.01$). The highest pooled prevalence was observed in the South-East Asian Region, whereas the lowest was in the European Region. Figure 4(a) shows the prevalence of ESBL carriage reported in studies with different types of healthcare contact. Figure 4(b) shows that there were subgroup differences for studies with different healthcare contacts ($P < 0.01$).

The pooled prevalence of ESBL *E. coli* in healthy individuals in community settings was 23.4% (95% CI, 14.7%–32.2%). Thirteen studies were included in the meta-analysis: two studies apiece from Iran and Japan and one study each from Benin, Brazil, Cambodia, China, Germany, Nepal, Norway, Taiwan and Zambia. Ten studies were cross-sectional and three were prospective. Furthermore, the pooled prevalence of ESBL *E. coli* in inpatients in healthcare settings was 27.7% (95% CI, 18.8%–36.7%). Twelve studies were included in the meta-analysis: two studies from Taiwan and one study each from Central Ethiopia, Indonesia, Iran, Kenya, Laos, Lebanon, Nigeria, Pakistan, Switzerland and Tanzania. Ten studies were cross-sectional and two were prospective. There were no statistically significant subgroup differences in terms of study design, study settings (community setting or healthcare settings) and ESBL confirmation method. Figure 5(a) shows the global map of ESBL *E. coli*

prevalence in the WHO regions based on the results of the current study.

Figure S2 provides a sensitivity analysis as demonstrated by the leave-one-out test, which suggested that the results were generally robust.

Discussion

This systematic review and meta-analysis comprehensively summarized the available literature and assessed the current situation regarding the global prevalence of faecal carriage of ESBL-producing *E. coli* during and after the COVID-19 pandemic. The overall pooled prevalence of ESBL *E. coli* was 25.4% (95% CI, 19.7%–31.1%). The pooled prevalences of ESBL *E. coli* in healthy individuals in community settings and healthcare settings were 23.4% (95% CI, 14.7%–32.2%) and 27.7% (95% CI, 18.8%–36.7%), respectively. The finding of a higher pooled prevalence of ESBL *E. coli* in healthcare settings is consistent with the results from a previous study.[8] In contrast, our study showed a trend of further increase in the pooled prevalence of ESBL *E. coli* in both community and healthcare settings. A previous meta-analysis[46] showed a higher prevalence of ESBL *E. coli*, 31% in India and 42% in Pakistan. In contrast to our current study, this earlier meta-analysis included prevalence studies of ESBL-producing organisms isolated from clinical specimens and confirmed by PCR only. Overuse of antibiotics during COVID-19 may be one of the important contributing factors. The consumption of antibiotics during the COVID-19 pandemic increased tremendously in Brazil,[47] Lebanon,[48] Spain,[49] Italy,[50] India,[51] the UK[52] and the USA.[53] Increased exposure to antibiotics leads to AMR.[54] An increase in resistant Gram-negative bacteria was reported during COVID-19 compared with the pre-pandemic period.[55] A higher prevalence of MDR organisms and antibiotic use were reported in low- and medium-income countries, including the Middle East, South Asia and North Africa.[56]

Differences in ESBL carriage rates can be accounted for by the cultural backgrounds of different members in the population and the fact that immigrant communities can have much higher rates of travel to countries with high rates of community carriage, resulting in their colonization. The prevalence of CTX-M ESBL-producing Enterobacterales in England was 7.3% overall, but with a particularly high prevalence for those born in Afghanistan (60%) and travellers to South Asia (38.5%).[57] Caution is required in the interpretation of studies of ESBL prevalence that reported a single carriage rate without investigation of the travel history of the subjects.

Excessive use of antibiotics in various sectors, including agriculture, livestock and human medicine, is another contributor to the development of AMR under the concept of One Health.[58] The use of antibiotics in livestock for growth promotion and disease prevention may contribute to development of AMR in animals and subsequent transmission to humans via the food chain.[59] A recent study showed significant associations were identified between animal antimicrobial consumption and AMR in food-producing animals and between human antimicrobial consumption and AMR specifically in WHO critical priority and high priority pathogens.[60] Efforts from multiple stakeholders, including healthcare professionals, veterinarians, researchers and policymakers are required to combat AMR.

Table 1. Data extraction table for all 25 studies included in the meta-analysis

WHO area	Study name	Country	Year of study	Average (approximated) year of study	Study design	Study setting	Healthcare contact	Total number of individuals screened (stool sample)	Number of ESBL E. coli-positive individuals among screened	Faecal ESBL E. coli carriage rate, %	Method of ESBL detection (stool sample), screening, confirmatory	Quality score
African Region	Sintondji et al.[20]	Benin	2023	2023	Cross-sectional	Community setting	Healthy individuals	296	66	22.3	MacConkey agar supplemented with cefotaxime (4 µg/mL) DDST, PCR	8
Eastern Mediterranean Region	Malekzadegan et al.[21]	Iran	2020	2020	Cross-sectional	Healthcare	Admitted (time of screening not specified)	118	49	41.5	Combination disc test PCR	7
Western Pacific Region	De Lauzanne et al.[22]	Cambodia	2015–2016	2016	Cross-sectional	Community setting	Healthy individuals	423	315	74.5	Drigalski plates supplemented with cefotaxime 2 mg/L DDST, PCR	9
African Region	Shenkute et al.[23]	Central Ethiopia	2020-2021	2021	Cross-sectional	Healthcare	Admitted £48 h	347	90	25.9	MacConkey agar DDST	8
Eastern Mediterranean Region	Habibzadeh et al.[24]	Iran	2017	2017	Cross-sectional	Community setting	Healthy individuals	305	51	16.7	DDST	8
African Region	Tornberg-Belanger et al.[25]	Kenya	2011–2013	2012	Cross-sectional	Healthcare	Admitted (time of screening not specified)	406	180	44.3	DDST	8
South-East Asian Region	Sulikah et al.[26]	Indonesia	2018	2018	Cross-sectional	Healthcare	Admitted £48 h	99	42	42.4	DDST, PCR	8
Western Pacific Region	Cheng et al.[27]	Taiwan	2016–2019	2018	Prospective	Healthcare	Admitted <72 h	179	37	20.7	CHROMagar ECC plate DDST, agar strip gradient methods	8
African Region	Mwansa et al.[28]	Zambia	2017–2018	2018	Cross-sectional	Community setting	Healthy individuals	58	2	3.4	MacConkey agar DDST	9
European Region	Symanzik et al.[29]	Germany	2018–2019	2019	Prospective	Community setting	Healthy individuals	527	28	5.3	ESBL-selective CHROMagar	9

Region	Author	Country	Study period	Year	Study design	Setting	Population	N	n	%	Method	Quality score
Western Pacific Region	Liu et al.[30]	China	2021	2021	Cross-sectional	Community setting	Healthy individuals	330	118	35.8	Chromogenic plates, DDST	8
Eastern Mediterranean Region	Hajihasani et al.[31]	Iran	2018	2018	Cross-sectional	Community setting	Healthy individuals	540	233	43.1	CHROMagar ESBL agar, DDST, PCR	8
Eastern Mediterranean Region	Moghnieh et al.[32]	Lebanon	2020	2020	Cross-sectional	Healthcare	Admitted (time of screening not specified)	132	25	18.9	DDST, PCR	7
Eastern Mediterranean Region	Qureshi et al.[33]	Pakistan	2019	2019	Cross-sectional	Healthcare	Admitted <72 h	322	174	54.0	DDST	9
Western Pacific Region	Masui et al.[34]	Japan	2015–2019	2017	Cross-sectional	Community setting	Healthy individuals	547	53	9.7	DDST, PCR	8
Western Pacific Region	Sewunet et al.[35]	Laos	2019	2019	Cross-sectional	Healthcare	Admitted (time of screening not specified)	137	10	7.3	Chromogenic agar, DDST	8
European Region	Raffelsberger et al.[36]	Norway	2015–2016	2016	Cross-sectional	Community setting	Healthy individuals	4999	180	3.6	DDST	9
Western Pacific Region	Kawata et al.[37]	Japan	2020–2021	2020	Prospective	Community setting	Healthy individuals	149	28	18.8	PCR	8
Western Pacific Region	Lin et al.[38]	Taiwan	2019	2019	Prospective	Healthcare	Admitted <72 h	100	13	13.0	PCR	7
South-East Asian Region	Sapkota et al.[39]	Nepal	2017	2017	Cross-sectional	Community setting	Healthy individuals	208	66	31.7	DDST	7
Western Pacific Region	Chuang et al.[40]	Taiwan	2019–2022	2020	Prospective	Community setting	Healthy individuals	159	53	33.3	PCR	9
African Region	Letara et al.[41]	Tanzania	2016	2016	Cross-sectional	Healthcare	Admitted (time of screening not specified)	350	76	21.7	DDST	8
Region of the Americas	de Pinho Rodrigues et al.[42]	Brazil	2015–2019	2017	Cross-sectional	Community setting	Healthy individuals	623	47	7.5	MacConkey agar, PCR	9
African Region	Abayomi et al.[43]	Nigeria	2023	2023	Cross-sectional	Healthcare	Admitted ≤48 h	144	50	34.7%	MacConkey agar, DDST	8
European Region	Martischang et al.[44]	Switzerland	2010–2020	2015	Cross-sectional	Healthcare	LTCF	2403	252	10.5	ChromID ESBL, DDST	8

DDST, double-disc synergy test; LTCF, long-term care facility.
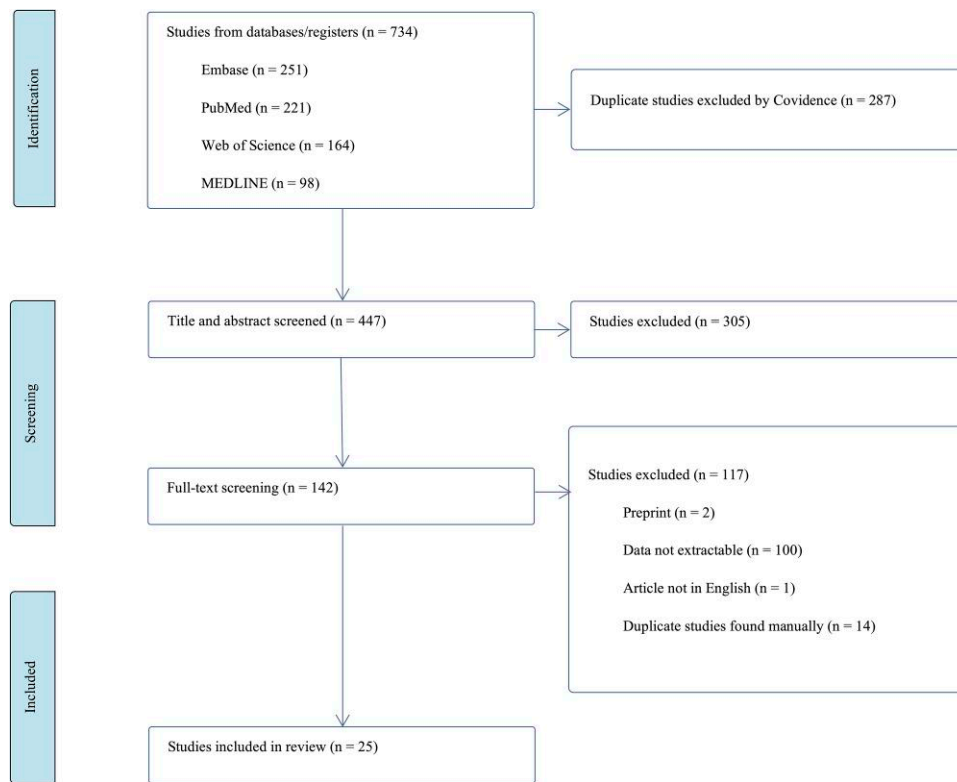
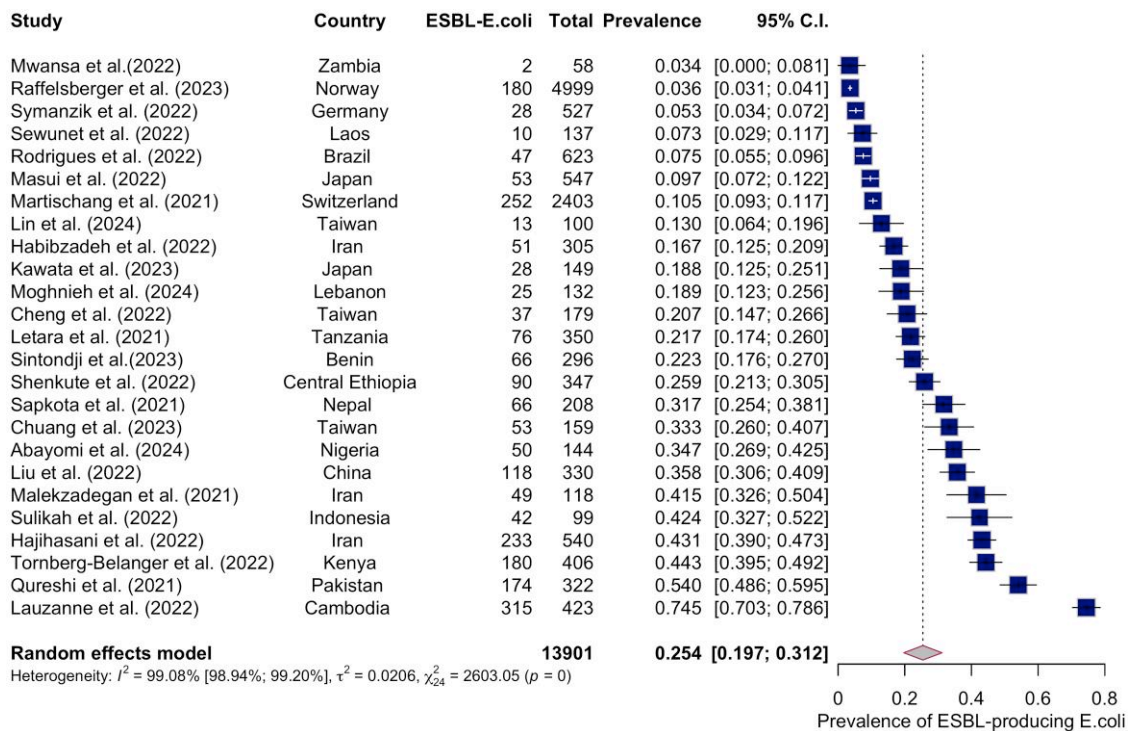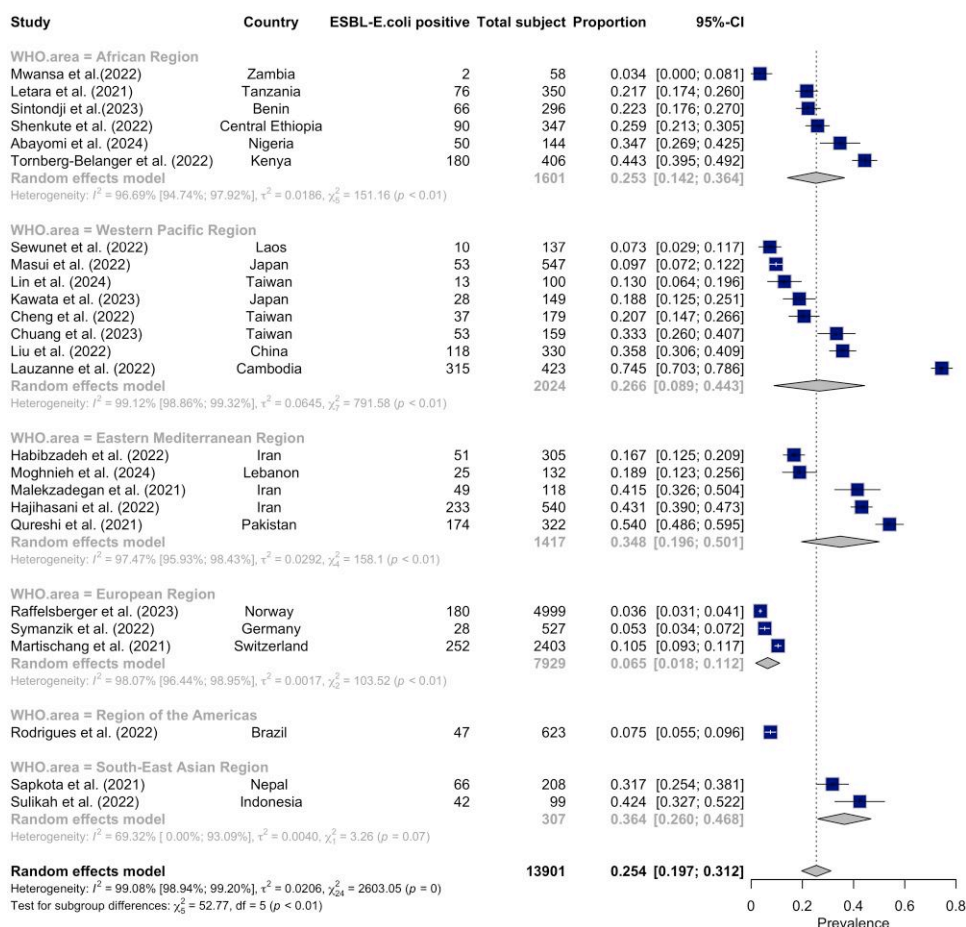**Figure 1.** Study flow diagram.

Figure 2. Overall pooled prevalence of human intestinal carriage of ESBL *E. coli* in healthcare and community settings. Squares represent the prevalence of human intestinal carriage of ESBL *E. coli* for each study. Error bars indicate the 95% CIs. The diamond represents the overall prevalence.

Figure 3. Prevalence of human intestinal carriage of ESBL *E. coli* for different WHO regions. Squares represent the prevalence of human intestinal carriage of ESBL *E. coli* for each study. Error bars indicate the 95%CIs. The diamond represents the overall prevalence.

Our results showed that the highest pooled prevalence was observed in the South-East Asian Region, whereas the lowest was in the European Region. This finding was also consistent with a previous study (Figure 5b).[61] There has been a worrying increase in AMR in the South East Asian Region, particularly in Bangladesh, India, Indonesia, Nepal, Sri Lanka and Thailand.[62] Lack of an infrastructure of laboratories and standardized surveillance protocols may account for an under-recognition of the severity of resistance.[63] Development of national networks of laboratories for AMR surveillance is a priority for the international community. The WHO has recently developed the Global Tricycle Surveillance programme, monitoring ESBL *E. coli* across the human, animal and environmental sectors to facilitate the establishment of the integrated multisectoral surveillance of AMR. Our study provides critical baseline data for future surveillance of faecal carriage of ESBL *E. coli* in the global community.[13]

This meta-analysis has several limitations. First, most of the studies were from the Western Pacific Region, which may lead to bias and lack of certainty in generalizing the results to other regions. Second, heterogeneities between the examined studies warrant attention. The study population differed to a certain degree; for example, some studies focused on specific individuals, eight studies included children, two studies included pregnant

women, one included the elderly, and others had a broader demographic focus. Although we performed a rigorous sensitivity analysis to validate the results, a potential association between study heterogeneities and the pooled effect remains. Third, variations in the method of ESBL confirmation including use of PCR could potentially lead to overestimation of ESBL prevalence. Fourth, the small number of studies included in some of the groups may have biased some subgroup analysis results.[64] Fifth, the low number of studies in some subgroups and the range of sample sizes of included studies alongside the higher rate of ESBL prevalence in inpatients admitted £48 h may lead to bias in prevalence estimates and accuracy of the results. Sixth, only English-language articles were included, which may have led to language bias due to selection of reports published in English language.

Conclusions

The findings of this meta-analysis show that the pooled prevalence of ESBL *E. coli* remains high, and there was a significant between-group difference for different WHO regions, with the highest being in Asian regions. The inappropriate use of antibiotics may account for the finding during the COVID-19 pandemic
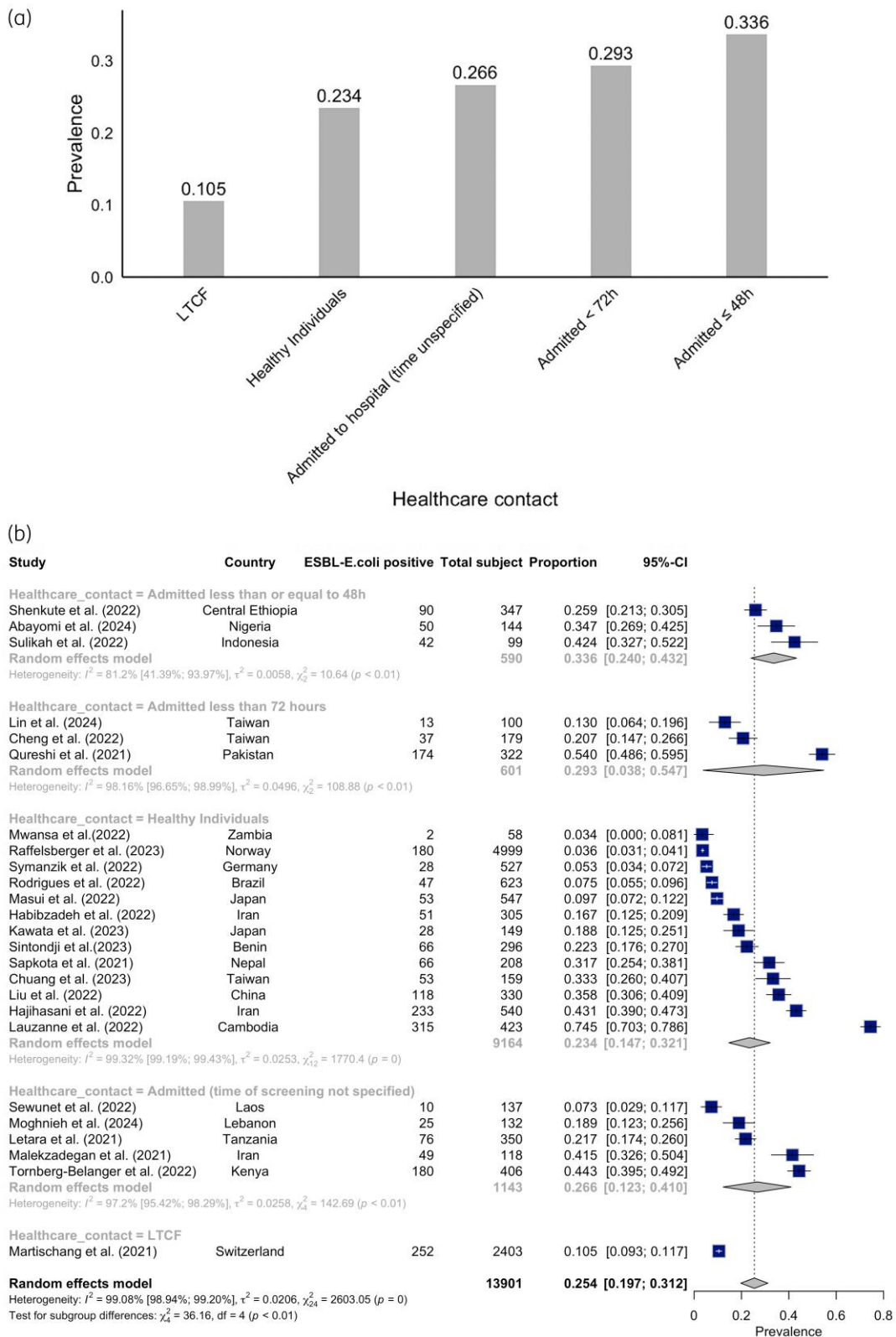
Figure 4. (a) Bar graph showing prevalence of human intestinal carriage of ESBL *E. coli* with different types of healthcare contact. (b) Prevalence of human intestinal carriage of ESBL *E. coli* with different types of healthcare contact. Squares represent the prevalence of human intestinal carriage of ESBL *E. coli* for each study. Error bars indicate the 95% CIs. The diamond represents the overall prevalence. LTCF, long-term care facility.
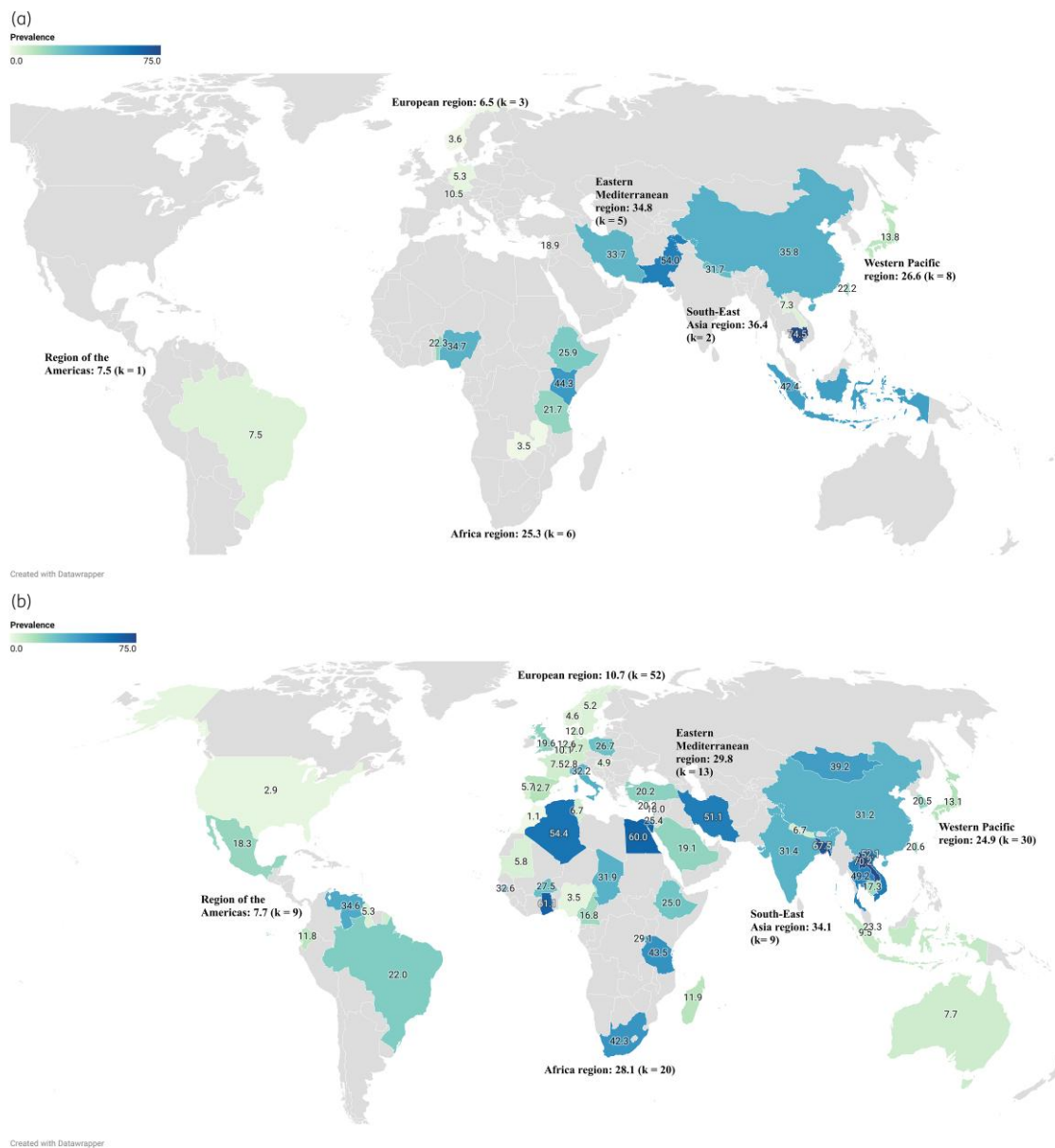
Figure 5. (a) A global map of ESBL *E. coli* prevalence based on the current study. (b) A global map of ESBL *E. coli* prevalence based on a previous study by Bezabih *et al*. (2022).[8] (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9160884/). k, k refers to the number of studies.

but there may be continued overuse. Standardized surveillance of AMR and antibiotic stewardship programmes are urgently needed for control of this healthcare emergency. Furthermore, due to complexities in the population characteristics, travel history and nosocomial outbreaks in estimating the ESBL prevalence, further research is warranted to identify the best methodologies to determine the human intestinal carriage rates of ESBL in different geographical regions of the world.

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Transparency declarations

None to declare.

Author contributions

M.I. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: M.I. Development of search strategy: L.Y. Screening of articles and extraction of data: R.W.Y.N. and S.H.L. Statistical analysis: L.Y. Drafting of the manuscript: R.W.Y.N. Critical revision of the manuscript for important intellectual content: P.H. and M.I. Administrative, technical or material support: R.W.Y.N., L.Y., S.H.L. and M.I. Supervision: P.H and M.I. All authors read and agreed to the published version of the manuscript.

Supplementary data

Figures S1 and S2 and Appendices S1 and S2 are available as Supplementary data at *JAC-AMR* Online.

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