J Antimicrob Chemother 2021; **76**: 22–29
doi:10.1093/jac/dkaa399 Advance Access publication 9 October 2020

Journal of Antimicrobial Chemotherapy

The global prevalence and trend of human intestinal carriage of ESBL-producing *Escherichia coli* in the community

Yihienew M. Bezabih [1]*, Wilber Sabiiti[2], Endalkachew Alamneh[3], Alamneh Bezabih[4], Gregory M. Peterson[3], Woldesellassie M. Bezabhe[3] and Anna Roujeinikova[5]

[1]*Arsi University College of Health Sciences, Arsi University, PO Box 0193, Asella, Ethiopia;* [2]*School of Medicine, University of St Andrews, St Andrews KY16 9TF, UK;* [3]*School of Pharmacy and Pharmacology, University of Tasmania, Australia;* [4]*École nationale vétérinaire, agroalimentaire et de l'alimentation, Nantes-Atlantique, BIOEPAR (UMR1300 INRA/ONIRIS), Nantes, France;* [5]*Department of Microbiology, Monash University, Clayton, Victoria 3800, Australia*

*Corresponding author. E-mail: yihienew.bezabih@arsiun.edu.et or myihienew@gmail.com

Received 3 June 2020; accepted 28 August 2020

Objectives: Intestinal colonization by ESBL *Escherichia coli* and its association with community-acquired MDR infections is of great concern. This review determined the worldwide prevalence of human faecal ESBL *E. coli* carriage and its trend in the community over the past two decades.

Methods: A systematic literature search was conducted using PubMed, EMBASE and Google Scholar to retrieve articles published between 1 January 2000 and 13 February 2020 that contained data on the prevalence of faecal carriage of ESBL *E. coli* among healthy individuals. A cumulative (for the whole period) meta-analysis was used to estimate the global and regional pooled prevalence rates. Articles were grouped into study periods of 3 years, and subgroup meta-analyses were undertaken to examine the global pooled prevalence over time.

Results: Sixty-two articles covering 29 872 healthy persons were included in this meta-analysis. The cumulative (2003–18) global pooled prevalence of ESBL *E. coli* intestinal carriage in the community was 16.5% (95% CI 14.3%–18.7%; $P < 0.001$). The pooled prevalence showed an upward trend, increasing from 2.6% (95% CI 1.6%–4.0%) in 2003–05 to 21.1% (95% CI 15.8%–27.0%) in 2015–18. Over the whole period, the highest carriage rate was observed in South-East Asia (27%; 95% CI 2.9%–51.3%), while the lowest occurred in Europe (6.0%; 95% CI 4.6%–7.5%).

Conclusions: Globally, an 8-fold increase in the intestinal carriage rate of ESBL *E. coli* in the community has occurred over the past two decades. Prevention of its spread may require new therapeutic and public health strategies.

Introduction

The gut microbiota is a reservoir of antimicrobial resistance genes.[1] Among Enterobacteriaceae, *Escherichia coli* is becoming a major storehouse of ESBL genes, which impart resistance to a number of β-lactam antibiotics.[2–4]

E. coli, a Gram-negative facultative anaerobe[5,6] whose primary habitat is the distal intestines of humans and animals,[7,8] is the most common cause of urinary tract infections[9] and urosepsis in humans.[10] Acquisition of drug resistance genes by *E. coli* makes the treatment of these infections difficult. For example, ESBL-producing *E. coli* are resistant to many β-lactam antibiotics, including penicillins, aztreonam and most cephalosporins.[11] ESBL *E. coli* can emerge in the human or animal gut following the use of antibiotics.[12,13] Since *E. coli* are generally transmitted through the faecal–oral route,[14] MDR forms of ESBL *E. coli* are transmissible through contact with humans, animals or the environment, or ingestion of contaminated food or water.[15–19] In fact, one study showed that 60% of community-acquired ESBL *E. coli* were attributable to human to human transmission, whereas food accounted for about 20%.[20]

The intestinal carriage of ESBL *E. coli* is usually asymptomatic and persistent.[21] However, many studies have shown the association of faecal carriage with ESBL *E. coli* infections.[22–25] Unlike infections with β-lactam-susceptible *E. coli*, ESBL *E. coli* infections have poor clinical outcomes. For instance, the mortality rate of ESBL *E. coli* sepsis (60%) is three times higher than for β-lactam-susceptible strains (20%).[26]

Two systematic reviews on ESBL Enterobacteriaceae in 2011 and 2016 showed a steady increase in the worldwide community prevalence.[27,28] Faecal ESBL *E. coli* carriage, in particular, has

become a global pandemic, which can lead to widespread infections with limited therapeutic options.[28] Understanding the current status of this MDR bacterium is critical for developing effective methods for its control, including the prevention of its transmission and decolonization of carriers. The 2016 review[27] covered Enterobacteriaceae in general, but did not provide specific details on ESBL *E. coli*. The meta-analysis presented here highlights the global prevalence and evolution of faecal ESBL *E. coli* carriage in healthy individuals over the past two decades.

Methods

This study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 checklist (Table S1 available as Supplementary data at *JAC* Online).[29]

Data sources and search terms

A systematic literature search was conducted in PubMed, EMBASE and Google Scholar to retrieve relevant articles published from 1 January 2000 to 13 February 2020. We used four groups of search terms: (i) *Escherichia coli* OR *E. coli*; (ii) extended spectrum β-lactamase OR ESBL; (iii) faecal OR faeces OR stool OR intestinal OR gastrointestinal tract; and (iv) community OR community-acquired. These groups of search terms were then connected by the Boolean operator 'AND' to find papers that contained the terms anywhere in the article. The search retrieved 122, 173 and 280 articles indexed in PubMed, EMBASE and Google Scholar, respectively, for further screening (Figure 1). Two authors (Y.B. and W.B.) screened titles and abstracts to select studies. Another author (A.B.) was involved in reaching a consensus for discrepancies.

Study selection: inclusion and exclusion criteria

Studies that reported the prevalence of ESBL *E. coli* carriage among healthy individuals of any age group were eligible. A healthy individual was defined as an asymptomatic person who lived in the community or visited a hospital only for a routine wellness check-up, antenatal care, vaccination, pre-international travel screening or for transrectal biopsy screening for prostate cancer. We excluded studies that reported faecal ESBL *E. coli* prevalence among hospital outpatients, admitted patients, residents of aged-care facilities and household contacts of colonized individuals, as well as studies that analysed non-faecal samples or involved only non-human study subjects. Our analysis included original articles written in English and excluded reviews, retrospective studies, case–control studies and conference abstracts. In addition, we only included studies that confirmed ESBL production with at least the double-disc synergy test (DDST) or PCR, and excluded those studies that relied solely on antibiotic susceptibility testing. Studies that determined the faecal carriage of ESBL Enterobacteriaceae, but did not perform bacterial species identification or did not specify the total number of ESBL *E. coli*-positive persons, were excluded (Figure 1).

Data extraction and quality control

The main outcome of interest was the prevalence of gastrointestinal colonization by ESBL *E. coli* in healthy individuals. The prevalence was obtained by dividing the total number of confirmed ESBL *E. coli*-positive individuals by the total number of individuals screened via stool testing. For each research article, year of study, study design, nature of study participants, method of ESBL confirmation and study location (country and WHO region)[30] were recorded and shown in a spreadsheet (Table S2). For studies that took more than a year (e.g. 2012–13), the approximate mean (2013) was taken as the 'year of study'.

The methodological quality of each study was assessed using the Quality Assessment Tool for Observational Cohort and Cross-Sectional

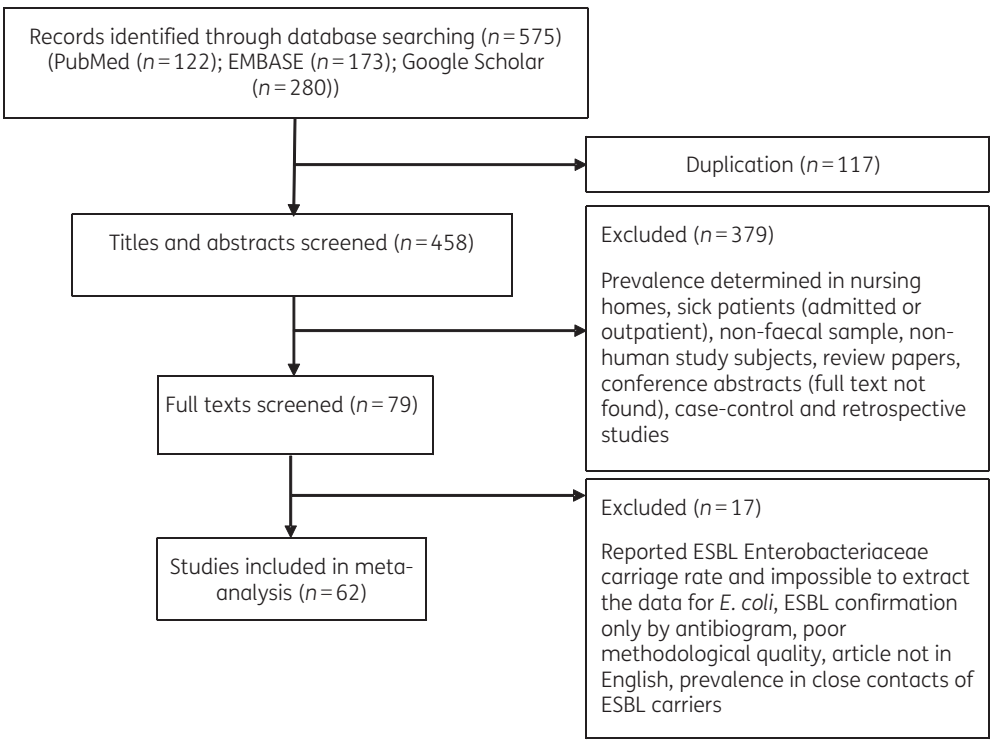

Figure 1. Flow chart showing selection of articles for meta-analysis.

Studies developed by the National Heart, Lung, and Blood Institute of the NIH (Table S3).[31]

Data analysis

A random-effects meta-analysis using the DerSimonian and Laird method[32] was performed to obtain a pooled prevalence and estimate the global trend of faecal ESBL *E. coli* carriage. Subgroup meta-analyses were performed by grouping studies using the WHO regions[30] and 3 year intervals of the study period. The Freeman–Tukey arcsine methodology[33] was used to stabilize the variance of raw proportions, and no studies with 0% or 100% proportions were excluded.[34] The I^2 statistic was the measure of heterogeneity,[32] and probability values less than 0.05 at a 95% CI were considered significant. The presence of publication bias was assessed using Egger's regression test.[35] The meta-analysis was performed using OpenMeta (Analyst).[36] GraphPad Prism (version 8.0.2, San Diego, CA, USA) was used to create linear regression plots and bar graphs.

Results

Study characteristics and quality assessment

Of the 575 relevant articles produced by the search, 62 were included in our meta-analysis (Figure 1). They comprised 20 prospective and 42 cross-sectional studies deemed to be of fair to good quality. The characteristics and quality assessment of the selected studies are presented in Table S2.

Prevalence of faecal ESBL E. coli carriage in the community

The 62 studies covered a total of 29 872 healthy individuals from the six WHO regions. This gave a global pooled prevalence of ESBL *E. coli* intestinal carriage in the community of 16.5% (95% CI 14.3%–18.7%) (Figure 2). The highest carriage rates occurred in South-East Asia (27%; 95% CI 2.9%–51.3%), followed by Western Pacific (24.5%; 95% CI 17.6%–31.4%), Africa (21.4%; 95% CI 12.7%–30.1%) and Eastern Mediterranean (20.6%; 95% CI 10.2%–30.1%). The lowest pooled prevalence was reported from European studies (6.0%; 95% CI 4.6%–7.5%) (Figure 2 and Table S2).

Looking at the country level, the highest community prevalence was reported from Tanzania (76.3%), followed by Vietnam (75.1%), Laos (70.2%), China (58.5%), Thailand (56.1%), Egypt (45.1%) and Lebanon (38.5%). Australia (with a prevalence of 1.9%) and the USA (at a carriage rate of up to 3.5%) were among countries with the lowest prevalence (Figure S1 and Table S2).

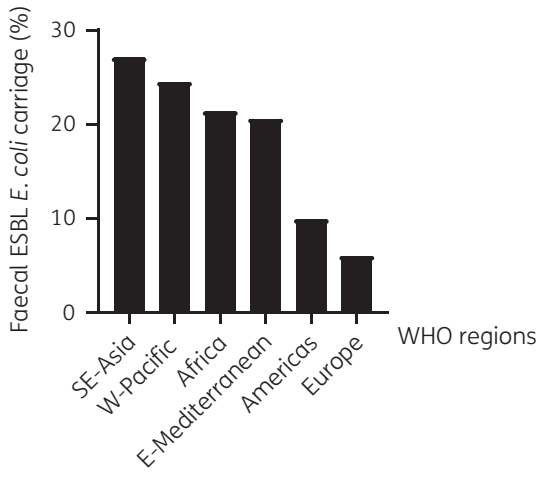

Figure 2. Pooled prevalence of intestinal ESBL *E. coli* carriage among healthy individuals in six WHO regions.[30] E-Mediterranean, Eastern Mediterranean; SE-Asia, South-East Asia; W-Pacific, Western Pacific region.

Global trend in prevalence of human intestinal ESBL E. coli carriage

The results of subgroup meta-analyses performed by dividing the study period into 3 year intervals are shown in Figure S2. The pooled prevalence increased steadily from 2.6% (95% CI 1.6–4.0) in 2003–05 to 21.1% (95% CI 15.8%–27.0%) in 2015–18, representing an average increase of 1.2% per year (Figure 3a and Figure S2). Similarly, an estimated projection from linear regression analysis revealed a 1.5% yearly increase, with an estimated global prevalence of just under 30% in 2020 ($P = 0.021$) (Figure 3b).

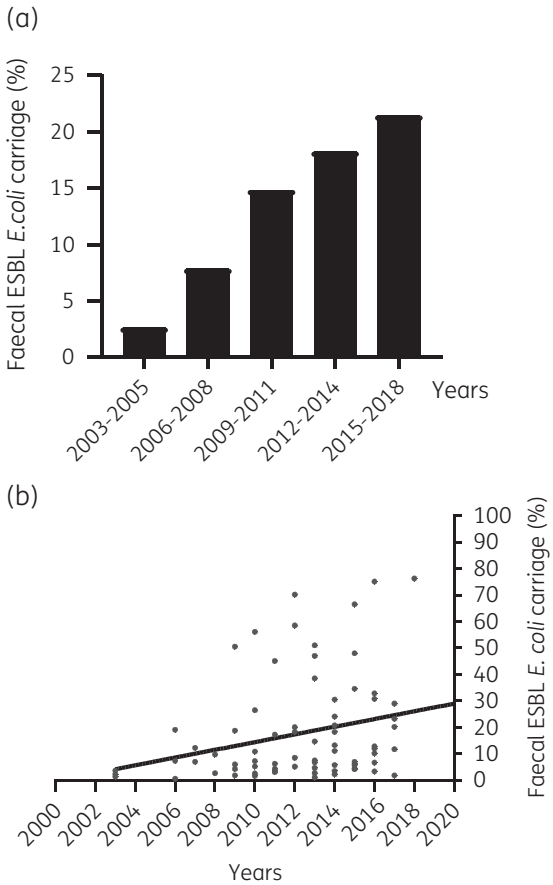

Figure 3. Global trend in faecal ESBL *E. coli* carriage among healthy individuals. (a) Pooled prevalence showing a clear increase from one 3 year interval to another. (b) A simple linear regression plot depicting the trend of carriage (1.5% rise per year, $P = 0.021$).

Discussion

We studied the intestinal carriage of MDR ESBL *E. coli* among healthy people as it has very significant clinical and public health implications.[37,38] Healthy carriers may develop serious urinary, intra-abdominal or bloodstream infections at some point in their lifetime.[22] Mortality rates following ESBL *E. coli* infections are generally high,[26] and last-resort carbapenems are the only reliable treatment options.[38] Even mild urinary tract infections have a tendency to become recurrent, leading to increased morbidity.[39,40] From a public health perspective, human to human transmission of ESBL *E. coli* and its extensive spread throughout the world is a great concern.[37] Clonal and plasmid-mediated spread are responsible for the increasing global incidence of MDR *E. coli*, as seen, for example, with the pandemic *E. coli* ST131 clone and the $bla_{CTX\text{-}M}$ plasmid.[37,41] Furthermore, the possible horizontal transfer of ESBL genes to other flora within the human gut is another concern.[21]

Using a 15 year pooled prevalence, this study found that at least a sixth (16.5%) of the world's population is colonized by ESBL *E. coli*. Subgroup meta-analysis by every 3 years of the study period showed an increasing trend, with a much higher carriage rate in recent years. For example, the pooled prevalence for the period 2015–18 was 21.1% (95% CI 15.8%–27.0%). This is almost a 3-fold increase when compared with the pooled prevalence of 10 years earlier [7.8% (95% CI 2.2%–13.3%) in 2006–08)] and an 8-fold increase from 2003 to 2005 [2.6% (95% CI 1.6%–4.0%)]. The global pooled prevalence in our study is higher than that reported by Karanika *et al.*, who found a 14% global pooled prevalence for the intestinal carriage of ESBL Enterobacteriaceae (*E. coli*, *Klebsiella pneumoniae*, etc.) among healthy people.[27] However, Karanika *et al.* considered studies conducted between 1978 and 2015, so missing 2015–18, which our analysis showed was a period of further increase in prevalence. A study by Woerther *et al.* also showed an increasing trend of ESBL Enterobacteriaceae between 2002 and 2011 in each of the six WHO regions.[30]

By WHO region,[30] the pooled prevalence was highest in South-East Asia, whereas Europe and the Americas had the lowest carriage. These relative estimates concurred with those presented by Karanika *et al.*, who showed the highest prevalence rate in South-East Asia (46%; 95% CI 29%–63%) and the lowest prevalence rates in the Americas [North (2%; 95% CI 0%–5%) and South (3%; 95% CI 0%–7%)] and Europe [central (3%; 95% CI 1%–5%), northern (4%; 95% CI 2%–6%) and southern (6%; 95% CI 1%–12%)].[27] Differences in the regional carriage rates compared with our study are most probably due to variation in the study periods and methods (inclusion and exclusion criteria). For instance, our study determined carriage rates specific for ESBL *E. coli* and we included only those confirmed by at least DDST or PCR.

There could be several explanations for the successful worldwide spread of ESBL *E. coli*. The first, and most likely, is a high transmission rate, as seen in the rates of ESBL *E. coli* colonization among travellers. A Swiss study recruited 170 Swiss travellers to South Asia (India, Bhutan, Nepal and Sri Lanka) who initially were negative for ESBL *E. coli* upon pre-travel stool screening. Surprisingly, on return, 118/170 (70%) of these travellers were found to have been colonized with ESBL *E. coli* (86% among travellers to India).[42] A Danish study also reported a >90% colonization rate among travellers to India.[43] Second, the faecal titre of ESBL *E. coli* was high among colonized humans (10^2–10^8 cfu/g of stool)[44] and animals (10^3–10^7 cfu/g of stool).[45,46] This high faecal ESBL *E. coli* titre among carriers could relate to the documented high rate of human to human transmission related to poor post-toilet hygiene. Hence, effective faeco-oral transmission seems to be the main driving factor for the increasing worldwide prevalence.

Our findings suggest that the presence of MDR ESBL *E. coli* is dramatically increasing outside the hospital setting. This is concerning, given the risk of persistent intestinal carriage,[21] as well as the possible horizontal transfer of ESBL genes to other flora within the human gut.[47–49] In addition, because ESBL *E. coli* are resistant to most of the available antibiotics, our findings signal that the world could be heading toward the worst phase of a 'post-antibiotic era', where common infections that used to be easily treated will no longer respond to currently existing medications. Since *E. coli* is a common cause of urinary tract infections, sepsis and neonatal meningitis, increasing prevalence of ESBL *E. coli* has significant clinical implications, with an anticipated increase in morbidity and mortality. With antimicrobial resistance projected to become the number one killer of humans by 2050,[50] ESBL *E. coli* could become one of the main culprits. The WHO's global antimicrobial resistance surveillance system (GLASS) has already been monitoring the resistance profile of *E. coli* from blood and urine samples obtained during routine clinical care since 2015.[51] However, since ESBL *E. coli* is no longer restricted to the hospital setting, and given the high community carriage shown by our results, we believe control strategies by the WHO and other organizations would be better informed by including monitoring of faecal carriage of ESBL *E. coli* among healthy individuals.

A strength of this review is in following a strict inclusion criterion on the method of ESBL *E. coli* detection. In addition, we used subgroup meta-analysis to show the temporal pattern. It is important to note, however, that the study also had several limitations. First, it determined the pooled prevalence in each WHO region,[30] which may lead to an overestimation or underestimation of the prevalence for certain member countries, and the findings need careful interpretation. For example, a 9.9% pooled prevalence in the Americas was mainly contributed to by the high carriage rate in South America, not the USA. Second, there were a limited number of studies in certain locations, such as Africa, South-East Asia, North America and Australia. This might have overestimated or underestimated the prevalence in these areas. Third, the review only considered articles published in English, and relevant data published in other languages may have been missed. Finally, the varying time periods of studies from different WHO regions[30] might have underestimated or overestimated the regional cumulative prevalence and the global trend.

Conclusions

The intestinal carriage of MDR ESBL *E. coli* showed a high and increasing prevalence among healthy individuals worldwide. Based on the findings, we recommend that the WHO and other institutions should consider a community stool ESBL *E. coli* surveillance scheme and implement preventive measures to address its community spread.

Acknowledgements

Special thanks to Yohannes Gishen for his valuable support.

Funding

This study was conducted as part of our routine work.

Transparency declarations

None to declare.

Supplementary data

Tables S1 to S3 and Figures S1 and S2 are available as Supplementary data at *JAC* Online.

Data sharing

All data are available in the manuscript or the supplementary materials.

References

1 Jean C. The gut is the epicentre of antibiotic resistance. *Antimicrob Resist Infect Control* 2012; **1**: 39.

2 Ny S, Löfmark S, Börjesson S *et al.* Community carriage of ESBL-producing *Escherichia coli* is associated with strains of low pathogenicity: a Swedish nationwide study. *J Antimicrob Chemother* 2017; **72**: 582–8.

3 Díaz-Agero Pérez C, López-Fresneña N, Rincon Carlavilla AL *et al.* Local prevalence of extended-spectrum β-lactamase (ESBL) producing Enterobacteriaceae intestinal carriers at admission and co-expression of ESBL and OXA-48 carbapenemase in *Klebsiella pneumoniae*: a prevalence survey in a Spanish University Hospital. *BMJ Open* 2019; **9**: e024879.

4 Kurz MSE, Bayingana C, Ndoli JM *et al.* Intense pre-admission carriage and further acquisition of ESBL-producing Enterobacteriaceae among patients and their caregivers in a tertiary hospital in Rwanda. *Trop Med Int Health* 2017; **22**: 210–20.

5 von Wulffen J, RecogNice-Team, Sawodny O *et al.* Transition of an anaerobic *Escherichia coli* culture to aerobiosis: balancing mRNA and protein levels in a demand-directed dynamic flux balance analysis. *PLoS One* 2016; **11**: e0158711.

6 Carlson R, Srienc F. Fundamental *Escherichia coli* biochemical pathways for biomass and energy production: identification of reactions. *Biotechnol Bioeng* 2004; **85**: 1–19.

7 Savageau MA. *Escherichia coli* habitats, cell types, and molecular mechanisms of gene control. *Am Nat* 1983; **122**: 732–44.

8 Smith HW. Observations on the flora of the alimentary tract of animals and factors affecting its composition. *J Pathol Bacteriol* 1965; **89**: 95–122.

9 Flores-Mireles AL, Walker JN, Caparon M *et al.* Urinary tract infections: epidemiology, mechanisms of infection and treatment options. *Nat Rev Microbiol* 2015; **13**: 269–84.

10 Dreger NM, Degener S, Ahmad-Nejad P *et al.* Urosepsis—etiology, diagnosis, and treatment. *Dtsch Arzteblatt Int* 2015; **112**: 837–47; quiz 848.

11 Paterson DL, Bonomo RA. Extended-spectrum β-lactamases: a clinical update. *Clin Microbiol* 2005; **18**: 657–86.

12 FAO. *Drivers, Dynamics and Epidemiology of Antimicrobial Resistance in Animal Production*. Food and Agriculture Organization of the United Nations, 2016.

13 Marshall BM, Levy SB. Food animals and antimicrobials: impacts on human health. *Clin Microbiol Rev* 2011; **24**: 718–33.

14 Russell JB, Jarvis GN. Practical mechanisms for interrupting the oral–fecal lifecycle of *Escherichia coli*. *J Mol Microbiol Biotechnol* 2001; **3**: 265–72.

15 Schmithausen R, Schulze-Geisthoevel S, Heinemann C *et al.* Reservoirs and transmission pathways of resistant indicator bacteria in the biotope pig stable and along the food chain: a review from a One Health perspective. *Sustainability* 2018; **10**: 3967.

16 Rousham EK, Unicomb L, Islam MA. Human, animal and environmental contributors to antibiotic resistance in low-resource settings: integrating behavioural, epidemiological and One Health approaches. *Proc R Soc B Biol Sci* 2018; **285**: 20180332.

17 Guet-Revillet H, Le Monnier A, Breton N *et al.* Environmental contamination with extended-spectrum β-lactamases: is there any difference between *Escherichia coli* and *Klebsiella* spp? *Am J Infect Control* 2012; **40**: 845–8.

18 O'Connor C, Philip RK, Kelleher J *et al.* The first occurrence of a CTX-M ESBL-producing *Escherichia coli* outbreak mediated by mother to neonate transmission in an Irish neonatal intensive care unit. *BMC Infect Dis* 2017; **17**: 16.

19 Leverstein-van Hall MA, Dierikx CM, Cohen Stuart J *et al.* Dutch patients, retail chicken meat and poultry share the same ESBL genes, plasmids and strains. *Clin Microbiol Infect* 2011; **17**: 873–80.

20 Mughini-Gras L, Dorado-García A, van Duijkeren E *et al.* Attributable sources of community-acquired carriage of *Escherichia coli* containing β-lactam antibiotic resistance genes: a population-based modelling study. *Lancet Planet Health* 2019; **3**: e357–69.

21 Bar-Yoseph H, Hussein K, Braun E *et al.* Natural history and decolonization strategies for ESBL/carbapenem-resistant Enterobacteriaceae carriage: systematic review and meta-analysis. *J Antimicrob Chemother* 2016; **71**: 2729–39.

22 Reddy P, Malczynski M, Obias A *et al.* Screening for extended-spectrum β-lactamase-producing Enterobacteriaceae among high-risk patients and rates of subsequent bacteremia. *Clin Infect Dis* 2007; **45**: 846–52.

23 Bert F, Larroque B, Paugam-Burtz C *et al.* Pretransplant fecal carriage of extended-spectrum β-lactamase-producing Enterobacteriaceae and infection after liver transplant. *Emerg Infect Dis* 2012; **18**: 908–16.

24 Adler A, Gniadkowski M, Baraniak A *et al.* Transmission dynamics of ESBL-producing *Escherichia coli* clones in rehabilitation wards at a tertiary care centre. *Clin Microbiol Infect* 2012; **18**: E497–505.

25 Ruppé E, Lixandru B, Cojocaru R *et al.* Relative fecal abundance of extended-spectrum-β-lactamase-producing *Escherichia coli* strains and their occurrence in urinary tract infections in women. *Antimicrob Agents Chemother* 2013; **57**: 4512–17.

26 Melzer M, Petersen I. Mortality following bacteraemic infection caused by extended spectrum β-lactamase (ESBL) producing *E. coli* compared to non-ESBL producing *E. coli*. *J Infect* 2007; **55**: 254–9.

27 Karanika S, Karantanos T, Arvanitis M *et al.* Fecal colonization with extended-spectrum β-lactamase-producing Enterobacteriaceae and risk factors among healthy individuals: a systematic review and metaanalysis. *Clin Infect Dis* 2016; **63**: 310–18.

28 Woerther P-L, Burdet C, Chachaty E *et al.* Trends in human fecal carriage of extended-spectrum β-lactamases in the community: toward the globalization of CTX-M. *Clin Microbiol Rev* 2013; **26**: 744–58.

29 PRISMA. *PRISMA Checklist*. http://prisma-statement.org/prismastatement/Checklist.aspx.

30 WHO. *Definition of Region Groupings*. 2017. https://www.who.int/healthinfo/global_burden_disease/definition_regions/en/.

31 NIH National Heart, Lung, and Blood Institute. *Study Quality Assessment Tools*. https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools.

32 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7**: 177–88.

33 Fazel S, Khosla V, Doll H *et al*. The prevalence of mental disorders among the homeless in western countries: systematic review and meta-regression analysis. *PLoS Med* 2008; **5**: e225.

34 Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. *Arch Public Health* 2014; **72**: 39.

35 Egger M, Davey Smith G, Schneider M *et al*. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; **315**: 629–34.

36 Wallace BC, Lajeunesse MJ, Dietz G *et al*. *Open MEE*: intuitive, open-source software for meta-analysis in ecology and evolutionary biology. *Methods Ecol Evol* 2017; **8**: 941–7.

37 Mathers AJ, Peirano G, Pitout JDD. The role of epidemic resistance plasmids and international high-risk clones in the spread of multidrug-resistant Enterobacteriaceae. *Clin Microbiol Rev* 2015; **28**: 565–91.

38 Pana ZD, Zaoutis T. Treatment of extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBLs) infections: what have we learned until now? *F1000Res* 2018; **7**: F1000 Faculty Rev-1347.

39 Karami N, Lindblom A, Yazdanshenas S *et al*. Recurrence of urinary tract infections with ESBL-producing *Escherichia coli* caused by homologous strains among which clone ST131-O25b is dominant. *J Glob Antimicrob Resist* 2020; **22**: 126–32.

40 DeBusscher J, Zhang L, Buxton M *et al*. Persistent extended-spectrum β-lactamase urinary tract infection. *Emerg Infect Dis* 2009; **15**: 1862–4.

41 van Duin D, Doi Y. The global epidemiology of carbapenemase-producing Enterobacteriaceae. *Virulence* 2017; **8**: 460–9.

42 Kuenzli E, Jaeger VK, Frei R *et al*. High colonization rates of extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* in Swiss travellers to South Asia—a prospective observational multicentre cohort study looking at epidemiology, microbiology and risk factors. *BMC Infect Dis* 2014; **14**: 528.

43 Dall LB, Lausch KR, Gedebjerg A *et al*. Do probiotics prevent colonization with multi-resistant Enterobacteriaceae during travel? A randomized controlled trial. *Travel Med Infect Dis* 2019; **27**: 81–6.

44 Girlich D, Bouihat N, Poirel L *et al*. High rate of faecal carriage of extended-spectrum β-lactamase and OXA-48 carbapenemase-producing Enterobacteriaceae at a university hospital in Morocco. *Clin Microbiol Infect* 2014; **20**: 350–4.

45 Horton RA, Randall LP, Snary EL *et al*. Fecal carriage and shedding density of CTX-M extended-spectrum β-lactamase-producing *Escherichia coli* in cattle, chickens, and pigs: implications for environmental contamination and food production. *Appl Environ Microbiol* 2011; **77**: 3715–19.

46 Hansen KH, Damborg P, Andreasen M *et al*. Carriage and fecal counts of cefotaxime M-producing *Escherichia coli* in pigs: a longitudinal study. *Appl Environ Microbiol* 2013; **79**: 794–8.

47 Anjum M, Madsen JS, Nesme J *et al*. Fate of CMY-2-encoding plasmids introduced into the human fecal microbiota by exogenous *Escherichia coli*. *Antimicrob Agents Chemother* 2019; **63**: e02528–18.

48 Grasselli E, François P, Gutacker M *et al*. Evidence of horizontal gene transfer between human and animal commensal *Escherichia coli* strains identified by microarray. *FEMS Immunol Med Microbiol* 2008; **53**: 351–8.

49 Hagbø M, Ravi A, Angell IL *et al*. Experimental support for multidrug resistance transfer potential in the preterm infant gut microbiota. *Pediatr Res* 2020; **88**: 57–65.

50 O'Neill J. *The Review on Antimicrobial Resistance*. 2016. https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf.

51 WHO. *Global Antimicrobial Resistance Surveillance System (GLASS)* Report. http://www.who.int/glass/resources/publications/early-implementation-report/en/.

52 Moubareck C, Daoud Z, Hakime NI *et al*. Countrywide spread of community- and hospital-acquired extended-spectrum β-lactamase (CTX-M-15)-producing Enterobacteriaceae in Lebanon. *J Clin Microbiol* 2005; **43**: 3309–13.

53 Kader AA, Kamath KA. Faecal carriage of extended-spectrum β-lactamase-producing bacteria in the community. *East Mediterr Health J* 2009; **15**: 6.

54 Abdul Rahman EM, El-Sherif RH. High rates of intestinal colonization with extended-spectrum lactamase-producing Enterobacteriaceae among healthy individuals. *J Investig Med* 2011; **59**: 1284–6.

55 Barguigua A, Ouair H, El Otmani F *et al*. Fecal carriage of extended-spectrum β-lactamase-producing Enterobacteriaceae in community setting in Casablanca. *Infect Dis* 2015; **47**: 27–32.

56 Hijazi SM, Fawzi MA, Ali FM *et al*. Multidrug-resistant ESBL-producing Enterobacteriaceae and associated risk factors in community infants in Lebanon. *J Infect Dev Ctries* 2016; **10**: 947–55.

57 Elkersh T, Marie MA, Al-Sheikh YA *et al*. Prevalence of fecal carriage of extended-spectrum- and metallo-β-lactamase-producing gram-negative bacteria among neonates born in a hospital setting in central Saudi Arabia. *Ann Saudi Med* 2015; **35**: 240–7.

58 Ferjani S, Saidani M, Hamzaoui Z *et al*. Community fecal carriage of broad-spectrum cephalosporin-resistant *Escherichia coli* in Tunisian children. *Diagn Microbiol Infect Dis* 2017; **87**: 188–92.

59 Hashemizadeh Z, Kalantar-Neyestanaki D, Mansouri S. Clonal relationships, antimicrobial susceptibilities, and molecular characterization of extended-spectrum β-lactamase-producing *Escherichia coli* isolates from urinary tract infections and fecal samples in Southeast Iran. *Rev Soc Bras Med Trop* 2018; **51**: 44–51.

60 Valverde A, Coque TM, Sanchez-Moreno MP *et al*. Dramatic increase in prevalence of fecal carriage of extended-spectrum β-lactamase-producing Enterobacteriaceae during nonoutbreak situations in Spain. *J Clin Microbiol* 2004; **42**: 4769–75.

61 Leflon-Guibout V, Blanco J, Amaqdouf K *et al*. Absence of CTX-M enzymes but high prevalence of clones, including clone ST131, among fecal *Escherichia coli* isolates from healthy subjects living in the area of Paris, France. *J Clin Microbiol* 2008; **46**: 3900–5.

62 Guimarães B, Barreto Â, Radhouani H *et al*. Genetic detection of extended-spectrum β-lactamase-containing *Escherichia coli* isolates and vancomycin-resistant enterococci in fecal samples of healthy children. *Microb Drug Resist* 2009; **15**: 211–16.

63 Tukenmez Tigen E, Tandogdu Z, Ergonul O *et al*. Outcomes of fecal carriage of extended-spectrum β-lactamase after transrectal ultrasound-guided biopsy of the prostate. *Urology* 2014; **84**: 1008–15.

64 Janvier F, Mérens A, Delaune D *et al*. Portage digestif d'entérobactéries résistantes aux céphalosporines de troisième génération dans une population d'adultes jeunes asymptomatiques: évolution entre 1999 et 2009. *Pathol Biol* 2011; **59**: 97–101.

65 Kaarme J, Molin Y, Olsen B *et al*. Prevalence of extended-spectrum β-lactamase-producing Enterobacteriaceae in healthy Swedish preschool children. *Acta Paediatr* 2013; **102**: 655–60.

66 Valenza G, Nickel S, Pfeifer Y *et al*. Extended-spectrum-β-lactamase-producing *Escherichia coli* as intestinal colonizers in the German community. *Antimicrob Agents Chemother* 2014; **58**: 1228–30.

67 Nicolas-Chanoine M-H, Gruson C, Bialek-Davenet S *et al*. 10-Fold increase (2006–11) in the rate of healthy subjects with extended-spectrum β-lactamase-producing *Escherichia coli* faecal carriage in a Parisian check-up centre. *J Antimicrob Chemother* 2013; **68**: 562–8.

68 Meyer E, Gastmeier P, Kola A *et al*. Pet animals and foreign travel are risk factors for colonisation with extended-spectrum β-lactamase-producing *Escherichia coli*. *Infection* 2012; **40**: 685–7.

69 Lübbert C, Straube L, Stein C *et al*. Colonization with extended-spectrum β-lactamase-producing and carbapenemase-producing Enterobacteriaceae in international travelers returning to Germany. *Int J Med Microbiol* 2015; **305**: 148–56.

70 Ebrahimi F, Mózes J, Mészáros J *et al*. Asymptomatic faecal carriage of ESBL producing enterobacteriaceae in Hungarian healthy individuals and in long-term care applicants: a shift towards CTX-M producers in the community. *Infect Dis* 2016; **48**: 557–9.

71 van den Bunt G, van Pelt W, Hidalgo L *et al*. Prevalence, risk factors and genetic characterisation of extended-spectrum β-lactamase and carbapenemase-producing Enterobacteriaceae (ESBL-E and CPE): a community-based cross-sectional study, the Netherlands, 2014 to 2016. *Euro Surveill* 2019; **24**: 1800594.

72 Ulstad CR, Solheim M, Berg S *et al*. Carriage of ESBL/AmpC-producing or ciprofloxacin non-susceptible *Escherichia coli* and *Klebsiella* spp. in healthy people in Norway. *Antimicrob Resist Infect Control* 2016; **5**: 57.

73 Jiménez-Rámila C, López-Cerero L, Aguilar Martín MV *et al*. Vagino-rectal colonization and maternal–neonatal transmission of Enterobacteriaceae producing extended-spectrum β-lactamases or carbapenemases: a cross-sectional study. *J Hosp Infect* 2019; **101**: 167–74.

74 Kaarme J, Riedel H, Schaal W *et al*. Rapid increase in carriage rates of *Enterobacteriaceae* producing extended-spectrum β-lactamases in healthy preschool children. *Emerg Infect Dis* 2018; **24**: 1874–81.

75 Ruh E, Zakka J, Hoti K *et al*. Extended-spectrum β-lactamase, plasmid-mediated AmpC β-lactamase, fluoroquinolone resistance, and decreased susceptibility to carbapenems in Enterobacteriaceae: fecal carriage rates and associated risk factors in the community of Northern Cyprus. *Antimicrob Resist Infect Control* 2019; **8**: 98.

76 Mathai D, Kumar VA, Paul B *et al*. Fecal carriage rates of extended-spectrum β-lactamase-producing *Escherichia coli* among antibiotic naive healthy human volunteers. *Microb Drug Resist* 2015; **21**: 59–64.

77 Luvsansharav U-O, Hirai I, Nakata A *et al*. Prevalence of and risk factors associated with faecal carriage of CTX-M β-lactamase-producing Enterobacteriaceae in rural Thai communities. *J Antimicrob Chemother* 2012; **67**: 1769–74.

78 Babu R, Kumar A, Karim S *et al*. Faecal carriage rate of extended-spectrum β-lactamase-producing Enterobacteriaceae in hospitalised patients and healthy asymptomatic individuals coming for health check-up. *J Glob Antimicrob Resist* 2016; **6**: 150–3.

79 Maharjan A, Bhetwal A, Shakya S *et al*. Ugly bugs in healthy guts! Carriage of multidrug-resistant and ESBL-producing commensal Enterobacteriaceae in the intestine of healthy Nepalese adults. *Infect Drug Resist* 2018; **11**: 547–54.

80 Tian SF, Chen BY, Chu YZ *et al*. Prevalence of rectal carriage of extended-spectrum β-lactamase-producing *Escherichia coli* among elderly people in community settings in China. *Can J Microbiol* 2008; **54**: 781–5.

81 Li B, Sun J-Y, Liu Q-Z *et al*. High prevalence of CTX-M β-lactamases in faecal *Escherichia coli* strains from healthy humans in Fuzhou, China. *Scand J Infect Dis* 2011; **43**: 170–4.

82 Kennedy K, Collignon P. Colonisation with *Escherichia coli* resistant to 'critically important' antibiotics: a high risk for international travellers. *Eur J Clin Microbiol Infect Dis* 2010; **29**: 1501–6.

83 Qin X, Hu F, Wu S *et al*. Comparison of adhesin genes and antimicrobial susceptibilities between uropathogenic and intestinal commensal *Escherichia coli* strains. *PLoS One* 2013; **8**: e61169.

84 Nakane K, Kawamura K, Goto K *et al*. Long-term colonization by $bla_{CTX\text{-}M}$-harboring *Escherichia coli* in healthy Japanese people engaged in food handling. *Appl Environ Microbiol* 2016; **82**: 1818–27.

85 Atterby C, Osbjer K, Tepper V *et al*. Carriage of carbapenemase- and extended-spectrum cephalosporinase-producing *Escherichia coli* and *Klebsiella pneumoniae* in humans and livestock in rural Cambodia; gender and age differences and detection of $bla_{OXA\text{-}48}$ in humans. *Zoonoses Public Health* 2019; **66**: 603–17.

86 Zhou Y, Wu X, Zhang J *et al*. High prevalence of CTX-M β-lactamases in Enterobacteriaceae from healthy individuals in Guangzhou, China. *Microb Drug Resist* 2015; **21**: 398–403.

87 Nakamura A, Komatsu M, Noguchi N *et al*. Analysis of molecular epidemiologic characteristics of extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* colonizing feces in hospital patients and community dwellers in a Japanese city. *J Infect Chemother* 2016; **22**: 102–7.

88 Nakayama T, Ueda S, Huong BTM *et al*. Wide dissemination of extended-spectrum β-lactamase-producing *Escherichia coli* in community residents in the Indochinese peninsula. *Infect Drug Resist* 2015; **8**: 1–5.

89 Joo E-J, Kim SJ, Baek M *et al*. Fecal carriage of antimicrobial-resistant Enterobacteriaceae in healthy Korean adults. *J Microbiol Biotechnol* 2018; **28**: 1178–84.

90 Sadahira T, Wada K, Araki M *et al*. Impact of selective media for detecting fluoroquinolone-insusceptible/extended-spectrum β-lactamase-producing *Escherichia coli* before transrectal prostate biopsy. *Int J Urol* 2017; **24**: 842–7.

91 Kamei J, Yagihara Y, Kume H *et al*. Prevalence and characteristics of fecal antimicrobial-resistant *Escherichia coli* in a cohort of Japanese men undergoing prostate biopsy. *Int J Urol* 2017; **24**: 295–300.

92 Ni Q, Tian Y, Zhang L *et al*. Prevalence and quinolone resistance of fecal carriage of extended-spectrum β-lactamase-producing *Escherichia coli* in 6 communities and 2 physical examination center populations in Shanghai, China. *Diagn Microbiol Infect Dis* 2016; **86**: 428–33.

93 Thi Quynh Nhi L, Thanh Tuyen H, Duc Trung P *et al*. Excess body weight and age associated with the carriage of fluoroquinolone and third-generation cephalosporin resistance genes in commensal *Escherichia coli* from a cohort of urban Vietnamese children. *J Med Microbiol* 2018; **67**: 1457–66.

94 Wu P-C, Wang J-L, Hsueh P-R *et al*. Prevalence and risk factors for colonization by extended-spectrum β-lactamase-producing or ST 131 *Escherichia coli* among asymptomatic adults in community settings in Southern Taiwan. *Infect Drug Resist* 2019; **12**: 1063–71.

95 Mo Y, Seah I, Lye PSP *et al*. Relating knowledge, attitude and practice of antibiotic use to extended-spectrum β-lactamase-producing Enterobacteriaceae carriage: results of a cross-sectional community survey. *BMJ Open* 2019; **9**: e023859.

96 Higa S, Sarassari R, Hamamoto K *et al*. Characterization of CTX-M type ESBL-producing Enterobacteriaceae isolated from asymptomatic healthy individuals who live in a community of the Okinawa prefecture, Japan. *J Infect Chemother* 2019; **25**: 314–17.

97 Lonchel CM, Meex C, Gangoué-Piéboji J *et al*. Proportion of extended-spectrum β-lactamase-producing Enterobacteriaceae in community setting in Ngaoundere, Cameroon. *BMC Infect Dis* 2012; **12**: 53.

98 Mshana SE, Falgenhauer L, Mirambo MM *et al*. Predictors of $bla_{CTX\text{-}M\text{-}15}$ in varieties of *Escherichia coli* genotypes from humans in community settings in Mwanza, Tanzania. *BMC Infect Dis* 2016; **16**: 187.

99 Ouédraogo A-S, Sanou S, Kissou A *et al*. Fecal carriage of Enterobacteriaceae producing extended-spectrum β-lactamases in hospitalized patients and healthy community volunteers in Burkina Faso. *Microb Drug Resist* 2017; **23**: 63–70.

100 Herindrainy P, Rabenandrasana MAN, Andrianirina ZZ *et al*. Acquisition of extended spectrum β-lactamase-producing enterobacteriaceae in neonates: a community based cohort in Madagascar. *PLoS One* 2018; **13**: e0193325.

101 Akinduti PA, Olasehinde GI, Oluwaseun E *et al*. Fecal carriage and phylodiversity of community-acquired bla_{TEM} enteric bacilli in Southwest Nigeria. *Infect Drug Resist* 2018; **11**: 2425–33.

102 Ouchar Mahamat O, Tidjani A, Lounnas M *et al*. Fecal carriage of extended-spectrum β-lactamase-producing Enterobacteriaceae in hospital and community settings in Chad. *Antimicrob Resist Infect Control* 2019; **8**: 169.

103 Büdel T, Kuenzli E, Clément M *et al*. Polyclonal gut colonization with extended-spectrum cephalosporin- and/or colistin-resistant Enterobacteriaceae: a normal status for hotel employees on the island of Zanzibar, Tanzania. *J Antimicrob Chemother* 2019; **74**: 2880–90.

104 Woerther P-L, Angebault C, Jacquier H *et al*. Characterization of fecal extended-spectrum-β-lactamase-producing *Escherichia coli* in a remote community during a long time period. *Antimicrob Agents Chemother* 2013; **57**: 5060–6.

105 Weisenberg SA, Mediavilla JR, Chen L *et al*. Extended spectrum β-lactamase-producing Enterobacteriaceae in international travelers and non-travelers in New York City. *PLoS One* 2012; **7**: e45141.

106 Cortés-Cortés G, Lozano-Zarain P, Torres C *et al*. Extended-spectrum β-lactamase-producing *Escherichia coli* isolated from healthy humans in Mexico, including subclone ST131-B2-O25:H4-H30-Rx. *J Glob Antimicrob Resist* 2017; **9**: 130–4.

107 Islam S, Selvarangan R, Kanwar N *et al*. Intestinal carriage of third-generation cephalosporin-resistant and extended-spectrum β-lactamase-producing Enterobacteriaceae in healthy US children. *J Pediatr Infect Dis Soc* 2018; **7**: 234–40.

108 Araque M, Labrador I. Prevalence of fecal carriage of CTX-M-15 β-lactamase-producing *Escherichia coli* in healthy children from a rural Andean village in Venezuela. *Osong Public Health Res Perspect* 2018; **9**: 9–15.