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Comparison of the global prevalence and trend of human intestinal carriage of ESBL-producing *Escherichia coli* between healthcare and community settings: a systematic review and meta-analysis

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Objectives: The widespread intestinal carriage of ESBL-producing *Escherichia coli* (ESBL *E. coli*) among both patients and healthy individuals is alarming. However, the global prevalence and trend of this MDR bacterium in healthcare settings remains undetermined. To address this knowledge gap, we performed a comparative meta-analysis of the prevalence in community and healthcare settings.

Methods: Our systematic review included 133 articles published between 1 January 2000 and 22 April 2021 and indexed in PubMed, EMBASE or Google Scholar. A random-effects meta-analysis was performed to obtain the global pooled prevalence (community and healthcare settings). Subgroup meta-analyses were performed by grouping studies using the WHO regions and 5 year intervals of the study period.

Results: We found that 21.1% (95% CI, 19.1%–23.2%) of inpatients in healthcare settings and 17.6% (95% CI, 15.3%–19.8%) of healthy individuals worldwide carried ESBL *E. coli* in their intestine. The global carriage rate in healthcare settings increased 3-fold from 7% (95% CI, 3.7%–10.3%) in 2001–05 to 25.7% (95% CI, 19.5%–32.0%) in 2016–20, whereas in community settings it increased 10-fold from 2.6% (95% CI, 1.2%–4.0%) to 26.4% (95% CI, 17.0%–35.9%) over the same period.

Conclusions: The global and regional human intestinal ESBL *E. coli* carriage is increasing in both community and healthcare settings. Carriage rates were generally higher in healthcare than in community settings. Key relevant health organizations should perform surveillance and implement preventive measures to address the spread of ESBL *E. coli* in both settings.

Introduction

The widespread intestinal carriage of ESBL-producing *Escherichia coli* (ESBL *E. coli*) among patients and healthy individuals is alarming.[1] This is because ESBL *E. coli* can cause MDR infections that are difficult to treat. In healthcare settings it can cause serious hospital-acquired infections that have a 3-fold increased mortality compared with infections caused by non-drug-resistant *E. coli* strains.[2] In a community setting, it can lead to community-acquired MDR infections, such as recurrent urinary tract infections (UTIs), with an increased risk of morbidity.[3–6]

In many studies, human faecal ESBL *E. coli* carriage prevalence was higher in hospital settings than in the community.[7–9] This could be related to the use of antibiotics, which is an independent risk factor for ESBL *E. coli* faecal colonization.[10–14] In addition, antibiotic-mediated dysbiosis and loss of gut colonization resistance could facilitate the transmission (person-to-person contact, food and water ingestion, environmental contact) and acquisition of ESBL *E. coli* in the hospital setting.

In our recent systematic review and meta-analysis that evaluated the prevalence of faecal carriage of ESBL *E. coli* among healthy individuals, we found a global community prevalence

of 16.5%, showing a dramatic 8-fold rise over the last two decades.[1] Our findings were in line with the earlier studies that showed that the pooled prevalence of ESBL Enterobacteriaceae in the community (more than 90% of which is accounted for by ESBL *E. coli*[10]) was 14% in 2016.[15]

However, the global prevalence and trend over time of this MDR bacterium in healthcare settings remains undetermined. In addition, no prior study has compared global carriage rates among patients and healthy individuals. Hence, in this meta-analysis, we explored the global prevalence of human ESBL *E. coli* faecal carriage in healthcare settings and compared it with the values found in the community. Furthermore, as the acquisition of intestinal ESBL *E. coli* carriage could rise with increasing hospital stay,[9,14] we compared carriage rates among patients with varying duration of hospitalization and in individuals living in nursing care facilities.

Methods

This meta-analysis was conducted following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2020 checklist[16] (Table S1, available as Supplementary data at *JAC-AMR* Online).

Data sources and search terms

The data sources were articles published between 1 January 2000 and 22 April 2021 and obtained by a systematic search in PubMed, EMBASE and Google Scholar. Four groups of search terms were used to find articles that determined the intestinal carriage rate of ESBL *E. coli* among patients admitted to healthcare settings (including individuals living in a nursing care facility): (i) *Escherichia coli* OR *E. coli*; (ii) extended spectrum β-lactamase OR ESBL; (iii) faecal OR faeces OR stool OR intestinal OR gastrointestinal tract; (iv) hospital OR hospital-acquired or admitted OR inpatient OR nursing home. These groups of search terms were then connected by the Boolean operator 'AND' to find papers that contained the terms anywhere in the article. Similarly, articles for the community setting were found using the above search terms except for the substitution of 'community OR community-acquired' in place of 'hospital OR hospital-acquired or admitted OR inpatient OR nursing home'. For the healthcare setting, we retrieved a total of 1239 articles (328, 631 and 280 articles indexed in PubMed, EMBASE and Google Scholar, respectively) for further screening. For the community setting, we obtained a total of 590 articles (129, 181 and 280 articles indexed in PubMed, EMBASE and Google Scholar, respectively). The reference lists of the included papers were also checked to identify relevant studies. Screening of the articles by their titles and abstracts was performed by two authors (Y.M.B. and W.M.B.), and one author (A.B.) helped in reaching a consensus with any discrepancies.

Study selection: inclusion and exclusion criteria

Studies that determined the prevalence of ESBL *E. coli* carriage among patients (healthcare settings) or healthy individuals (community setting) of any age were eligible. Patients in the healthcare settings were defined as individuals who were kept at the emergency department or admitted to wards, ICU or a nursing care facility for any kind of treatment or care. Healthy individuals were defined as asymptomatic individuals living in the community, including those who visited a health facility for a routine wellness check-up, vaccination, antenatal care, pre-international travel screening, or transrectal biopsy screening for prostate cancer. In this manuscript, the terms 'healthy individuals' and 'asymptomatic individuals' were interchangeably used to describe individuals living in the community setting, and do not imply the absence of comorbidities or symptoms of illness. We used the term 'stool sample' for faecal samples collected either by the routine stool or rectal sampling.

We made four categories of study subjects 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 ≥48 h; and (iv) living in nursing care facilities. We considered healthy individuals as having zero time of contact in a healthcare setting, whereas individuals living in nursing care were considered to have an indefinite time of contact. We categorized patients as 'admitted <48 h' if the faecal carriage rate in these patients was determined using a stool sample that was taken at admission or within 48 h of hospital admission. Participants were categorized as 'admitted ≥48 h' if the prevalence was determined from a stool sample taken after 48 h of admission, or from serial culturing from admission till discharge, or if the time of sampling was not specified.

We included original articles written in English and excluded case-control studies, reviews and conference abstracts. Studies that reported the prevalence of faecal ESBL *E. coli* among outpatients with recurrent UTI were excluded due to disproportionately high intestinal carriage rates of ESBL *E. coli* in such patients.[17,18] We have also excluded studies that determined ESBL *E. coli* carriage rates in returning travellers from countries with a high prevalence or among household contacts of colonized individuals; those that involved non-human study subjects or analysed non-faecal samples; and studies that measured the prevalence of faecal carriage of ESBL Enterobacteriaceae, but without bacterial species identification. Furthermore, we only included studies that used at least the double-disc synergy test (DDST) or PCR to confirm ESBL production and excluded those studies that relied on the routine antibiogram to detect resistance to cephalosporins. A flow chart showing the selection of articles pertaining to ESBL *E. coli* prevalence in both community and healthcare settings is shown in Figure 1.

Data extraction and quality control

The prevalence of the human intestinal carriage of ESBL *E. coli* (the main outcome of interest) was calculated by dividing the total number of ESBL *E. coli*-positive individuals by the total number of individuals screened in each study. We also extracted data on the year of study, study design, nature of study participants, method of ESBL confirmation and study location (country and WHO region) (Table S2).

The quality of each study was assessed using the quality assessment tool for observational cohort and cross-sectional studies developed by the National Heart, Lung, and Blood Institute of the NIH[19] (Table S3).

Data analysis

A random-effects meta-analysis using the DerSimonian and Laird method[20] was performed to obtain the global pooled prevalence for each setting (community and healthcare). Subgroup meta-analyses were performed by grouping studies using the WHO regions[21] and 5 year intervals of the study period. For studies with a duration of more than 1 year (e.g. 2013–14), the approximate mean (2014) was taken as the year of study. The global trend of faecal ESBL *E. coli* carriage was demonstrated in two ways: (i) linear regression analysis and (ii) by using a pooled prevalence after articles grouped by 5 year intervals of the study period. The Freeman–Tukey arcsine methodology[22] was used to stabilize the variance of raw proportions, and no studies with 0% or 100% proportions were excluded.[23] The measure of heterogeneity was the I^2 statistic.[20] Probability values less than 0.05 at a 95% CI were considered significant. Egger's regression test was used to assess the presence of publication bias.[24] The OpenMeta (Analyst) software was used to perform the meta-analysis.[25] GraphPad Prism (version 8.0.2, San Diego, CA, USA) was used to create linear regression plots and bar graphs.

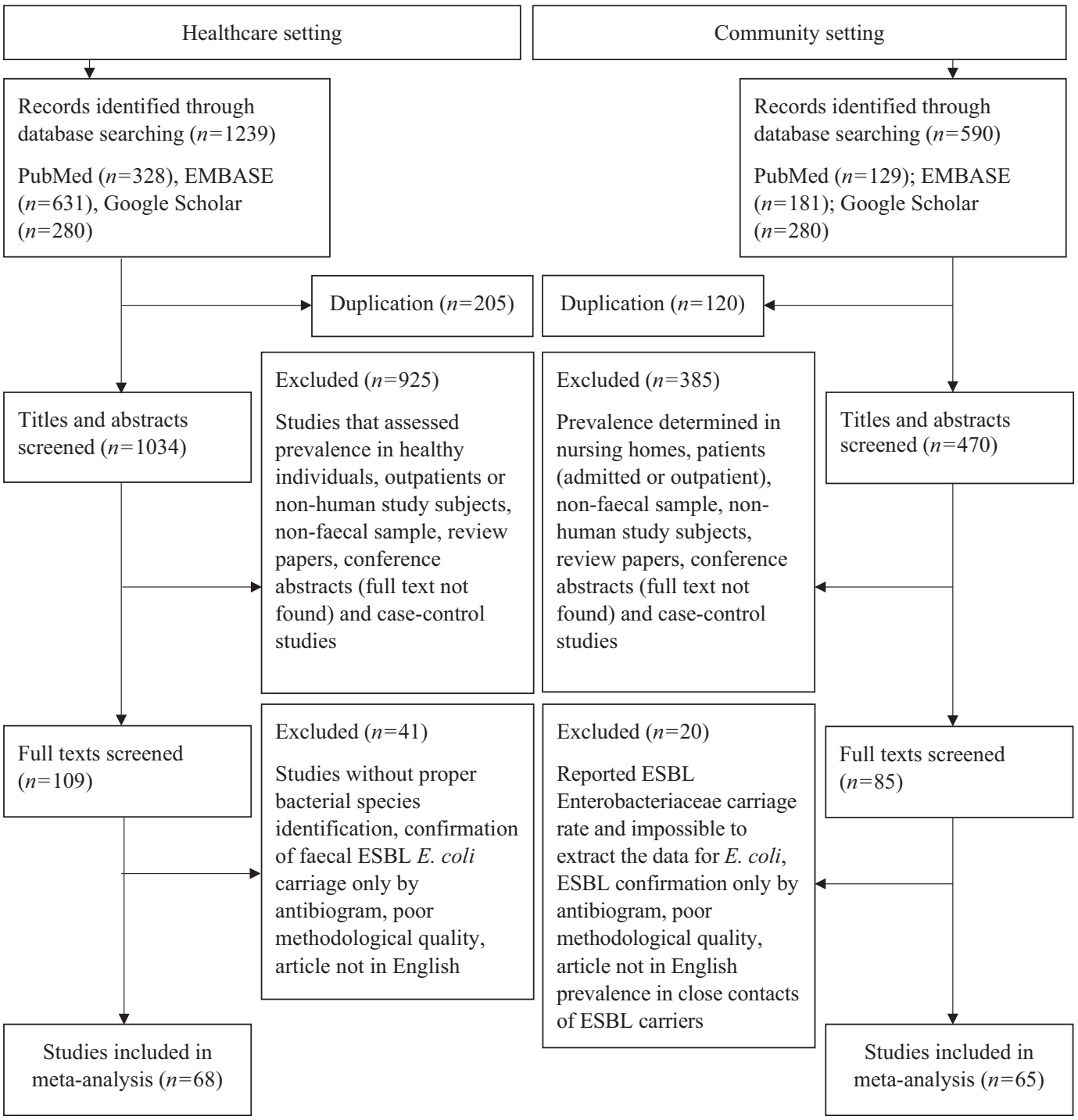


Figure 1. Selection of articles for the meta-analysis. Note: studies reporting the prevalence in both the community and healthcare settings were not discarded.

Results

Study characteristics and quality assessment

A total of 133 articles covering 73 318 participants were included in the meta-analysis (Figure 2, Figure S1). This included non-duplicate stool samples from 30 633 healthy individuals (65 articles in community settings) and 42 685 inpatients (68 articles in healthcare settings) (Figures 1 and 2, Figure S1). The majority of the studies in both the community (19/65, 29.2%) and healthcare (33/68, 48.5%) settings were from Europe (Figure 2). The study

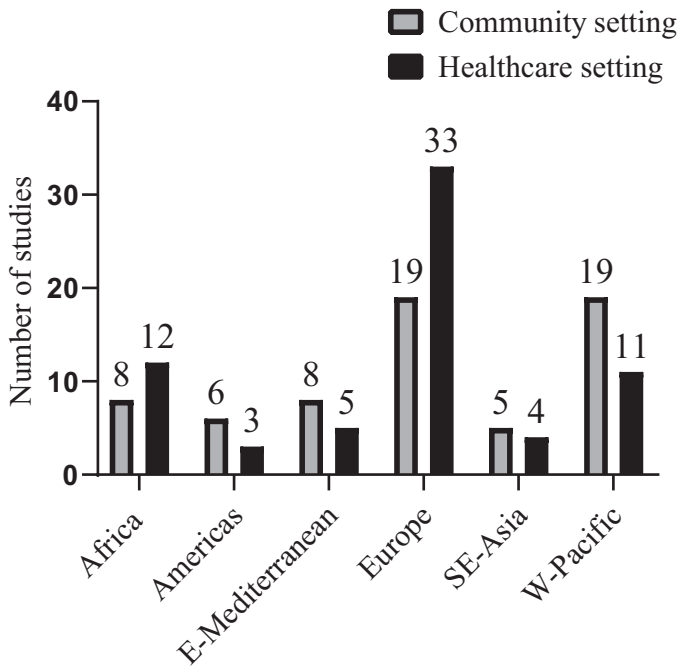


Figure 2. Number of studies included by WHO region and study setting. The absolute numbers of participants (ESBL *E. coli* positive/total screened) in the community settings were (by region): Africa (270/1786), America (109/1242), South-East Asia (494/1502), Europe (887/15168), Eastern Mediterranean (479/2084) and West Pacific (1713/8851). The absolute numbers of participants (ESBL *E. coli* positive/total screened) in the healthcare settings were (by region): Africa (682/2206), America (107/2236), South-East Asia (304/1494), Europe (3370/32464), Eastern Mediterranean (218/711) and West Pacific (1040/3574).

period of the included studies ranged from 2003 to 2018 for the community setting and 2002 to 2019 for the healthcare setting. All included studies were either cohort or cross-sectional studies with a fair to good quality (Table S2).

Comparison of global and regional prevalence in faecal ESBL E. coli carriage between the community and healthcare settings

Overall, the global and regional carriage rates generally appeared higher in healthcare than in community settings, although the 95% CIs overlapped in most of our analyses (Figure 3). Globally, the cumulative (2000–21) pooled prevalence of intestinal ESBL *E. coli* carriage in healthcare settings was 21.1% (95% CI, 19.1%–23.2%) compared with 17.6% (95% CI, 15.3%–19.8%) in the community settings (Figure 3a, Figure S1).

In the community setting, by WHO region, the highest carriage rates occurred in South-East Asia (35.1%, 95% CI, 10.3%–60.0%), followed by the West Pacific (25.3%, 95% CI, 18.5%–32.1%), Africa (21.4%, 95% CI, 12.7%–30.1%) and Eastern Mediterranean (20.6%, 95% CI, 10.2%–31.0%). Europe (6.0%, 95% CI, 4.6%–7.5%) and the Americas (10.3%, 95% CI, 5.1%–15.6%) had the lowest reported ESBL *E. coli* colonization in the community (Figure 3b and c, Figures S2 and S3).

In contrast, in healthcare settings, the highest carriage rate was found in the Eastern Mediterranean (45.6%, 95% CI, 23.0%–68.2%), followed by South-East Asia (32.9%, 95% CI, 10.6%–55.1%), Africa (32.4%, 95% CI, 23.8%–41.0%) and the West Pacific (24.1%, 95% CI, 17.3%–30.8%), whereas the lowest colonization rate was seen in the Americas (4.9%, 95% CI, 0.6%–9.2%) and Europe (13.8%, 95% CI, 11.6%–16.0%) (Figure 3b and c, Figures S2 and S3).

Global and regional trends in prevalence of human intestinal ESBL E. coli carriage

Globally, and in each WHO region, the prevalence of human intestinal ESBL *E. coli* carriage showed a progressive increase from 2000 to 2021 (Figure 4a and c). Based on an estimation projection from linear regression analysis, and as shown in Figure 4(a), the global prevalence in the intestinal carriage of ESBL *E. coli* in the community was rising at a faster rate (a 1.5% yearly increase) than in the healthcare settings (1.3% annual rise). The global intestinal carriage rate of ESBL *E. coli* in the community increased 10-fold from 2.6% (95% CI, 1.2%–4.0%) in 2001–05 to 26.4% (95% CI, 17.0%–35.9%) in 2016–20 (Figure 4b and d, Figure S4), whereas in the healthcare setting, it increased from 7% (95% CI, 3.7%–10.3%) in 2001–05 to 25.7% (19.5%–32.0%) in 2016–20 (Figure 4b and d, Figure S5).

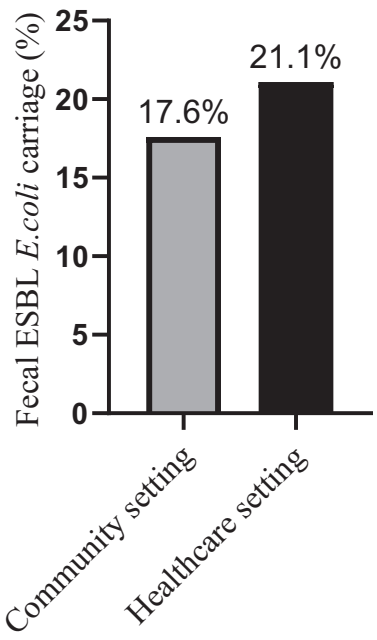
Analysis of correlation between human intestinal ESBL E. coli carriage rates and duration of stay in healthcare setting

An interesting finding, based on data from Europe, was that faecal ESBL *E. coli* colonization increased with increasing duration of contact/stay in a healthcare setting (Figure 5, Figure S6). Particularly, the prevalence of faecal ESBL *E. coli* colonization among patients admitted for more than 48 h was double the prevalence in healthy individuals, and in nursing care residents it was 3-fold higher than the prevalence in healthy individuals living in the community (Figure 5, Figure S6). Note, the other WHO regions had an insufficient number of studies for such analysis (Figure 2).

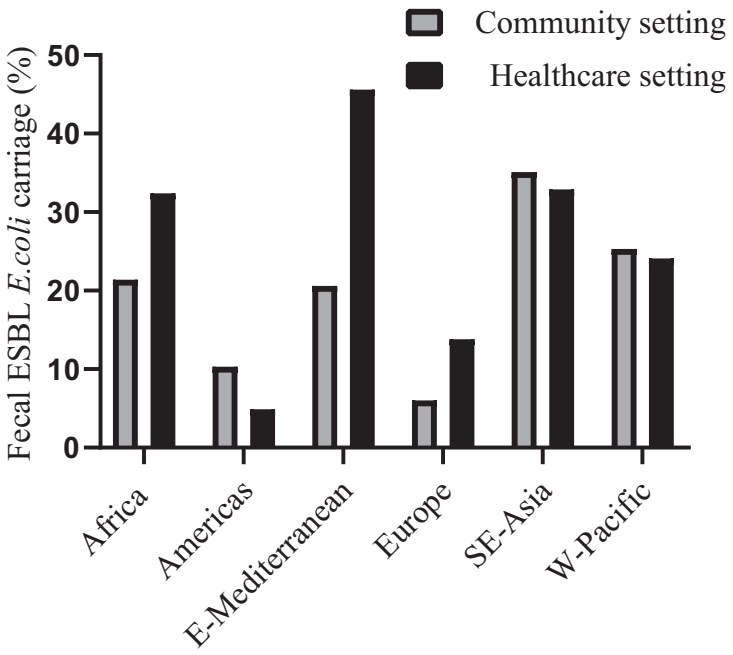
Discussion

In this study, based on 73 318 samples, 21.1% of inpatients in healthcare settings and 17.6% of healthy individuals in the community worldwide carried MDR ESBL *E. coli* bacteria in their intestines. While Europe and the Americas had the lowest colonization rate, all the other WHO regions had a carriage rate of above 20% in both community and healthcare settings. Over the past 20 years (2000–21), the global human intestinal ESBL *E. coli* carriage rate increased steadily in both healthcare and community settings. The upward trend was observed in each of the six WHO regions. The rate of increase appeared to be higher in the community than in healthcare settings, and colonization rates in the community were approaching values in the healthcare areas. The reason for a slower pace of rise in healthcare settings is unknown, although we think this could be due to the practice of standard precautions (note, contact precautions had no added benefit over standard precautions[26,27]).

(a)



(b)



(c)

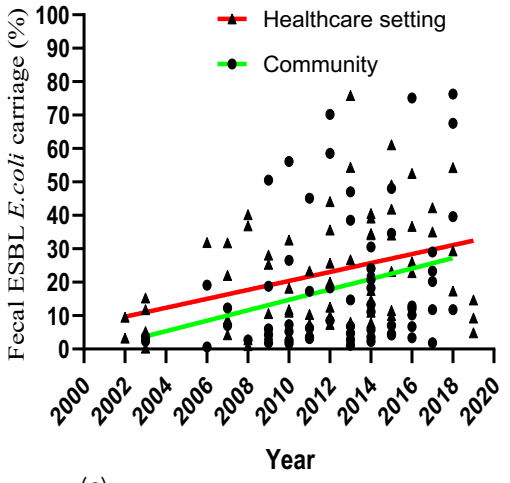
Pooled prevalence of human faecal ESBL *E. coli* carriage (with 95% CI) by WHO region		
WHO regions	Community setting, % (95% CI)	Healthcare setting, % (95% CI)
Africa	21.4% (12.7%–30.1%)*	32.4% (23.8%–41.0%)*
Americas	10.3% (5.1%–15.6%)*	4.9% (0.6%–9.2%)*
Europe	6.0% (4.6%–7.5%)*	13.8% (11.6%–16.0%)*
South-East Asia	35.1% (10.3%–60.0%)*	32.9% (10.6%–55.1%)*
Eastern Mediterranean	20.6% (10.2%–31.0%)*	45.6% (23.0%–68.2%)*
Western Pacific	25.3% (18.5%–32.1%)*	24.1% (17.3%–30.8%)*
Global (all regions)	17.6% (15.3%–19.8%)*	21.1% (19.1%–23.2%)*
**P* value=0.000		

Figure 3. The global and regional prevalence of human intestinal ESBL *E. coli* carriage. (a) The global pooled prevalence of faecal ESBL *E. coli* carriage in community and healthcare settings (forest plot in Figure S1). (b) Regional pooled prevalence of faecal ESBL *E. coli* carriage in the six WHO regions (forest plot in Figures S2 and S3). (c) A summary of global and regional human intestinal ESBL *E. coli* carriage with 95% CI as obtained from forest plots in Figures S1–S3. *P* values are the *P* values for heterogeneity.

To our knowledge, this is the first study that has determined the global prevalence of the human intestinal carriage of ESBL *E. coli* in healthcare settings. We showed that at least one in five inpatients (21.1%) worldwide were carriers. The global carriage rate in the community (17.6%) was close to that reported in our previous publication (16.5%) (with the slight increase likely being the result of inclusion of more recent studies).[1] By WHO region, South-East Asia had the highest carriage rate (35.1%) in the community, while the Eastern Mediterranean had the highest carriage rate (45.6%) in healthcare settings.

Although confidence intervals overlap, the global intestinal ESBL *E. coli* carriage rate appeared higher in healthcare than in community settings (Figures 4a and 5a). Regardless, there was a clear and statistically significant higher carriage rate in healthcare than community settings in Europe (where the number of included studies was large enough). However, in certain regions, such as the Americas and South-East Asia (regions with the lowest number of studies) and the Western Pacific, the carriage rate in the community appeared to be higher than in healthcare settings (Figure 3b and c). These findings may be attributable to a

(a)



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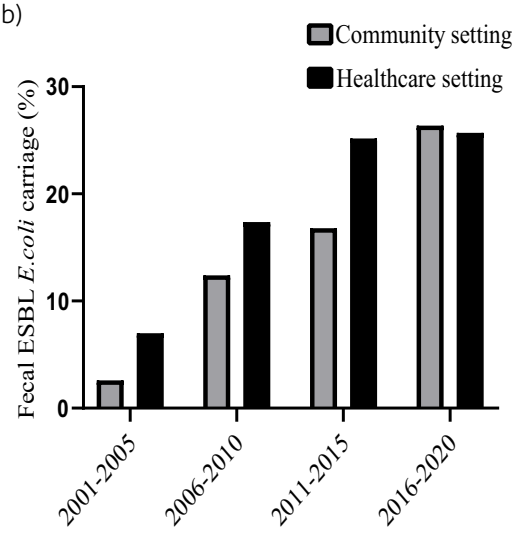

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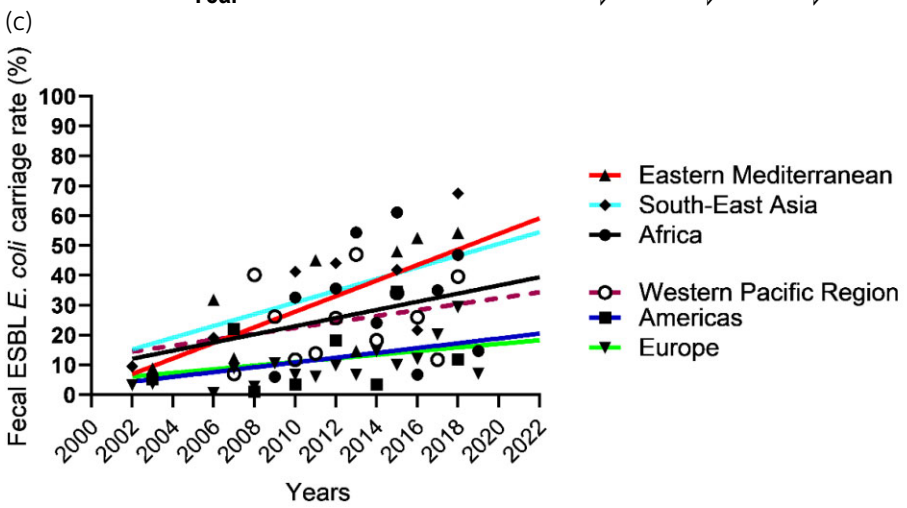

(d)

The global trend in the pooled prevalence of faecal ESBL *E. coli* carriage		
Time interval Q5 years	Community setting, % (95% CI)	Healthcare setting, % (95% CI)
2001–05	2.6% (1.2%–4.0%), *P*=0.495	7% (3.7%–10.3%)*
2006–10	12.4% (7.6%–17.3%)*	17.4% (13.4%–21.4%)*
2011–15	16.8% (14.2%–19.3%)*	25.2% (21.7%–28.7%)*
2016–20	26.4% (17.0%–35.9%)*	25.7% (19.5%–32.0%)*
Cumulative (2001–20)	17.6% (15.3%–19.8%)*	21.1% (19.1%–23.2%)*
**P* value=0.000		

Figure 4. The global and regional trends in the prevalence of faecal ESBL *E. coli* carriage. (a) Linear regression plots showing the global trend in the carriage rate in the community (1.5% yearly increase, *P*=0.027) and healthcare settings (1.3% annual rise, *P*=0.003). (b) A bar graph depicting pooled prevalence by 5 year intervals of the study period (forest plots in Figures S4 and S5). In (c), studies of both community and healthcare settings were combined to show the regional trend in the six WHO regions (*P* values were not significant (>0.05) for all the regions). (d) A summary of global trend in human intestinal ESBL *E. coli* carriage with 95% CI as obtained from forest plots in Figures S4 and S5. *P* values are the *P* values for heterogeneity. Note: in (b) and (d), for the year interval 2001–05 there were only two studies for community setting and this might result in underestimation of the real prevalence.

(a)

Pooled prevalence of faecal ESBL *E. coli* carriage by the duration of contact with healthcare settings in Europe, % (95% CI)	
Community (no contact)	6.0% (4.6%–7.5%)*
Admitted <48 h	9.8% (6.3%–13.4%)*
Admitted ≥48 h	11.5% (8.7%–14.2%)*
Nursing care	20.1% (13.2%–27.0%)*
*P value=0.000	

(b)

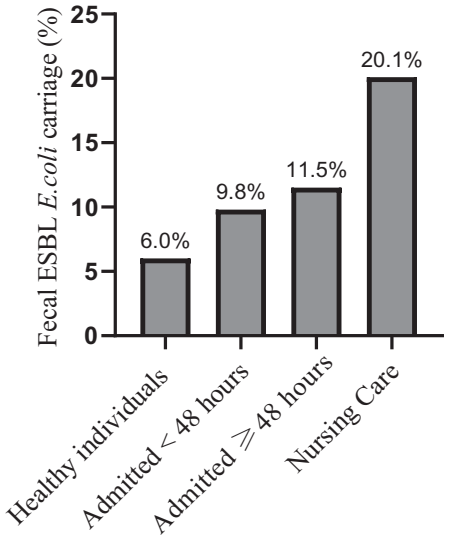

Figure 5. Comparison of faecal ESBL *E. coli* carriage rate between healthy individuals and inpatients in Europe. Carriage rates among inpatients increased with increasing duration of stay in healthcare settings. Summary table (a) and bar graph (b) were based on the meta-analysis forest plot in Figure S6. *P* values are the *P* values for heterogeneity. In this subgroup analysis, the absolute numbers of participants (ESBL *E. coli* positive/total screened) in Europe were: community setting (887/15168), admitted <48 h (1254/11983), admitted ≥48 h (1445/16589) and nursing care (671/3892).

spatial 'maldistribution' of the individual studies used to calculate the pooled prevalence. For example, for the Americas, the regional pooled prevalence appeared higher in the community than healthcare setting. This was because, in this region, most of the individual studies describing prevalence in the community were from South America (area of high colonization), whereas most of the individual studies that measured carriage rate in healthcare settings were from North America (area of low colonization). We confirmed this with further sub-meta-analysis by sub-region of the Americas, which showed ESBL *E. coli* colonization rates actually appeared higher in healthcare than community settings in South America (Figure S7) and North America (Figure S8) (values were statistically insignificant). Sub-meta-analysis findings by sub-regions of Europe and the West Pacific are provided in the supplementary materials (Figures S9–S13) for further comparison.

This study also found that prolonged stay in a healthcare setting was associated with an increase in human intestinal colonization by ESBL *E. coli*. We demonstrated this using data from Europe, where nearly half of all the included studies in the healthcare setting were undertaken. This finding is consistent with other studies which found that prolonged hospitalization was an independent risk factor for intestinal ESBL *E. coli* colonization.[9,14] Further, as antibiotics are commonly used in healthcare settings, the resulting gut dysbiosis (loss of gut colonization resistance) coupled with longer exposure to a high-prevalence healthcare setting (during a prolonged hospital stay) could provide a synergistic combination for increased acquisition.

This study has several limitations. First, as mentioned above, overestimation or underestimation of the global and regional pooled prevalence could result from the spatial 'maldistribution' of the individual studies included in the meta-analysis. For example, certain WHO regions might consist of countries with low and high colonization rates, and hence regional carriage rates in the community might appear higher than in healthcare settings. This occurs whenever a preponderance of studies included to calculate regional pooled prevalence for the community setting are from countries of high prevalence, while the studies used to measure regional carriage rates for the healthcare setting are from countries of low prevalence. A similar problem was seen when we grouped studies every 5 years to show the global trend. For instance, for the years 2016–20, the global cumulative prevalence in the community (26.4%) appeared higher than the values in healthcare settings (25.7%). However, our linear regression analysis found that the global human ESBL *E. coli* carriage in healthcare settings was always higher than in the community setting for all the years (2000–21) (Figure 4a). Hence, linear regression was used to offset such an intrinsic bias during the grouping of studies for pooled prevalence. In addition, there was a limited number of studies in some WHO regions.

Laboratory methods of ESBL identification improved over the years and this might have an influence on the rising trend in ESBL *E. coli* carriage. Besides, the techniques and sensitivity of the tests used might also differ in different regions of the world, leading to differences in ESBL *E. coli* prevalence. Publication bias (Figure S14), selection bias and the setting of studies (usually with interactions with the healthcare system) might have resulted in some overestimation of the prevalence in the community setting. For example, the total number of participants used to calculate the prevalence in the community included individuals who visited a health facility for a routine wellness check-up, but those individuals may have had prior interactions with a

healthcare facility. The other limitation of this study is that the analysis was limited to the predominant ESBL-producing species—*E. coli*. The comparative prevalence of other Enterobacteriaceae needs to be addressed in future studies. Finally, the location of sample collection (community versus hospital versus nursing care) and the increased age of the nursing care residents may have introduced bias not accounted for in the calculation of the prevalence in the healthcare setting.[28]

Conclusions

Global and regional human intestinal ESBL *E. coli* carriage is increasing in both community and healthcare settings. Carriage rates were generally higher in healthcare than in community settings. Based on data from Europe, where the most robust data were available, the faecal ESBL *E. coli* carriage rate among inpatients admitted for ≥48 h and nursing home residents was 2- and 3-fold, respectively, compared with the prevalence in healthy individuals living in the community. Key relevant health organizations should perform surveillance and implement preventive measures to address the spread of ESBL *E. coli* in both settings.

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This study was conducted as part of our routine work.

Transparency declarations

None to declare.

Data sharing

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

Supplementary data

Tables S1–S3 and Figures S1–S14 are available as Supplementary data at *JAC-AMR* Online.

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