Human faeces-associated extended-spectrum β-lactamase-producing *Escherichia coli* discharge into sanitation systems in 2015 and 2030: a global and regional analysis

David Berendes, Amy Kirby, Joe Brown, Astrid L Wester

Summary

Background Improving management of and treatment within sanitation waste streams could slow the development and transmission of antimicrobial-resistant organisms, but the magnitude of impact has not been quantified. Extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* are a major cause of antimicrobial-resistant infections and are frequently detected in faecal waste streams, making them model indicators of the distribution of antimicrobial-resistant organisms that are transmitted through the faecal–oral route. We aimed to estimate the mass of faeces containing ESBL-producing *E coli* entering different levels of the sanitation ladder globally and by WHO region to determine the global scale at which sanitation infrastructure serves as a vehicle for dissemination of antimicrobial-resistant organisms.

Methods In this global and regional analysis, we used publicly available sanitation coverage data from the WHO/UNICEF Joint Monitoring Programme and most recent available scientific literature on human faecal production (2018) and carriage of ESBL-producing *E coli* by healthy individuals (2016) to estimate the quantity of faeces that has been discharged that contains ESBL-producing *E coli* for 2015 and projected for 2030. We estimated the mass of faeces containing ESBL-producing *E coli* by WHO region and at different levels of the Sustainable Development Goal sanitation ladder—ie, into at-least basic (ie, safely managed or basic) systems, limited systems, and unimproved systems, and via open defecation. We modelled three scenarios in which the proportion of ESBL-producing *E coli* among all *E coli* that was excreted by carriers varied on the basis of the scientific literature: 100% (scenario A), 10% (scenario B), or 1% (scenario C).

Findings Under scenario B, we estimated that approximately 19 billion kg of faeces carrying ESBL-producing *E coli* was excreted in 2015 globally. Approximately 65·8% (1·2–120 billion kg depending on modelled scenario) of this faecal biomass was managed in at-least basic sanitation systems, 8·4% (160 million–16 billion kg) in limited sanitation systems, 14·4% (270 million–27 billion kg) in unimproved sanitation systems, and 11·4% (220 million–22 billion kg) was openly defecated. The regions with the highest proportion of openly defecated faeces containing ESBL-producing *E coli* were the South-East Asia (29·4%) and African (21·8%) regions. The South-East Asia, Western Pacific, and African regions produced 524 billion kg (63%) of the total global human faecal biomass, but 16·9 billion kg (90%) of faeces containing ESBL-producing *E coli* under scenario B. By 2030, estimates under scenario B will have approximately doubled to 37·6 billion kg of faeces carrying ESBL-producing *E coli* under the most conservative projections.

Interpretation At-least basic sanitation does not guarantee effective removal or inactivation of antimicrobial-resistant organisms from faecal biomass. However, our findings indicate the need for mitigating transport of antimicrobial-resistant organisms via sanitation systems that are not safely managed, including open defecation, which might result in direct environmental discharge and subsequent risk of transmission back to humans.

Funding None.

Lancet Planet Health 2020; 4: e246–55

Waterborne Disease Prevention Branch, Division of Foodborne, Waterborne, and Environmental Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA (D Berendes PhD, A Kirby PhD); **School of Civil and Environmental Engineering, Georgia Institute of Technology, Atlanta, GA, USA** (J Brown PhD); **and Norwegian Institute of Public Health, Oslo, Norway** (A L Wester MD)

Correspondence to:
Dr David Berendes, Waterborne Disease Prevention Branch, Division of Foodborne, Waterborne, and Environmental Diseases, Centers for Disease Control and Prevention, Atlanta, 30329 GA, USA
dberendes@cdc.gov

Introduction

Antimicrobial resistance is one of the most pressing global public health threats. From 2000 to 2010, antimicrobial use increased by 65% worldwide, predominantly in low-income and middle-income countries.[1] Antimicrobial resistance is conservatively estimated to contribute to 700 000 deaths per year, a figure estimated to increase to 10 million deaths per year and cost $US10 000 per person by 2050 as current therapies lose their effectiveness and antimicrobial-resistant infections spread.[2,3]

Extended-spectrum β-lactamase (ESBL)-mediated resistance is an increasing concern. Identification of ESBL resistance mechanisms has increased rapidly over the past decade, both inside and outside of health-care settings, as shown by the prevalence of ESBL resistance mechanisms in the human gut, wastewater, and faecal sludge in high-income and low-income contexts.[4–7] ESBL-producing

Research in context

Evidence before this study

Human carriage of extended-spectrum β-lactamase (ESBL)-resistant organisms, including ESBL-producing *Escherichia coli*, has been increasing over the past several decades. As supported by exploratory review of the literature, this increase is indicative of one of many antimicrobial-resistant organisms of clinical importance with environmental transmission pathways. To date, improvements in water, sanitation, and hygiene systems globally are commonly implicated as important preventive measures for slowing the development of antimicrobial resistance (eg, proper treatment of drinking water to interrupt environmental transmission of many of these organisms, handwashing at key times to prevent infections). Sanitation systems in high-income settings have been found to be breeding grounds for antimicrobial-resistant organisms and their genes, and scientific efforts are ongoing to improve the understanding of how to treat these genes and organisms in high-income settings, but also understand the efficacy of onsite treatment technologies common in lower-income settings.

Added value of this study

To our knowledge, this study provides the first global estimates of mass of faeces containing ESBL-producing *E coli* passing through sanitation systems by region and quality of sanitation according to Sustainable Development Goal 6 indicator criteria. We also projected estimates to 2030 and found that major, comprehensive efforts are needed to combat the combination of increasing carriage rates and poor water, sanitation, and hygiene in low-income parts of the world.

Implications of all the available evidence

Sanitation systems in low-income settings, which are already disproportionately inferior in their treatment of susceptible organisms compared with high-income settings, receive the largest faecal biomass containing ESBL-producing *E coli*. When combined with available evidence of increasing human carriage of ESBL-producing *E coli*, the importance of sanitation systems—especially in low-income settings—increases exponentially. Improving sanitation systems in these settings should be included in efforts to prevent and combat antimicrobial resistance, as reducing infections and reducing antimicrobial-resistant organisms discharged into the environment can offset and reduce already strained clinical preventive and therapeutic measures.

enteric organisms, such as ESBL-producing *Escherichia coli*, have also been shown to have potential for rapid spread and colonisation via global travel,[8] with prevalent reservoirs in water, sewage, and soil.[5,9,10] Additionally, although a cause of serious clinical symptoms in patients, ESBL-producing *E coli* is also associated with a relatively high prevalence of asymptomatic carriage (and estimated transmission) among otherwise healthy individuals, with community-based estimates available.[11,12] All of these characteristics make ESBL-producing *E coli* a model indicator for antimicrobial-resistant enteric bacteria that are transmitted through the faecal–oral route.

Efforts to combat antimicrobial resistance have mainly focused on reducing and optimising antibiotic use and advocating for new antibiotics.[2] Beyond these two approaches, and in line with strategic objective three of the WHO global action plan on antimicrobial resistance,[13] improving the infrastructure of water, sanitation, and hygiene (WASH) might reduce both rates of infection (and therefore the need for antibiotics) and, in areas where water used for drinking or bathing might be contaminated with faeces, overall exposure to antimicrobial-resistant organisms.[2,14,15] Still, existing wastewater and faecal sludge treatment technologies in high-income and low-income settings might not eliminate antimicrobial-resistant organisms and their genes.[16–18] Although reports indicate access to WASH might be key in the fight against antimicrobial resistance,[19,20] the potential effect of WASH interventions on the frequency of infections caused by antimicrobial-resistant organisms, or even the number of antimicrobial-resistant organisms transmitted through the environment via faecal waste streams, has not been quantified.

To estimate the global scale at which sanitation infrastructure serves as a vehicle for dissemination of antimicrobial-resistant organisms (and could therefore reduce dissemination of such organisms if safely managed) and understand how these estimates might change with increasing population size and carriage rates, we calculated the total global human faecal discharge of ESBL-producing *E coli* (defined as PCR detection of a CTX-M-type, SHV-type, or TEM-type ESBL gene) into sanitation systems both in 2015 and estimated for 2030. We estimated discharge by WHO region and at different levels of the Sustainable Development Goal (SDG) sanitation ladder[21] to calculate region-specific and sanitation technology-specific loads, given 2015 coverage levels. To our knowledge, these estimates provide the first calculation of the dissemination of antimicrobial-resistant organisms through sanitation systems globally.

Methods

Study design and data sources

In this global and regional analysis, we estimated global and WHO region-specific production of human faeces. We sourced coverage and population estimates at each level of the SDG sanitation ladder produced by the Joint Monitoring Program (JMP) of WHO and UNICEF in 2015.[22] Other data sources were The World Bank,[23] and existing scientific literature.[12,24–28]

Data collection and analysis for 2015 estimates

Briefly, using methods described in our previous publication,[24] we estimated human faecal production in 2015 by combining the most recent population estimates available (2017) from The World Bank,[23] region-specific upper and lower estimates of average human body mass,[25] and a daily body-mass-faecal production equation for mammals, including humans,[26] that we extended to annual production. We obtained estimates from recent (2015) JMP data[22] of the population, by region and globally, at each level of the SDG sanitation ladder, in which quality of the sanitation facility is defined as safely managed, basic, limited, unimproved, or open defecation (ie, no facility).[21] For the African, Eastern Mediterranean, and South-East Asia regions, we could not quantify estimates for safely managed sanitation; therefore estimates are presented as at-least basic sanitation (a combination of basic and safely managed categories). We estimated the proportion of the population by region and globally who were carriers of ESBL-producing *E coli* using clinical and molecular studies of non-care-seeking healthy individuals collected by Karanika and colleagues in their 2016 meta-analysis.[12] We used region-specific mean estimates for the calculation of lower and upper bounds of 95% CIs to calculate low and high estimates. For our analysis, ESBL-producing *E coli* is limited to isolates with PCR detection of a CTX-M-type, SHV-type, or TEM-type ESBL gene.[12]

We calculated faecal biomass per person based on adults, given the lack of data on human body biomass for children, changing age distributions,[25] and paediatric carriage of ESBL-producing *E coli*. We also assumed region-specific prevalence of ESBL-producing *E coli*, based on previous literature,[12] applied uniformly across users of different sanitation systems in that region. Subregional and subnational variation might occur but are, as yet, unquantified. We also did not extend management of faeces to include estimates of the effectiveness of treatment, given substantial uncertainty in estimates of safe management and final treatment[21,29] and unresolved research into the efficacy of treatment systems at removing or mitigating mechanisms of antimicrobial resistance in excreta.[18] Healthy adults shed up to six unique clones of *E coli* in their stool, with most people (77%) shedding a single clone.[27] Given the lack of data on the extent to which carriers of ESBL-producing *E coli* (or other types of *E coli*) shed clonal versus multiple types of *E coli*,[27] we modelled $\log_{10}$-ordered scenarios in which ESBL-producing *E coli* shed by carriers represented 100% (carriage factor scenario A), 10% (minimum value from Johnson and colleagues'[27] analysis of *E coli* clonal carriage; carriage factor scenario B), and 1% (carriage factor scenario C) of all *E coli* excreted in faeces.

Using these data sources, we calculated—by region, and summed globally—the following estimates, where A is the proportion of the population (by region or globally) carrying ESBL-producing *E coli*, B is the population (by region or globally) using a particular sanitation system, C is the per capita mass (in kg) of human faeces produced annually (by region or globally), and D is the carriage factor (ie, proportion of *E coli* that is shed in the faeces of a carrier that is ESBL-producing *E coli*—ie, 100%, 10%, or 1%).

We calculated—by region and summed globally—the proportion of faeces that contains ESBL-producing *E coli* entering different levels of the SDG sanitation ladder in a given region or globally. We calculated our main estimate using

$$\frac{A_{\text{region}} \times B_{\text{region}} \times C_{\text{region}} \times D_{\text{carriage factor scenario}}}{A_{\text{global}} \times B_{\text{global}} \times C_{\text{global}} \times D_{\text{carriage factor scenario}}}$$

where A is the proportion of the population (by region or globally) carrying ESBL-producing *E coli*, B is the population (by region or globally) using a particular sanitation system, C is the per capita mass (in kg) of human faeces produced annually (by region or globally), and D is the carriage factor (ie, proportion of *E coli* that is shed in the faeces of a carrier that is ESBL-producing *E coli*—ie, 100%, 10%, or 1%).

We calculated our low estimate using

$$\frac{A_{\text{lower 95\% CI bound for region}} \times B_{\text{region}} \times C_{\text{low estimate for region}}}{A_{\text{lower 95\% CI bound for global}} \times B_{\text{global}} \times C_{\text{low estimate for global}} \times D_{\text{carriage factor scenario}}} \cdot \times D_{\text{carriage factor scenario}}$$

And we calculated our high estimate using

$$\frac{A_{\text{higher 95\% CI bound for region}} \times B_{\text{region}} \times C_{\text{high estimate for region}}}{A_{\text{higher 95\% CI bound for global}} \times B_{\text{global}} \times C_{\text{high estimate for global}} \times D_{\text{carriage factor scenario}}} \cdot \times D_{\text{carriage factor scenario}}$$

We calculated the mass of faeces in kg per year entering sanitation systems (by SDG sanitation level) that contained ESBL-producing *E coli*. We calculated our main estimate using

$$A_{\text{region}} \times B_{\text{region}} \times C_{\text{region}} \times D_{\text{carriage factor scenario}}.$$

We calculated our low estimate using

$$A_{\text{low 95\% CI bound for region}} \times B_{\text{region}} \times C_{\text{lower estimate for region}} \times D_{\text{carriage factor scenario}}$$

and we calculated our high estimate using

$$A_{\text{high 95\% CI bound for region}} \times B_{\text{region}} \times C_{\text{higher estimate for region}} \times D_{\text{carriage factor scenario}}.$$

Notably, high and low estimates are not 95% CIs for the mean value, but rather more conservative upper and lower bounds of the range, given current areas of uncertainty. Lower bounds of 95% CI for estimate of prevalence of ESBL-producing *E coli* carriage for the region of the Americas in Karanika and colleagues[12] was zero; therefore lower bounds for this region across all scenarios are zero.

Data collection and analysis for 2030 estimates

For predictions of global faecal biomass containing ESBL-producing *E coli* in 2030, we used World Bank projected population figures for 2030 at regional levels as population estimates[30] and estimated growth in concomitant faecal biomass in 2030,[24] accounting for growth in carriage rates of ESBL-producing *E coli* by projecting estimates of annual growth using data on trends of carriage of ESBL-producing *E coli* globally from Karanika et al[12] (5·38% increase in carriage per year) or ESBL-producing Enterobacteriaceae regionally from Woerther et al[28] (ranging from 0·5–7·7% per year by region) forwards to 2030. Current and projected carriage rate estimates from literature are summarised in the appendix (p 1).

See Online for appendix

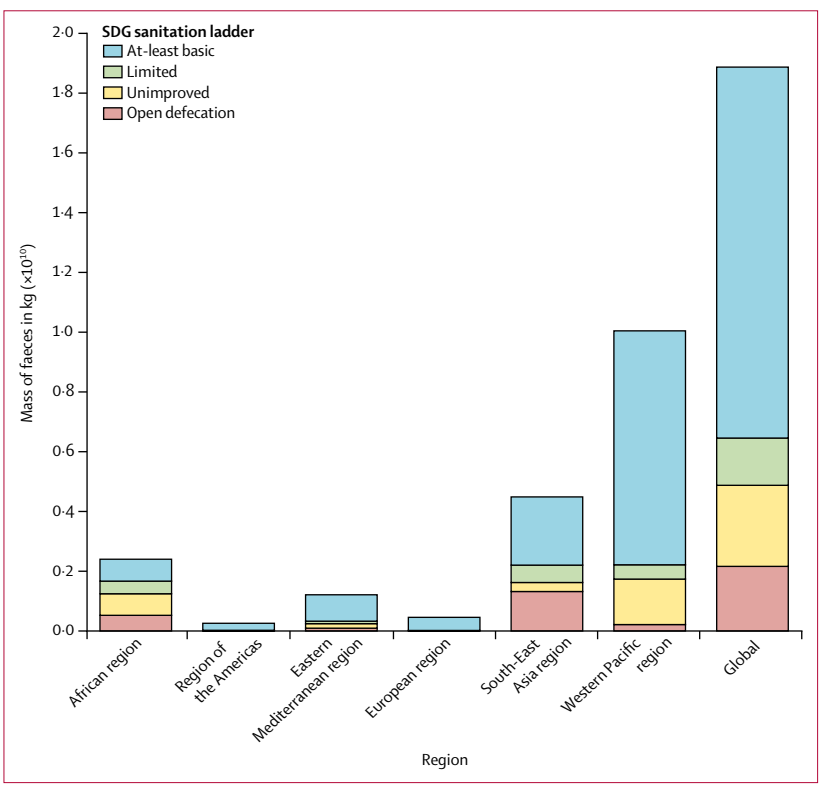

Figure 1: **Faecal biomass containing ESBL-producing *E coli* entering different levels of the SDG sanitation ladder by region and globally, in 2015**

Plot shows faecal biomass under scenario B, in which 10% of *E coli* shed by a carrier of ESBL-producing *E coli* is ESBL-producing. Under scenario A (100% ESBL-producing *E coli* shed) the absolute estimates would increase by ten times, and under scenario C (1% ESBL-producing *E coli* shed), they would decrease by ten times, but relative ratios of production would remain constant. ESBL=extended-spectrum β-lactamase. *E coli=Escherichia coli*. SDG=Sustainable Development Goal.

Using the most conservative global carriage trends (Karanika et al[12]) and less conservative estimates (Woerther et al[28]), we also estimated the increase in global faecal biomass containing ESBL-producing *E coli* from 2015 to 2030 under different hypothesised intervention scenarios. Intervention scenario 1 hypothesised a 50% reduction in the estimated annual rate of increase of ESBL-producing *E coli* carriage globally; intervention scenario 2 hypothesised that 2015 ESBL-producing *E coli* carriage rates were held constant; intervention scenario 3 hypothesised a 50% reduction in the estimated annual rate of increase of ESBL-producing *E coli* carriage in the African, South-East Asia, and Western Pacific region (where WASH efforts are most focused), and no intervention to reduce rates of increase in other regions; and intervention scenario 4 hypothesised that 2015 ESBL-producing *E coli* carriage rates are held constant in the African, South-East Asia, and Western Pacific regions, and no intervention to reduce rates of increase in other regions.

We did all analyses in Microsoft Excel 2016 and R (version 3.4.3).

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication

Results

Globally, we estimated that, under scenario A, 190 billion kg of faeces carrying ESBL-producing *E coli* were excreted in 2015, under scenario B, 19 billion kg of faeces carrying ESBL-producing *E coli* were excreted in 2015, and under scenario C, 1·9 billion kg of faeces carrying ESBL-producing *E coli* were excreted in 2015. Graphical presentation of how this biomass of faeces would enter different levels of the SDG sanitation ladder by region, in 2015, under scenario B, is shown in figure 1. Under scenario B in 2015, the Western Pacific (approximately 10·00 billion [53%] of 19 billion kg) and South-East Asia (4·50 billion [24%]) regions accounted for most of the annual ESBL-producing *E coli*-carrying faecal biomass globally, followed by the African region (2·40 billion [13%]), Eastern Mediterranean region (1·20 billion [6%]), European region (0·45 billion [2%]), and region of the Americas (0·25 billion [1%]; figure 2). Comparatively, in 2015 the Western Pacific region accounted for 216 billion (26%) of all annual human faecal biomass of 845 billion kg, followed by the South-East Asia region (201 billion [24%]), region of the Americas (127 billion [15%]), European region (114 billion [13%]) and African region (106 billion [13%]), and Eastern Mediterranean region (80 billion [9%]; global totals might be larger than the sum of the stated regional totals due to rounding).

Globally, almost two-thirds (65·8%; table 1) of total faecal biomass containing ESBL-producing *E coli* were

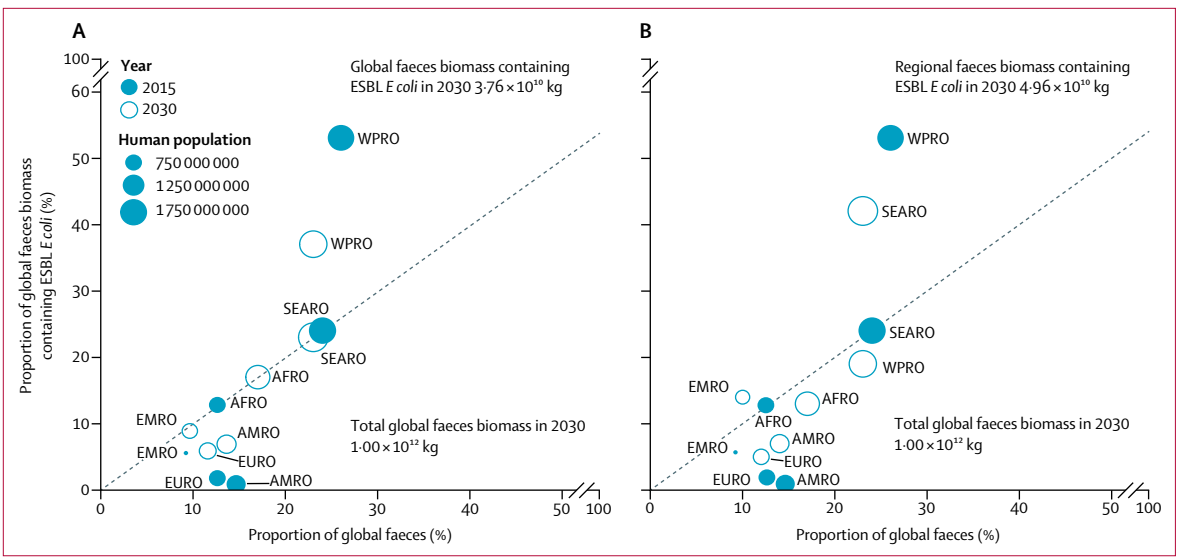

Figure 2: **Global and regional faecal biomass and faecal biomass containing ESBL-producing *E coli* in 2015 and 2030**
Plots show faecal biomass under scenario B, in which 10% of *E coli* shed by a carrier of ESBL-producing *E coli* are ESBL-producing. (A) Global and regional estimates of ESBL-producing *E coli* carriage trends are based on estimates in Karanika et al.[12] (B) Global and regional estimates based on ESBL-producing Enterobacteriaceae carriage trends in Woerther et al.[28] Estimates of regional composition of the global faecal biomass for both (A) and (B) are adapted from estimates in Berendes et al.[24] AFRO=African region. AMRO=Region of the Americas. *E coli=Escherichia coli*. EMRO=Eastern Mediterranean region. ESBL=extended-spectrum β-lactamase. EURO=European region. SEARO=South-East Asia region. WPRO=Western Pacific region.

discharged into at-least basic sanitation (1·2–120 billion kg depending on scenario; table 2). 8·4% (160 million–16 billion kg) of faeces carrying ESBL-producing *E coli* were discharged into limited sanitation systems, 14·4% (270 million–27 billion kg) into unimproved systems, and 11·4% (220 million–22 billion kg) were openly defecated (tables 1 and 2). The regions with the highest proportion of openly defecated faeces containing ESBL-producing *E coli* were South-East Asia (29·4%) and Africa (21·8%; figure 1, table 1). The African region had the most even distribution of faeces containing ESBL-producing *E coli* across different levels of the sanitation ladder (table 1), whereas in the other regions most faeces containing ESBL-producing *E coli* (>50%) was discharged into at-least basic sanitation.

In 2015, across scenarios, individuals in the South-East Asia region discharged the most faeces containing ESBL-producing *E coli* via open defecation alone (130 million–13 billion kg), followed by individuals in the African region (52 million–5·2 billion kg) and the Western Pacific region (22 million–2·2 billion kg; table 2). The Western Pacific region had the largest discharge of faeces containing ESBL-producing *E coli* into at-least basic systems (790 million–79 billion kg), followed by South-East Asia (230 million–23 billion kg).

When projected to 2030, using global trends in ESBL-producing *E coli*,[12] assuming scenario B, the global mass of faeces containing ESBL-producing *E coli* discharged would be 37·6 billion kg, almost double the 2015 estimate (figure 2A). Under less conservative region-specific trends for ESBL-producing Enterobacteriaceae,[28] global estimates increase about 2·5-times from 2015, to 49·6 billion kg (figure 2B). Generally, the Western Pacific region (when calculated using global trends) and the South-East Asia region (when calculated using the region-specific trends), contribute a higher proportion of faeces to total global faecal biomass containing ESBL-producing *E coli* than to total general global faecal biomass, but contributions from other regions, such as the African region, increase from 2015 to 2030 due to both increasing population size and increasing ESBL-producing *E coli* carriage beyond population increase alone.

When projected to 2030 using the most conservative carriage trend estimates,[12] under intervention scenarios 1–4, and assuming scenario B (figure 3),

	Safely managed	At-least basic*	Basic	Limited	Unimproved	Open defecation
African region	..	30·5%	..	17·6%	30·1%	21·8%
Region of the Americas	42·7%	..	48·1%	3·2%	4·0%	2·0%
Eastern Mediterranean region	..	72·9%	..	6·9%	12·5%	7·8%
European region	67·5%	..	28·5%	1·1%	2·8%	<0·1%
South-East Asia region	..	50·9%	..	13·0%	6·7%	29·4%
Western Pacific region	57·4%	..	20·6%	4·8%	15·1%	2·2%
Global	..	65·8%	..	8·4%	14·4%	11·4%

ESBL=extended-spectrum β-lactamase. *Safely managed sanitation estimates for Africa, Eastern Mediterranean, and South-East Asia regions could not be quantified in 2015, so estimates for at-least basic sanitation (combined basic and safely-managed categories) are given for these regions, and globally.

Table 1: **Proportion of faeces containing ESBL-producing *Escherichia coli* discharged into each sanitation system, regionally and globally, in 2015**

	Safely managed	At-least basic	Basic	Limited	Unimproved	Open defecation
Scenario A						
African region*	..	$7{\cdot}3\times10^{9}$ ($1{\cdot}5\times10^{9}$ to $1{\cdot}7\times10^{10}$)	..	$4{\cdot}2\times10^{9}$ ($8{\cdot}7\times10^{8}$ to $9{\cdot}9\times10^{9}$)	$7{\cdot}2\times10^{9}$ ($1{\cdot}5\times10^{9}$ to $1{\cdot}7\times10^{10}$)	$5{\cdot}2\times10^{9}$ ($1{\cdot}1\times10^{9}$ to $1{\cdot}2\times10^{10}$)
Region of the Americas†	$1{\cdot}1\times10^{9}$ (0 to $3{\cdot}0\times10^{9}$)	..	$1{\cdot}2\times10^{9}$ (0 to $3{\cdot}3\times10^{9}$)	$8{\cdot}3\times10^{7}$ (0 to $2{\cdot}2\times10^{8}$)	$1{\cdot}0\times10^{8}$ (0 to $2{\cdot}8\times10^{8}$)	$5{\cdot}0\times10^{7}$ (0 to $1{\cdot}4\times10^{8}$)
Eastern Mediterranean region*	..	$8{\cdot}8\times10^{9}$ ($2{\cdot}2\times10^{9}$ to $2{\cdot}0\times10^{10}$)	..	$8{\cdot}3\times10^{8}$ ($2{\cdot}0\times10^{8}$ to $1{\cdot}9\times10^{9}$)	$1{\cdot}5\times10^{9}$ ($3{\cdot}7\times10^{8}$ to $3{\cdot}4\times10^{9}$)	$9{\cdot}4\times10^{8}$ ($2{\cdot}3\times10^{8}$ to $2{\cdot}1\times10^{9}$)
European region	$3{\cdot}1\times10^{9}$ ($1{\cdot}4\times10^{9}$ to $4{\cdot}2\times10^{9}$)	..	$1{\cdot}3\times10^{9}$ ($6{\cdot}0\times10^{8}$ to $1{\cdot}8\times10^{9}$)	$5{\cdot}1\times10^{7}$ ($2{\cdot}3\times10^{7}$ to $6{\cdot}8\times10^{7}$)	$1{\cdot}3\times10^{8}$ ($5{\cdot}9\times10^{7}$ to $1{\cdot}7\times10^{8}$)	$1{\cdot}6\times10^{6}$ ($7{\cdot}5\times10^{5}$ to $2{\cdot}2\times10^{6}$)
South-East Asia region*	..	$2{\cdot}3\times10^{10}$ ($6{\cdot}6\times10^{9}$ to $5{\cdot}0\times10^{10}$)	..	$5{\cdot}8\times10^{9}$ ($1{\cdot}7\times10^{9}$ to $1{\cdot}3\times10^{10}$)	$3{\cdot}0\times10^{9}$ ($8{\cdot}6\times10^{8}$ to $6{\cdot}6\times10^{9}$)	$1{\cdot}3\times10^{10}$ ($3{\cdot}8\times10^{9}$ to $2{\cdot}9\times10^{10}$)
Western Pacific region	$5{\cdot}8\times10^{10}$ ($3{\cdot}3\times10^{10}$ to $8{\cdot}6\times10^{10}$)	..	$2{\cdot}1\times10^{10}$ ($1{\cdot}2\times10^{10}$ to $3{\cdot}1\times10^{10}$)	$4{\cdot}8\times10^{9}$ ($2{\cdot}8\times10^{9}$ to $7{\cdot}1\times10^{9}$)	$1{\cdot}5\times10^{10}$ ($8{\cdot}7\times10^{9}$ to $2{\cdot}3\times10^{10}$)	$2{\cdot}2\times10^{9}$ ($1{\cdot}2\times10^{9}$ to $3{\cdot}2\times10^{9}$)
Global	..	$1{\cdot}2\times10^{11}$ ($5{\cdot}7\times10^{10}$ to $2{\cdot}2\times10^{11}$)	..	$1{\cdot}6\times10^{10}$ ($5{\cdot}5\times10^{9}$ to $3{\cdot}2\times10^{10}$)	$2{\cdot}7\times10^{10}$ ($1{\cdot}2\times10^{10}$ to $5{\cdot}0\times10^{10}$)	$2{\cdot}2\times10^{10}$ ($6{\cdot}3\times10^{9}$ to $4{\cdot}7\times10^{10}$)
Scenario B						
African region*	..	$7{\cdot}3\times10^{8}$ ($1{\cdot}5\times10^{8}$ to $1{\cdot}7\times10^{9}$)	..	$4{\cdot}2\times10^{8}$ ($8{\cdot}7\times10^{7}$ to $9{\cdot}9\times10^{8}$)	$7{\cdot}2\times10^{8}$ ($1{\cdot}5\times10^{8}$ to $1{\cdot}7\times10^{9}$)	$5{\cdot}2\times10^{8}$ ($1{\cdot}1\times10^{8}$ to $1{\cdot}2\times10^{9}$)
Region of the Americas†	$1{\cdot}1\times10^{8}$ (0 to $3{\cdot}0\times10^{8}$)		$1{\cdot}2\times10^{8}$ (0 to $3{\cdot}3\times10^{8}$)	$8{\cdot}3\times10^{6}$ (0 to $2{\cdot}2\times10^{7}$)	$1{\cdot}0\times10^{7}$ (0 to $2{\cdot}8\times10^{7}$)	$5{\cdot}0\times10^{6}$ (0 to $1{\cdot}4\times10^{7}$)
Eastern Mediterranean region*	..	$8{\cdot}8\times10^{8}$ ($2{\cdot}2\times10^{8}$ to $2{\cdot}0\times10^{9}$)	..	$8{\cdot}3\times10^{7}$ ($2{\cdot}0\times10^{7}$ to $1{\cdot}9\times10^{8}$)	$1{\cdot}5\times10^{8}$ ($3{\cdot}7\times10^{7}$ to $3{\cdot}4\times10^{8}$)	$9{\cdot}4\times10^{7}$ ($2{\cdot}3\times10^{7}$ to $2{\cdot}1\times10^{8}$)
European region	$3{\cdot}1\times10^{8}$ ($1{\cdot}4\times10^{8}$ to $4{\cdot}2\times10^{8}$)	..	$1{\cdot}3\times10^{8}$ ($6{\cdot}0\times10^{7}$ to $1{\cdot}8\times10^{8}$)	$5{\cdot}1\times10^{6}$ ($2{\cdot}3\times10^{6}$ to $6{\cdot}8\times10^{6}$)	$1{\cdot}3\times10^{7}$ ($5{\cdot}9\times10^{6}$ to $1{\cdot}7\times10^{7}$)	$1{\cdot}6\times10^{5}$ ($7{\cdot}5\times10^{4}$ to $2{\cdot}2\times10^{5}$)
South-East Asia region*	..	$2{\cdot}3\times10^{9}$ ($6{\cdot}6\times10^{8}$ to $5{\cdot}0\times10^{9}$)	..	$5{\cdot}8\times10^{8}$ ($1{\cdot}7\times10^{8}$ to $1{\cdot}3\times10^{9}$)	$3{\cdot}0\times10^{8}$ ($8{\cdot}6\times10^{7}$ to $6{\cdot}6\times10^{8}$)	$1{\cdot}3\times10^{9}$ ($3{\cdot}8\times10^{8}$ to $2{\cdot}9\times10^{9}$)
Western Pacific region	$5{\cdot}8\times10^{9}$ ($3{\cdot}3\times10^{9}$ to $8{\cdot}6\times10^{9}$)	..	$2{\cdot}1\times10^{9}$ ($1{\cdot}2\times10^{9}$ to $3{\cdot}1\times10^{9}$)	$4{\cdot}8\times10^{8}$ ($2{\cdot}8\times10^{8}$ to $7{\cdot}1\times10^{8}$)	$1{\cdot}5\times10^{9}$ ($8{\cdot}7\times10^{8}$ to $2{\cdot}3\times10^{9}$)	$2{\cdot}2\times10^{8}$ ($1{\cdot}2\times10^{8}$ to $3{\cdot}2\times10^{8}$)
Global	..	$1{\cdot}2\times10^{10}$ ($5{\cdot}7\times10^{9}$ to $2{\cdot}2\times10^{10}$)	..	$1{\cdot}6\times10^{9}$ ($5{\cdot}5\times10^{8}$ to $3{\cdot}2\times10^{9}$)	$2{\cdot}7\times10^{9}$ ($1{\cdot}2\times10^{9}$ to $5{\cdot}0\times10^{9}$)	$2{\cdot}2\times10^{9}$ ($6{\cdot}3\times10^{8}$ to $4{\cdot}7\times10^{9}$)
Scenario C						
African region*	..	$7{\cdot}3\times10^{7}$ ($1{\cdot}5\times10^{7}$ to $1{\cdot}7\times10^{8}$)	..	$4{\cdot}2\times10^{7}$ ($8{\cdot}7\times10^{6}$ to $9{\cdot}9\times10^{7}$)	$7{\cdot}2\times10^{7}$ ($1{\cdot}5\times10^{7}$ to $1{\cdot}7\times10^{8}$)	$5{\cdot}2\times10^{7}$ ($1{\cdot}1\times10^{7}$ to $1{\cdot}2\times10^{8}$)
Region of the Americas†	$1{\cdot}1\times10^{7}$ (0 to $3{\cdot}0\times10^{7}$)	..	$1{\cdot}2\times10^{7}$ (0 to $3{\cdot}3\times10^{7}$)	$8{\cdot}3\times10^{5}$ (0 to $2{\cdot}2\times10^{6}$)	$1{\cdot}0\times10^{6}$ (0 to $2{\cdot}8\times10^{6}$)	$5{\cdot}0\times10^{5}$ (0 to $1{\cdot}4\times10^{6}$)
Eastern Mediterranean region*	..	$8{\cdot}8\times10^{7}$ ($2{\cdot}2\times10^{7}$ to $2{\cdot}0\times10^{8}$)	..	$8{\cdot}3\times10^{6}$ ($2{\cdot}0\times10^{6}$ to $1{\cdot}9\times10^{7}$)	$1{\cdot}5\times10^{7}$ ($3{\cdot}7\times10^{6}$ to $3{\cdot}4\times10^{7}$)	$9{\cdot}4\times10^{6}$ ($2{\cdot}3\times10^{6}$ to $2{\cdot}1\times10^{7}$)
European region	$3{\cdot}1\times10^{7}$ ($1{\cdot}4\times10^{7}$ to $4{\cdot}2\times10^{7}$)	..	$1{\cdot}3\times10^{7}$ ($6{\cdot}0\times10^{6}$ to $1{\cdot}8\times10^{7}$)	$5{\cdot}1\times10^{5}$ ($2{\cdot}3\times10^{5}$ to $6{\cdot}8\times10^{5}$)	$1{\cdot}3\times10^{6}$ ($5{\cdot}9\times10^{5}$ to $1{\cdot}7\times10^{6}$)	$1{\cdot}6\times10^{4}$ ($7{\cdot}5\times10^{3}$ to $2{\cdot}2\times10^{4}$)
South-East Asia region*	..	$2{\cdot}3\times10^{8}$ ($6{\cdot}6\times10^{7}$ to $5{\cdot}0\times10^{8}$)	..	$5{\cdot}8\times10^{7}$ ($1{\cdot}7\times10^{7}$ to $1{\cdot}3\times10^{8}$)	$3{\cdot}0\times10^{7}$ ($8{\cdot}6\times10^{6}$ to $6{\cdot}6\times10^{7}$)	$1{\cdot}3\times10^{8}$ ($3{\cdot}8\times10^{7}$ to $2{\cdot}9\times10^{8}$)
Western Pacific region	$5{\cdot}8\times10^{8}$ ($3{\cdot}3\times10^{8}$ to $8{\cdot}6\times10^{8}$)	..	$2{\cdot}1\times10^{8}$ ($1{\cdot}2\times10^{8}$ to $3{\cdot}1\times10^{8}$)	$4{\cdot}8\times10^{7}$ ($2{\cdot}8\times10^{7}$ to $7{\cdot}1\times10^{7}$)	$1{\cdot}5\times10^{8}$ ($8{\cdot}7\times10^{7}$ to $2{\cdot}3\times10^{8}$)	$2{\cdot}2\times10^{7}$ ($1{\cdot}2\times10^{7}$ to $3{\cdot}2\times10^{7}$)
Global	..	$1{\cdot}2\times10^{9}$ ($5{\cdot}7\times10^{8}$ to $2{\cdot}2\times10^{9}$)	..	$1{\cdot}6\times10^{8}$ ($5{\cdot}5\times10^{7}$ to $3{\cdot}2\times10^{8}$)	$2{\cdot}7\times10^{8}$ ($1{\cdot}2\times10^{8}$ to $5{\cdot}0\times10^{8}$)	$2{\cdot}2\times10^{8}$ ($6{\cdot}3\times10^{7}$ to $4{\cdot}7\times10^{8}$)

Data are mass in kg. Data in parentheses are conservative higher and lower bounds of the range, given current areas of uncertainty. Scenario A assumes that 100% of *E coli* shed by an individual carrying ESBL-producing *E coli* are ESBL-producing; scenario B assumes 10%; and scenario C assumes 1% as a conservative minimum value. *E coli*=*Escherichia coli*. ESBL=extended-spectrum β-lactamase. *Safely managed sanitation estimates for the African, Eastern Mediterranean, and South-East Asia regions could not be quantified in 2015, so estimates for at-least basic sanitation (combined basic and safely-managed categories) are given for these regions, and globally. †Lower bounds of 95% CI for estimate of prevalence of ESBL-producing *E coli* carriage in Karanika and colleagues[12] was zero; therefore lower bounds are zero.

Table 2: **Mass of faeces containing ESBL-producing *E coli* in sanitation systems, by modelled scenario, for 2015**

the global mass of faeces discharged carrying ESBL-producing *E coli* is estimated to be 37·2 billion kg under intervention scenario 1, a 1·1% decrease from our projection with no intervention (figure 2A). Under intervention scenario 2, we estimated global mass of faeces containing ESBL-producing *E coli* to be 21·7 billion kg, a 32% decrease compared with no intervention. Under intervention 3, we estimated the mass to be 37·3 billion kg, a 0·8% decrease compared with no intervention. And under intervention 4, we estimated the mass to be 27·6 billion kg, a 27% decrease compared with no intervention. Interventions 1–4 estimates under the less conservative trend estimate (Woerther et al),[28] which ranged from a 0·1% decrease (under intervention 3) to a 24% decrease (under intervention 2), are shown in the appendix (p 2).

Discussion

We combined estimates of human faecal biomass production with estimates of sanitation coverage and ESBL-producing *E coli* carriage to derive, to our knowledge, the first estimations of the distribution of human-associated faeces containing ESBL-producing *E coli*, for 2015 and projected to 2030, globally. Our methods and results are an initial estimation of the global distribution of antimicrobial-resistant organisms discharged via faeces and its associated load in human waste treatment systems. Of the total estimated faecal biomass containing ESBL-producing *E coli* discharged in 2015, two-thirds was discharged into at-least basic sanitation systems but a quarter was discharged into unimproved systems and via open defecation, mostly in regions comprising low-income and middle-income countries. Notably, even technologies on the highest SDG sanitation ladder level—safely-managed—do not guarantee effective treatment and removal of antimicrobial-resistant organisms, such as ESBL-producing *E coli*, and their antimicrobial-resistant genes.[31,32] Our projections to 2030 indicate that major comprehensive changes are needed to combat the combination of high and increasing carriage rates and poor WASH in high population and low-income areas of the world.

Both prevalent antibiotic use in young children—98% of children are thought to be exposed to antibiotics by age 6 months in low-income and middle-income countries[33]—and poor WASH conditions leading to frequent bacterial infections[34] will likely contribute to continued increases in carriage rates of ESBL-producing *E coli* and other faecal-associated antimicrobial-resistant organisms in these settings by 2030. Our projected results and intervention scenarios suggest that even a 50% reduction in the rate of change of ESBL-producing *E coli* carriage, such as through environmental (WASH) preventive measures and antibiotic stewardship or other interventions, would only have a small (<2%) effect on total mass of faeces containing ESBL-producing *E coli* in 2030. Large-scale efforts are needed to prevent new ESBL-producing *E coli* colonisation, especially in low-income and middle-income countries, and to safely manage or contain up to a third of faecal-derived ESBL-producing *E coli* that is currently being defecated openly or managed in unsafe facilitites and subsequently presenting hazards to the population.

Although our data suggest ESBL-producing *E coli* are shed in substantial quantities of faeces in most of the world, this analysis also suggests low-income settings—particularly the South-East Asia, Western Pacific, and African regions—are regions of focus for environmental efforts to curb its spread via faecal discharge. These regions comprised about two-thirds of the world's population (65%) and faecal discharge (63%) in 2015,[22–24] yet produced 90% of the global faeces containing ESBL-producing *E coli*. The South-East Asia and African regions had the largest proportions of faeces containing ESBL-producing *E coli* that were openly defecated, and most sanitation facilities in these regions are onsite decentralised systems (eg, pit latrines with emptying).[24] Correspondingly, these regions continue to have among the highest global burdens of diarrhoea, enteric infections, and other sanitation-related morbidities,[35] such that the addition of exposure to antimicrobial-resistant organisms in faeces might spread very quickly. These populations, and their associated human and animal faecal biomass—with and without ESBL-producing *E coli*—will also continue to increase, especially in Africa, which is projected to have the largest human population increases by 2030.[24,30] Notably, our data were limited to healthy, non-care-seeking individuals, as per previously-defined criteria,[12] which might result in an underestimation of true discharge because faeces from hospitals and other institutions caring for non-healthy individuals is omitted from analyses.[36] There might be additional variation in our estimates from the true faecal discharge of ESBL-producing *E coli* due to variation in human faecal production (eg, regionally by biomass of the individual, diet, and other factors[25,37]) and increased carriage rates beyond those estimated in 2015.[36,38] Notably, the modelled estimates of human production of faeces[26] that we used were slightly larger than those estimated empirically from sporadic studies with one-off estimates.[37]

Figure 3: **Estimated faecal biomass containing ESBL-producing *E coli* in 2030, by region and intervention scenario**

Plot shows faecal biomass under scenario B, in which 10% of *E coli* shed by a carrier of ESBL-producing *E coli* are ESBL-producing. Intervention scenario 1 projects a reduction in ESBL-producing *E coli* carriage of 50% in all regions. Intervention scenario 2 projects that 2015 trends in ESBL-producing *E coli* are held constant in all regions. Intervention scenario 3 projects that the estimated annual rate of increase in carriage trends decrease by 50% in the African, South-East Asia, and Western Pacific regions, but decrease by 0% in all other regions. Intervention scenario 4 projects that 2015 carriage rates are held constant in the African region, South-East Asia region, and Western Pacific region, but decrease by 0% in all other regions. *E coli*=*Escherichia coli*. ESBL=extended-spectrum β-lactamase.

Although we cannot directly estimate the treatment efficacy of onsite, decentralised sanitation facilities,[21] safe emptying, management, and treatment of pathogens remains a substantial challenge in low-income settings.[39] Onsite systems, such as latrines without slabs and proper lining, that are classified as unimproved sanitation on the SDG sanitation ladder are not considered to safely separate users from excrement and associated risks.[21] Among the improved systems that are shared (limited systems), concerns of about an increased risk of transmission of diarrhoea exist due to multiple daily users,[40] which could be extended to transmission of ESBL-producing *E coli*. However, mechanistic evidence of the exact transmission pathways for faecal contamination (including antimicrobial-resistant faecal contamination) in shared sanitation settings is needed.[41] Beyond onsite systems, a substantial proportion of faecal waste from sanitation facilities connected to drains or sewers in these settings might still go untreated;[29] therefore, unsafe management of faeces with ESBL-producing *E coli* is probably underestimated in our calculations.

Use of safely managed sanitation, such as sewered sanitation connected to a functional wastewater treatment plant, in itself does not imply total removal of ESBL-producing *E coli*, other antimicrobial-resistant organisms, or their resistant genes from faeces, faecal sludge, and wastewater before discharge into the environment. Moving from open defecation and unimproved sanitation to improved sanitation has been found to significantly reduce the environmental load of antimicrobial-resistant genes, with additional reductions when moving from secondary to tertiary treatment.[42] Viable antimicrobial-resistant bacteria, including ESBL-producing *E coli*, have been detected in effluent from wastewater treatment plants,[31,32,43,44] which might be a risk to public health if these waters are used for drinking, personal hygiene, irrigation, or recreation. Therefore, further research into effective technologies for removing these pathogens in both wastewater treatment plants and decentralised sanitation systems (faecal sludge treatment plants or onsite treatment) is urgently needed. Although studies have hypothesised selection pressure by residual antibiotics in the wastewater treatment stream to be the major contributor to discharge of antimicrobial-resistant organisms, evidence suggests that risk of detecting antimicrobial-resistant organisms in the environment is more highly correlated with the amount of faecal discharge in an area,[45] with the exception of waters downstream of antimicrobial manufacturing sites. These uncertainties suggest a need for further monitoring and evaluation of the discharge limits (ie, restrictions on the amount of treated or discharged waste), either based on risk evaluation or a best-available-techniques approach. Modifications to onsite treatment systems might also be warranted in settings where antimicrobial resistance is prevalent as understanding of pathogen die-off in latrines under different conditions increases.[46]

Insufficient treatment of antimicrobial-resistant organisms in safely managed systems combined with the potential discharge of untreated faeces with ESBL-producing *E coli* into the environment (including via open defecation) highlights a policy gap in linking WASH infrastructure to reductions in exposure to ESBL-producing *E coli* and similar antimicrobial-resistant organisms. These findings represent a dual research and policy need. Efforts to end open defecation and improve use of safe sanitation facilities are only beginning to be recognised in the global effort to combat antimicrobial resistance, which have broadly focused on clinical interventions to date.[15,47] Environmental contributions to clinical antimicrobial resistance are needed, including risk factor analyses examining the role WASH might have in increasing or decreasing transmission risks. The fate and transport of antimicrobial-resistant organisms, and their genes, in the environment (and associated environmental exposure pathways) and in sanitation systems of all types are beginning to be better described.[15]

Notably, we have not accounted for animals, which comprise a major source of faecal biomass and potentially ESBL-producing *E coli*,[5] because we could not systematically quantify their contribution. Animal faeces is often not safely managed in the onsite (household) and offsite environments (eg, concentrated animal feeding operations) and might be directly applied to agricultural land without treatment.[24] Although increasing antibiotic use in animals makes contact with them an important exposure risk, including during preparation of and consumption of their meat,[48] animal faeces might be an equally important and under-appreciated environmental source of ESBL-producing *E coli*.[49,50] Globally, β-lactam drugs are given both prophylactically and therapeutically to animals reared for food and the prevalence of ESBLs among commensal gut bacteria is estimated to range from <1% to 41%.[49] Animal faeces comprise two-thirds of onsite recoverable faeces worldwide, a statistic that is expected to increase in coming decades.[24] The global absence of safe management of animal faeces is beginning to be highlighted for its role in enteric pathogen transmission, especially in low-income settings.[51] Thus, the global prevalence of ESBL-producing *E coli* in animal faeces in these settings should be a focus of future study and included in future estimates.

Our calculations have several limitations. Crucially, the proportion of faeces from infected individuals that contained ESBL-producing *E coli* was a key point of uncertainty that we addressed in our model through scenarios informed by a smaller study of the carriage of *E coli*.[27] Additionally, although Karanika and colleagues[12] did not observe significant differences in carriage between studies focusing on adults compared with those focusing on children, their study is a single meta-analysis of existing ESBL-producing *E coli* carriage data and other evidence suggests that carriage of antimicrobial-resistant organisms among children differs from carriage in adults.[52,53] Improved understanding of differences in

carriage of antimicrobial-resistant organisms between individuals and across age groups could inform assumptions about applying generalised carriage estimates to children. Urban and rural differences in sanitation are well documented,[21] but additional investigation into differences in carriage of ESBL-producing *E coli* between people in these environments could allow for more precise modelling of disparities in carriage and treatment. Additionally, we did not account for short-term temporal variation in carriage of ESBL-producing *E coli* (eg, acquisition or loss of organisms or genes over time among those exposed), and instead assumed a static prevalence. However, temporal changes might be present—eg, during the 2011 outbreak of ESBL-carrying Shiga toxin-producing *E coli*, serotype O104:H4, the median duration of shedding in patients after they had been discharged from hospital was less than 20 days,[54] whereas household transmission was rare.[55] Additionally, a 2018 modelling study suggested that an individual's carriage status is acquired in 3 years (95% CI 1·6–6·3) and lost in 1·1 years (0·8–1·6);[56] thus future models at household or individual levels should account for individual changes in carriage status due to prevention of exposure, or other measures, when doing longitudinal assessments.[12] Beyond the recognised need to determine the effectiveness of wastewater treatment plants in removing ESBL-producing *E coli* and similar organisms and genes,[15,31,32,43,44] improved understanding of die-off of antimicrobial-resistant pathogens in onsite, decentralised systems (eg, pit latrines) is needed.[24] For example, specific gaps might include whether the antimicrobial-resistant status of an enteric pathogen alters bacterial communities in latrines and timescales from those known for susceptible pathogens and how onsite latrines might contribute to transfer of antimicrobial-resistant genes and emergence of new antimicrobial-resistant pathogens.[57,58]

In summary, to our knowledge, we present the first accounting of ESBL-producing *E coli* discharge through varying sanitation systems globally and by WHO region. At-least basic sanitation systems receive about two-thirds of faeces containing ESBL-producing *E coli* globally; however, these sanitation systems do not guarantee total removal of antimicrobial-resistant organisms. Importantly, more than 10% of faeces containing ESBL-producing *E coli*—about 220 million–22 billion kg per year—are openly defecated, and another 14% (270 million–27 billion kg per year) are discharged into unimproved systems. WASH, and specifically sanitation, has an underacknowledged role to play in mitigating the transport and outcome of antimicrobial-resistant organisms, such as ESBL-producing *E coli*, and efforts to improve WASH and reduce environmental loads and exposure to faeces should be further integrated with those to combat antimicrobial resistance.

Contributors

DB, AK, and ALW conceptualised the study. All authors contributed to the design of the methods. DB did the data validation, formal analysis, and data sourcing and experiments. DB wrote and prepared the first draft and all authors contributed to reviewing and editing of subsequent drafts. DB did visualisations. AK, JB, and ALW supervised the study. DB, AK, and ALW contributed to project administration.

Declaration of interests

We declare no completing interests.

Acknowledgments

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the US Centers for Disease Control and Prevention.

References

1 Klein EY, Van Boeckel TP, Martinez EM, et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. *Proc Natl Acad Sci USA* 2018; **115:** E3463–70.

2 O'Neill J. Tackling drug-resistant infections globally: final report and recommendations. Review on Antimicrobial Resistance, May 2016. https://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf (accessed April 16, 2020).

3 Clift C. Review of progress on antimicrobial resistance. London: Chatham House, the Royal Institute of International Affairs, October, 2019. https://www.chathamhouse.org/sites/default/files/publications/research/2019–10–04-AMR.pdf (accessed April 16, 2020).

4 Walsh TR, Weeks J, Livermore DM, Toleman MA. Dissemination of NDM-1 positive bacteria in the New Delhi environment and its implications for human health: an environmental point prevalence study. *Lancet Infect Dis* 2011; **11:** 355–62.

5 Huijbers PMC, Blaak H, de Jong MCM, Graat EAM, Vandenbroucke-Grauls CMJE, de Roda Husman AM. Role of the environment in the transmission of antimicrobial resistance to humans: a review. *Environ Sci Technol* 2015; **49:** 11993–2004.

6 Turner P, Pol S, Soeng S, Sar P. High prevalence of antimicrobial-resistant gram-negative colonization in hospitalized Cambodian infants. *Pediatr Infect Dis J* 2016; **35:** 856–61.

7 Chirindze LM, Zimba TF, Sekyere JO, et al. Faecal colonization of *E. coli* and *Klebsiella* spp. producing extended-spectrum beta-lactamases and plasmid-mediated AmpC in Mozambican university students. *BMC Infect Dis* 2018; **18:** 244.

8 Arcilla MS, van Hattem JM, Haverkate MR, et al. Import and spread of extended-spectrum β-lactamase-producing Enterobacteriaceae by international travellers (COMBAT study): a prospective, multicentre cohort study. *Lancet Infect Dis* 2017; **17:** 78–85.

9 Montealegre MC, Roy S, Böni F, et al. Risk factors for detection, survival, and growth of antibiotic-resistant and pathogenic *Escherichia coli* in household soils in rural Bangladesh. *Appl Environ Microbiol* 2018; **84:** e01978–18.

10 Talukdar PK, Rahman M, Rahman M, et al. Antimicrobial resistance, virulence factors and genetic diversity of *Escherichia coli* isolates from household water supply in Dhaka, Bangladesh. *PLoS One* 2013; **8:** e61090.

11 Kader AA, Kumar A, Kamath KA. Fecal carriage of extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* in patients and asymptomatic healthy individuals. *Infect Control Hosp Epidemiol* 2007; **28:** 1114–16.

12 Karanika S, Karantanos T, Arvanitis M, Grigoras C, Mylonakis E. Fecal colonization with extended-spectrum beta-lactamase-producing Enterobacteriaceae and risk factors among healthy individuals: a systematic review and metaanalysis. *Clin Infect Dis* 2016; **63:** 310–18.

13 WHO. Global action plan on antimicrobial resistance. Geneva: World Health Organization, 2015. http://www.who.int/drugresistance/global_action_plan/en/ (accessed April 17, 2020).

14 Vikesland PJ, Pruden A, Alvarez PJJ, et al. Towards a comprehensive strategy to mitigate dissemination of environmental sources of antibiotic resistance. *Environ Sci Technol* 2017; **51:** 13061–69.

15 Wuijts S, van den Berg HHJL, Miller J, et al. Towards a research agenda for water, sanitation and antimicrobial resistance. *J Water Health* 2017; **15:** 175–84.

16 Rizzo L, Manaia C, Merlin C, et al. Urban wastewater treatment plants as hotspots for antibiotic resistant bacteria and genes spread into the environment: a review. *Sci Total Environ* 2013; **447:** 345–60.

17 Ma Y, Wilson CA, Novak JT, et al. Effect of various sludge digestion conditions on sulfonamide, macrolide, and tetracycline resistance genes and class I integrons. *Environ Sci Technol* 2011; **45:** 7855–61.

18 Pehrsson EC, Tsukayama P, Patel S, et al. Interconnected microbiomes and resistomes in low-income human habitats. *Nature* 2016; **533:** 212–16.

19 Collignon P, Beggs JJ, Walsh TR, Gandra S, Laxminarayan R. Anthropological and socioeconomic factors contributing to global antimicrobial resistance: a univariate and multivariable analysis. *Lancet Planet Health* 2018; **2:** e398–405.

20 Hendriksen RS, Munk P, van Bunnik B, et al. Global monitoring of antimicrobial resistance based on human sewage. *Nat Commun* 2019; **10:** 1124.

21 UNICEF, WHO. Progress on drinking water, sanitation and hygiene, 2017. Geneva: World Health Organization, UN Children's Fund, 2017. http://apps.who.int/iris/bitstream/10665/258617/1/9789241512893-eng.pdf (accessed April 17, 2020).

22 WHO, UNICEF. Coverage of basic and safely managed sanitation by WHO and SDG regions. World Health Organization, UN Children's Fund, Joint Monitoring Programme. 2015 https://washdata.org/data/household#!/dashboard/1953 (accessed April 15, 2019).

23 The World Bank. Population, total. The World Bank, 2017. https://data.worldbank.org/indicator/SP.POP.TOTL (accessed June 1, 2020).

24 Berendes DM, Yang PJ, Lai A, Hu D, Brown J. Estimation of global recoverable human and animal faecal biomass. *Nat Sustain* 2018; **1:** 679–85.

25 Walpole SC, Prieto-Merino D, Edwards P, Cleland J, Stevens G, Roberts I. The weight of nations: an estimation of adult human biomass. *BMC Public Health* 2012; **12:** 439.

26 Yang PJ, LaMarca M, Kaminski C, Chu DI, Hu DL. Hydrodynamics of defecation. *Soft Matter* 2017; **13:** 4960–70.

27 Johnson JR, Owens K, Gajewski A, Clabots C. *Escherichia coli* colonization patterns among human household members and pets, with attention to acute urinary tract infection. *J Infect Dis* 2008; **197:** 218–24.

28 Woerther PL, Burdet C, Chachaty E, Andremont A. 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 Baum R, Luh J, Bartram J. Sanitation: a global estimate of sewerage connections without treatment and the resulting impact on MDG progress. *Environ Sci Technol* 2013; **47:** 1994–2000.

30 The World Bank. Population estimates and projections. The World Bank, 2017. https://datacatalog.worldbank.org/dataset/population-estimates-and-projections (accessed May 27, 2020).

31 Dolejska M, Frolkova P, Florek M, et al. CTX-M-15-producing *Escherichia coli* clone B2-O25b-ST131 and *Klebsiella* spp. isolates in municipal wastewater treatment plant effluents. *J Antimicrob Chemother* 2011; **66:** 2784–90.

32 Osińska A, Korzeniewska E, Harnisz M, Niestępski S. The prevalence and characterization of antibiotic-resistant and virulent *Escherichia coli* strains in the municipal wastewater system and their environmental fate. *Sci Total Environ* 2017; **577:** 367–75.

33 Rogawski ET, Platts-Mills JA, Seidman JC, et al. Use of antibiotics in children younger than two years in eight countries: a prospective cohort study. *Bull World Health Organ* 2017; **95:** 49–61.

34 Berendes D, Leon J, Kirby A, et al. Household sanitation is associated with lower risk of bacterial and protozoal enteric infections, but not viral infections and diarrhea, in a cohort study in a low-income urban neighborhood in Vellore, India. *Trop Med Int Healt* 2017; **22:** 1119–29.

35 Walker CLF, Rudan I, Liu L, et al. Global burden of childhood pneumonia and diarrhoea. *Lancet* 2013; **381:** 1405–16.

36 Hutinel M, Huijbers PMC, Fick J, Åhrén C, Larsson DGJ, Flach CF. Population-level surveillance of antibiotic resistance in *Escherichia coli* through sewage analysis. *Euro Surveill* 2019; **24:** 1–11.

37 Rose C, Parker A, Jefferson B, Cartmell E. The characterization of feces and urine: a review of the literature to inform advanced treatment technology. *Crit Rev Environ Sci Technol* 2015; **45:** 1827–79.

38 Thamlikitkul V, Tangkoskul T, Seenama C. Fecal carriage rate of extended-spectrum beta-lactamase-producing Enterobacteriaceae as a proxy composite indicator of antimicrobial resistance in a community in Thailand. *Open Forum Infect Dis* 2019; **6:** ofz425.

39 Peal A, Evans B, Blackett I, Hawkins P, Heymans C. Fecal sludge management: a comparative analysis of 12 cities. *J Water Sanit Hyg Dev* 2014; **4:** 563–75.

40 Fuller JA, Clasen T, Heijnen M, Eisenberg JN. Shared sanitation and the prevalence of diarrhea in young children: evidence from 51 countries, 2001–2011. *Am J Trop Med Hyg* 2014; **91:** 173–80.

41 Exley JLR, Liseka B, Cumming O, Ensink JHJ. The sanitation ladder, what constitutes an improved form of sanitation? *Environ Sci Technol* 2015; **49:** 1086–94.

42 Graham DW, Giesen MJ, Bunce JT. Strategic approach for prioritising local and regional sanitation interventions for reducing global antibiotic resistance. *Water* 2018; **11:** 27.

43 Bouki C, Venieri D, Diamadopoulos E. Detection and fate of antibiotic resistant bacteria in wastewater treatment plants: a review. *Ecotoxicol Environ Saf* 2013; **91:** 1–9.

44 Figueira V, Serra E, Manaia CM. Differential patterns of antimicrobial resistance in population subsets of *Escherichia coli* isolated from waste- and surface waters. *Sci Total Environ* 2011; **409:** 1017–23.

45 Karkman A, Pärnänen K, Larsson DGJ. Fecal pollution explains antibiotic resistance gene abundances in anthropogenically impacted environments. *Nat Commun* 2018; **10:** 341487.

46 WHO. Guidelines on sanitation and health. Geneva: World Health Organization, 2018.

47 Laxminarayan R, Duse A, Wattal C, et al. Antibiotic resistance—the need for global solutions. *Lancet Infect Dis* 2013; **13:** 1057–98.

48 Hammerum AM, Heuer OE. Human health hazards from antimicrobial-resistant *Escherichia coli* of animal origin. *Clin Infect Dis* 2009; **48:** 916–21.

49 Smet A, Martel A, Persoons D, et al. Broad-spectrum β-lactamases among Enterobacteriaceae of animal origin: molecular aspects, mobility and impact on public health. *FEMS Microbiol Rev* 2010; **34:** 295–316.

50 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.

51 Penakalapati G, Swarthout J, Delahoy MJ, et al. Exposure to animal feces and human health: a systematic review and proposed research priorities. *Environ Sci Technol* 2017; **51:** 11537–52.

52 Bielicki JA, Lundin R, Sharland M. Antibiotic resistance prevalence in routine bloodstream isolates from children's hospitals varies substantially from adult surveillance data in Europe. *Pediatr Infect Dis J* 2015; **34:** 734–41.

53 Logan LK, Hujer AM, Marshall SH, et al. Analysis of β-lactamase resistance determinants in Enterobacteriaceae from Chicago children: a multicenter survey. *Antimicrob Agents Chemother* 2016; **60:** 3462–69.

54 Vonberg RP, Höhle M, Aepfelbacher M, et al. Duration of fecal shedding of Shiga toxin-producing *Escherichia coli* O104:H4 in patients infected during the 2011 outbreak in Germany: a multicenter study. *Clin Infect Dis* 2013; **56:** 1132–40.

55 Sin MA, Takla A, Flieger A, et al. Carrier prevalence, secondary household transmission, and long-term shedding in 2 districts during the *Escherichia coli* O104:H4 outbreak in Germany, 2011. *J Infect Dis* 2013; **207:** 432–38.

56 Teunis PFM, Evers EG, Hengeveld PD, Dierikx CM, Wielders CCCH, van Duijkeren E. Time to acquire and lose carriership of ESBL/ pAmpC producing *E. coli* in humans in the Netherlands. *PLoS One* 2018; **13:** e0193834.

57 Torondel B, Ensink JHJ, Gundogdu O, et al. Assessment of the influence of intrinsic environmental and geographical factors on the bacterial ecology of pit latrines. *Microb Biotechnol* 2016; **9:** 209–23.

58 Pruden A, Ashbolt N, Miller J. Part three. Specific excreted pathogens: environmental and epidemiology aspects: overview of issues for water bacterial pathogens. In: Rose JB, Jimenez-Cisneros B, eds. Global Water Pathogens Project. Global Water Pathogen Project, 2017. http://www.waterpathogens.org/node/104 (accessed April 17, 2020).