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Global epidemiology of CTX-M β-lactamases: temporal and geographical shifts in genotype

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Globally, rates of ESBL-producing Enterobacteriaceae are rising. We undertook a literature review, and present the temporal trends in bla_{CTX-M} epidemiology, showing that $bla_{CTX-M-15}$ and $bla_{CTX-M-14}$ have displaced other genotypes in many parts of the world. Explanations for these changes can be attributed to: (i) horizontal gene transfer (HGT) of plasmids; (ii) successful *Escherichia coli* clones; (iii) ESBLs in food animals; (iv) the natural environment; and (v) human migration and access to basic sanitation. We also provide explanations for the changing epidemiology of $bla_{CTX-M-2}$ and $bla_{CTX-M-27}$. Modifiable anthropogenic factors, such as poor access to basic sanitary facilities, encourage the spread of bla_{CTX-M} and other antimicrobial resistance (AMR) genes, such as bla_{NDM}, bla_{KPC} and *mcr-1*. We provide further justification for novel preventative and interventional strategies to reduce transmission of these AMR genes.

Introduction

Extended-spectrum β-lactamases (ESBLs) hydrolyse the β-lactam ring of penicillins and third-generation cephalosporins (3GCs). They are mainly found in Enterobacteriaceae, which are part of the normal bowel flora, but can also be pathogenic, causing urinary tract infections and bloodstream infections.[1]

The largest group of ESBLs are CTX-Ms, first identified in Germany,[2] France[3] and South America.[4] They have become globally disseminated, with $bla_{CTX-M-15}$ and $bla_{CTX-M-14}$ being the predominant genotypes. CTX-M ESBLs have increased in prevalence since 2000,[5] and this presents huge challenges to healthcare, with restricted options to treat infections caused by CTX-M-producing bacteria. This has led to increased use of carbapenems,[6] leading to the emergence and spread of carbapenemase-producing Enterobacteriaceae.[7] Developing countries with low levels of sanitation provide opportunities for the transfer of antimicrobial resistance (AMR) genes in Enterobacteriaceae, including bla_{CTX-M}, between humans, animals and the natural environment.[8,9]

Origin of CTX-M enzymes

Humeniuk *et al.*[10] demonstrated that *Kluyvera ascorbata*, associated with the rhizosphere (the soil closely associated with plant roots), carries the chromosomal bla_{KLUA} gene, which confers resistance to 3GCs. The chromosomal bla_{KLUA} gene and its flanking regions are highly related to bla_{CTX-M} enzymes and the flanking sequences on plasmids.[10] Each main cluster of CTX-M genotypes has a corresponding progenitor gene sharing homology with different *Kluyvera* spp., from which bla_{CTX-M} genes originated.[11] Chromosomal bla_{KLUA} from *K. ascorbata* is identical to $bla_{CTX-M-2}$, which is usually plasmid mediated, and therefore $bla_{CTX-M-2}$ is likely to have originated from *K. ascorbata*.[12] Similarly, $bla_{CTX-M-14}$ originates from a chromosomal gene in *K. georgiana*.[13] The CTX-M group 1 variant CTX-M-3 originated from *K. ascorbata*,[14] whereas CTX-M-37 is derived from *K. cryocrescens*.[15] It is likely that IS*Ecp1*, frequently found upstream of $bla_{CTX-M-14}$[16] and $bla_{CTX-M-15}$[17] in human isolates of *Escherichia coli*, played a key role in their mobilization.[10]

The rise and global distribution of CTX-M variants

ESBL prevalence increased over time in all WHO geographical regions, but these upward trends are statistically significant only for Europe ($R^2 = 0.429$, $P = 0.04$) (Figure S1, available as Supplementary data at *JAC* Online). A linear regression analysis showed a statistically significant rise in community ESBL rates over time for all regions ($R^2 = 0.22$, $P < 0.005$, plot not shown), supporting previous analyses.[5,18] In particular, there is a strong upward trend in ESBL rates when this analysis is undertaken for developing countries only ($R^2 = 0.814$, $P = 0.0004$; Figure S2).

The global picture of CTX-M variants is a complex one, but it is clear that $bla_{CTX-M-15}$ has increased over time in most countries, and is dominant in most regions (Figure 1). Exceptions are China, South-East Asia, South Korea, Japan and Spain, where group 9 variants (especially CTX-M-14) are dominant, and South America, where $bla_{CTX-M-2}$ is still significant (Figure 1).

Our investigation of ESBL global epidemiology has focused on the temporal changes in bla_{CTX-M} (Figure 1). We propose a number

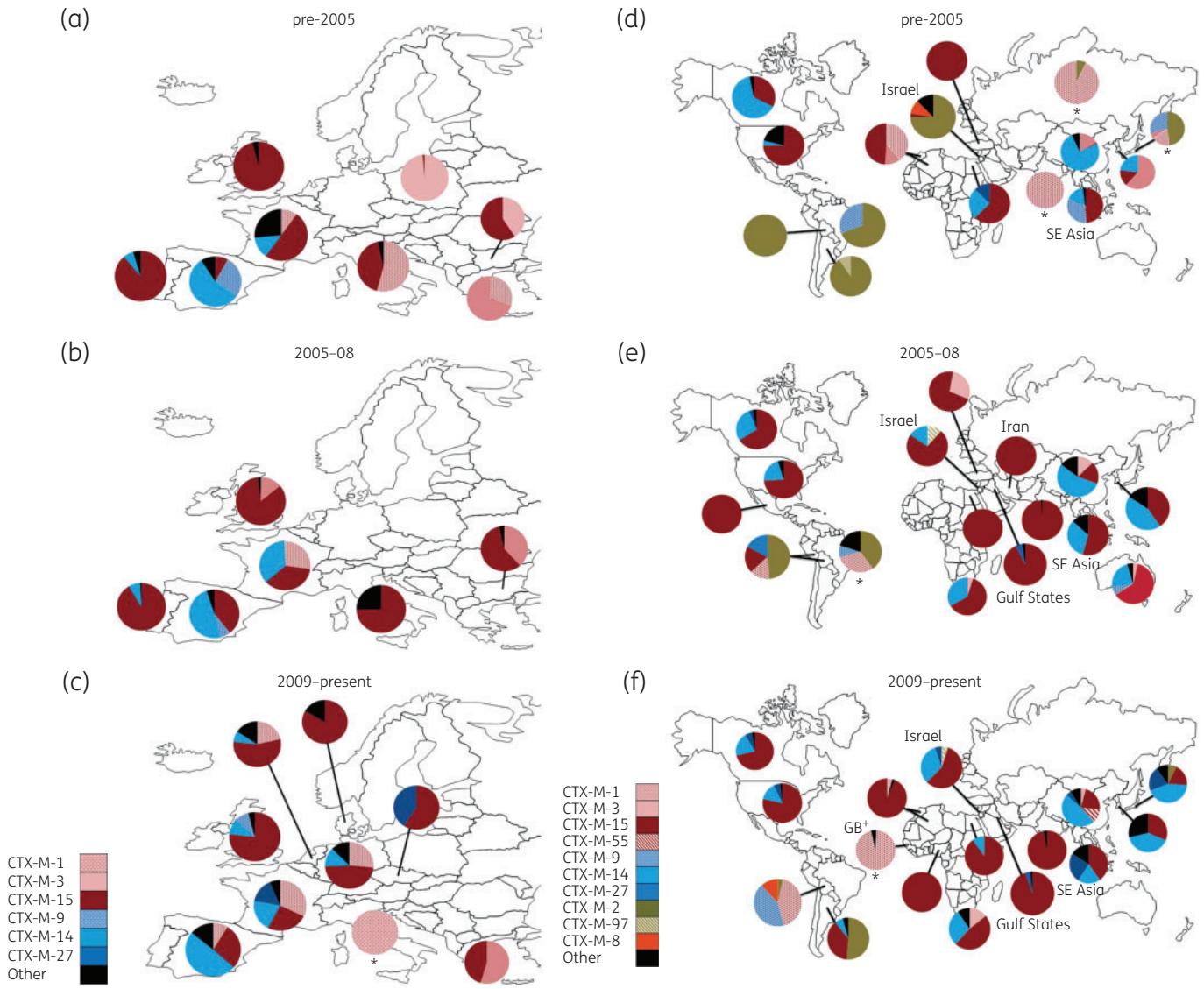

Figure 1 (a, b, c) CTX-M trends over three time periods for Europe (data include both hospital and community isolates). An asterisk indicates that, for these areas, only CTX-M grouping was done and these were not subdivided into genotypes. Note: many countries have no published data for certain time periods. Colour shades represent CTX-M groups: red, group 1; blue, group 9. (d, e, f) CTX-M trends over three time periods for the rest of the world (data include both hospital and community isolates). An asterisk indicates that, for these areas, only CTX-M grouping was done and these were not subdivided into genotypes. Note: many countries have no published data for certain time periods. South-East (SE) Asia includes Cambodia, Indonesia, Malaysia, The Philippines, Taiwan and Vietnam. Gulf States include Kuwait, Saudi Arabia and United Arab Emirates. Data for Australia and New Zealand are combined. GB^+, Guinea-Bissau. Colour shades represent CTX-M groups: red, group 1; green, group 2; orange, group 8/25; blue, group 9. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

of interlinked factors as explanations for these global changes: (i) plasmids and horizontal gene transfer (HGT); (ii) successful *E. coli* clones; (iii) food animals; (iv) the natural environment; and (v) human migration and access to basic sanitation.

Methods

Search strategy and selection criteria

We searched the NCBI PubMed database without restrictions using the following search terms: 'CTX-M' and 'extended spectrum beta lactamase (ESBL)' plus 'Europe', 'North America', 'South America', 'Africa', 'Australasia', 'Asia' or 'South East Asia', as well as individual country names. These searches generated 2735 papers. Article inclusion criteria were as follows: (i) human Enterobacteriaceae isolates from community or hospital origin, from studies reporting infecting strains or from faecal carriage studies; (ii) isolates must have been identified using suitable screening media; (iii) collection dates and location of sampling; and (iv) $bla_{CTX\text{-}M}$ genotyping or multiplex PCR grouping data had to be provided. Articles were screened by reading abstracts. Using the inclusion criteria we identified 220 English articles for review, which were also checked for additional references not captured in the original searches.

Statistics

Linear regression plots for the frequency of ESBL faecal carriage over time were plotted for each WHO region (Figure S1) and for developing countries (Figure S2).

Role of plasmid spread and HGT

The HGT of bla_{CTX-M} genes on conjugative plasmids is fundamental to their evolution and global spread.[19] Several studies have shown that plasmids of the IncF family are the predominant group that carry $bla_{CTX-M-15}$,[20–24] whereas $bla_{CTX-M-14}$ is carried on a variety of plasmid types, including on IncF, especially in the Far East,[25] and on IncK, in Western Europe.[26] Horizontal transfer of antimicrobial resistance plasmids by conjugation in Enterobacteriaceae occurs in the human gut,[27–29] animals[30] and the environment.[8,31]

The IncF family plasmids have a narrow host range, being mainly restricted to Enterobacteriaceae, and contain a number of mechanisms, e.g. addiction systems and post-segregational killing machinery, favouring plasmid stability.[32] As a result, IncF plasmids are stably maintained in commensal *E. coli* within the gastrointestinal tract of humans and animals, without antimicrobial pressure,[33] perhaps explaining the global increase in community ESBL carriage (Figure S1). Most bla_{CTX-M} genes are carried by *E. coli*, but other members of the Enterobacteriaceae are associated with specific bla_{CTX-M} genotypes.[33,34]

Identical plasmids which are found across genetically diverse strains have been termed 'epidemic plasmids',[33] and their dissemination helps to explain some of the global trends in bla_{CTX-M} epidemiology. Examples of epidemic plasmids include pCT[26] and pHK01[35] (which both carry $bla_{CTX-M-14}$), pC151a[36] (which carries $bla_{CTX-M-15}$) and the closely related plasmids pEK516 and pEC_B24 (which also encode $bla_{CTX-M-15}$).[32,37] In South China it has been proposed that a discrete group of $bla_{CTX-M-15}$ epidemic plasmids are circulating that share significant homology to pKF3-94—a Chinese reference plasmid isolated from *Klebsiella pneumoniae*—but are quite different from the pC151a-like plasmids described in Europe.[38] An epidemic IncI1 plasmid carrying $bla_{CTX-M-1}$ has also been shown to be highly prevalent across food animal isolates and human isolates in the Netherlands, suggesting transmission of $bla_{CTX-M-1}$ via the food chain.[39] Moreover, since the first description of $bla_{CTX-M-1}$ from a clinical isolate in Germany in 1989,[2] $bla_{CTX-M-1}$ has maintained a significant presence in several countries in Western Europe (Figure 1). Globally, CTX-M-1 is less common, and therefore the ongoing persistence of this genotype in Europe could well be due to the spread of epidemic plasmids.[39]

One of the earliest reports of epidemic plasmid spread was the $bla_{CTX-M-3}$ IncL/M plasmid, pCTX-M-3, which disseminated $bla_{CTX-M-3}$ first in Poland,[40] and then throughout Europe. The genotype $bla_{CTX-M-15}$ differs from $bla_{CTX-M-3}$ by only one amino acid substitution, but the different genetic surroundings of these genes in Europe suggest that the evolution and subsequent spread of $bla_{CTX-M-3}$ from Poland occurred independently of the subsequent rise of $bla_{CTX-M-15}$ in the other regions.[41] Interestingly, Inc L/M plasmids carrying $bla_{CTX-M-3}$ in China and Australia share significant homology, suggesting a common evolutionary origin.[42,43]

Perhaps the most worrying feature of bla_{CTX-M}-bearing plasmids is their ability to capture additional resistance determinants, including carbapenemase genes.[44–46] For instance, p271A, which has close homology to the $bla_{CTX-M-65}$ plasmid pJIE137, has a putative transposon bearing bla_{NDM-1}.[44] bla_{OXA-48} has been found on the same transposon as $bla_{CTX-M-15}$[46] and a hospital outbreak of *K. pneumoniae* producing OXA-48 and CTX-M-15 occurred in the Netherlands.[45] This situation, where globally successful bla_{CTX-M} epidemic plasmids become effective vectors of carbapenemase genes, is extremely worrisome.

ISs, transposons and integrons have played a key role in the dissemination of bla_{CTX-M}[47] via a diversity of genetic platforms.[11] IS*Ecp1* is the most common insertion element associated with bla_{CTX-M} genes and has been described as being associated with all bla_{CTX-M} genotypes.[11] IS*Ecp1* has two important characteristics: (i) it encodes a transposase, allowing mobilization of the bla_{CTX-M} gene onto the particular plasmid; and (ii) it acts as a strong promoter for the expression of bla_{CTX-M}.[48]

The transposition element IS*26* has also been important in the dissemination of group 1 and group 9 bla_{CTX-M} variants.[11] Ensor *et al.*[49] investigated 130 ESBL-producing *E. coli* and *K. pneumoniae* isolates collected in 2003–05 from three Indian hospitals. Most of these isolates (73%) produced CTX-M-15 and, in 31% of these, IS*26* was found within IS*Ecp1*, upstream of $bla_{CTX-M-15}$.[49] However, another group did not find IS*26* in CTX-M-producing Enterobacteriaceae isolated in the late 1990s.[50] Therefore a specific event after 2000 led to capture of $bla_{CTX-M-15}$ in India by IS*26*, which has been suggested as an event that has allowed stable maintenance of bla_{CTX-M} in the gene pool thereafter.[49] Subsequently, IS*26* has been found again in India[51] and worldwide.[11] More recently, Johnson *et al.*[52] investigated the association of IncF plasmids and IS*26*, and the clonal *E. coli* sub-group ST131 *H*30-Rx, using plasmid sequencing. Their results suggest that plasmids from *H*30-S and *H*30-R sub-groups were highly related to plasmids isolated from the later *H*30-Rx sub-group of ST131, except that only the *H*30-Rx group contained $bla_{CTX-M-15}$.[52] In contrast to the early studies from India,[50,53] it was suggested that IS*26*, which was found in high copy number across all isolates, was involved in mediating transposition of $bla_{CTX-M-15}$ onto a common plasmid backbone.[52]

Clearly, the selective pressure imparted by the use of 3GCs in humans and animals will increase the chance of the mobilization of bla_{CTX-M}. Mobilization of MDR class I integrons, which are often associated with IS*Ecp1* and IS*CR1* (particularly with group 2 and group 9 CTX-M[11]), is particularly problematic because they often contain MDR cassettes. These include bla_{CTX-M}, but also genes encoding resistance to clinically important antibiotics, such as fluoroquinolones, chloramphenicol, aminoglycosides and trimethoprim.[54] Therefore the overuse of any antibiotic with resistance in an MDR cassette provides evolutionary pressure for maintenance of all the MDR genes, and increased spread of the associated plasmid.

In addition to the clear roles of plasmid conjugation and transposition, or movement of bla_{CTX-M} genes via integration or transposition, the role of bacteriophage-mediated transduction may be a key component of bla_{CTX-M} transmission between bacteria and the environment.[55] Bacteriophages commonly carry antimicrobial resistance genes and have been found to be associated with bla_{CTX-M} genotypes, which include $bla_{CTX-M-10}$,[56] $bla_{CTX-M-27}$[57] and $bla_{CTX-M-15}$.[58] In addition, AMR genes were found to be more abundant in phage DNA than in bacterial DNA.[59] Moreover, in mice treated with ciprofloxacin and amoxicillin, phage DNA was found

to be more highly enriched with antimicrobial resistance genes to these antibiotics compared with untreated mice.[60]

There are clearly a number of different factors involved in the transfer of bla_{CTX-M}; this is likely to be a highly opportunistic process, influenced by the genetic composition of particular ESBL gene reservoirs and differential antibiotic selective pressures, thus leading to convergent/divergent evolution in different parts of the world.

The role of successful *E. coli* clones

In developed countries, *E. coli* causes more cases of bacteraemia than any other organism.[61–63] Worldwide surveys in 2008 led to the discovery of the international ESBL *E. coli* clone ST131, which belongs to phylogenetic group B2, serotype O25b:H4, and is now the major global extraintestinal pathogenic *E. coli* (ExPEC) strain.[64,65] The clonal spread of virulent strains such as *E. coli* B2 O25:H4-ST131, which commonly carries $bla_{CTX-M-15}$, plays an important role in its global dissemination.[66,67] The most widespread ESBL-producing ST131 sub-clone is *H*30-Rx, which commonly carries $bla_{CTX-M-15}$.[68]

ST131 has been found mostly in human clinical *E. coli* isolates, but also in animals[69] and the environment.[31,70] Successful in Western Europe and North America,[71] ST131 has been found only occasionally in India[72,73] and China.[74–76] The most common bla_{CTX-M} genotype in most regions of the world is $bla_{CTX-M-15}$ (Figure 1), and a large proportion of CTX-M-producing *E. coli* are ST131.

Due to its relatively low prevalence in non-human isolates, ST131 probably originated from human sources.[71] The most common ST131 lineage, *H*30, has acquired fluoroquinolone resistance, followed by $bla_{CTX-M-15}$ acquisition on a plasmid; both are associated with the sub-lineage *H*30-Rx.[68] Recent sequence analysis of global ST131 isolates suggests that *H*30-Rx originated in North America in around 1991.[77] The capture of fluoroquinolone resistance and $bla_{CTX-M-15}$ by ST131 was a highly evolutionarily advantageous event given the high rates of use of fluoroquinolones and cephalosporins in the USA at that time.[77] One possibility is that the spread of $bla_{CTX-M-15}$ and $bla_{CTX-M-14}$ by human carriage from India and China, respectively, to North America, occurred.[78] This led to the capture of $bla_{CTX-M-15}$ and $bla_{CTX-M-14}$ by ST131 (onto pre-existing plasmids in ST131 strains, via IS*26*-mediated transposition as discussed above), followed by clonal dissemination. Presumably the spread of ST131 *E. coli* out of North America was a later event. This theory is based on the assumption that, because $bla_{CTX-M-14}$ and $bla_{CTX-M-15}$ were first described in China and India, respectively, these countries were also the origin of these genotypes. This hypothesis is supported by phenotypic data from India and China in the late 1990s showing comparatively high rates of resistance to 3GCs,[79,80] whereas in the USA around the same time <1% of Gram negatives were 3GC resistant.[81]

Importation of the successful *H*30-Rx sub-clone via human migration has probably led to the dominance of ST131 *E. coli* with $bla_{CTX-M-15}$ in many regions of the world, such as Canada,[82,83] Japan[84] and Israel.[85] In addition, non-Rx *H*30 strains of ST131 have also played a role in the clonal dissemination of bla_{CTX-M} genes, such as in Japan, where *H*30-R ST131 isolates are associated with $bla_{CTX-M-27}$.[86] Moreover, non-*H*30 sub-clones such as *H*41 and *H*22[86] have also been associated with bla_{CTX-M} genes in Japan[86] and Hong Kong.[87]

Human migration is likely to have caused the spread of ST131 and has probably led to the displacement of existing genotypes by $bla_{CTX-M-15}$ in other regions, especially South America and Western Europe (Figure 1). ST131 is also known to carry bla_{CTX-M} genotypes from all four main CTX-M groups, and notably is associated with $bla_{CTX-M-14}$ (particularly in Canada, China, Japan and Spain).[66]

Food animals

The use of antimicrobials in food animals provides selective pressure for the propagation in animals of AMR bacteria that are often human pathogens.[88] Variants of bla_{CTX-M} colonize the gut in farmed birds and mammals,[89,90] as well as raw meat for human consumption.[91,92]

There is evidence for the transmission of ESBL-producing *E. coli* between animals and humans,[39,93] and in the UK animal *E. coli* strains probably acquired the bla_{CTX-M} plasmid from human strains.[94]

Epidemic plasmid spread among animal and human *E. coli* strains has been found in the Netherlands,[39] China[35] and the UK.[90] In the Netherlands, HGT between human and animal strains has a greater role than the clonal spread of *E. coli* strains between these niches, and plasmids in genetically diverse human and animal strains were almost identical.[39]

The potential spread of bla_{CTX-M} between animals and humans via the food chain,[39,91] through animal handling[95] and from animals to the environment[96,97] is made worse by the high prevalence of unregulated wet food markets in the developing world, for example in China.[98] Wet food markets sell a variety of foods, including meat/raw poultry without refrigeration or safe food handling practices. This microbial habitat, combined with heavy use of antibiotics in food animal production in China,[99] provides the perfect conditions for HGT from animal to human strains. This dynamic evolutionary situation explains why there is a tremendous diversity of bla_{CTX-M} genotypes isolated from food animals in China (Figure S3). The prevalence of bacteria producing CTX-M-55 in China has grown significantly in recent years in both animal[100] and human populations,[76] and it has been suggested that $bla_{CTX-M-55}$ in human isolates arose from food animal sources.[101] Isolates of human and food animal origin share dominant bla_{CTX-M} genotypes (Figures 1 and S3), suggesting that there is clonal or horizontal exchange of bla_{CTX-M} between these settings. Worldwide antibiotic use in food animals is projected to rise by 67% by 2030, and the role of food animals as a source of AMR genes is therefore likely to become more prominent.[102]

Natural environment

The natural environment is inextricably linked to human and animal reservoirs of ESBL producers.[5,9] Since CTX-M enzymes originated in *Kluyvera* spp.—which normally inhabit the rhizosphere—environmental sources probably play an important role in the dissemination of bla_{CTX-M}. ESBLs have been found in sewage,[103] in rivers downstream of wastewater treatment facilities,[31] in urban freshwater,[104–106] in marine environments[107] and on farms.[108–110]

Pollution of the environment with Enterobacteriaceae from human and animal waste is an issue in developing and developed

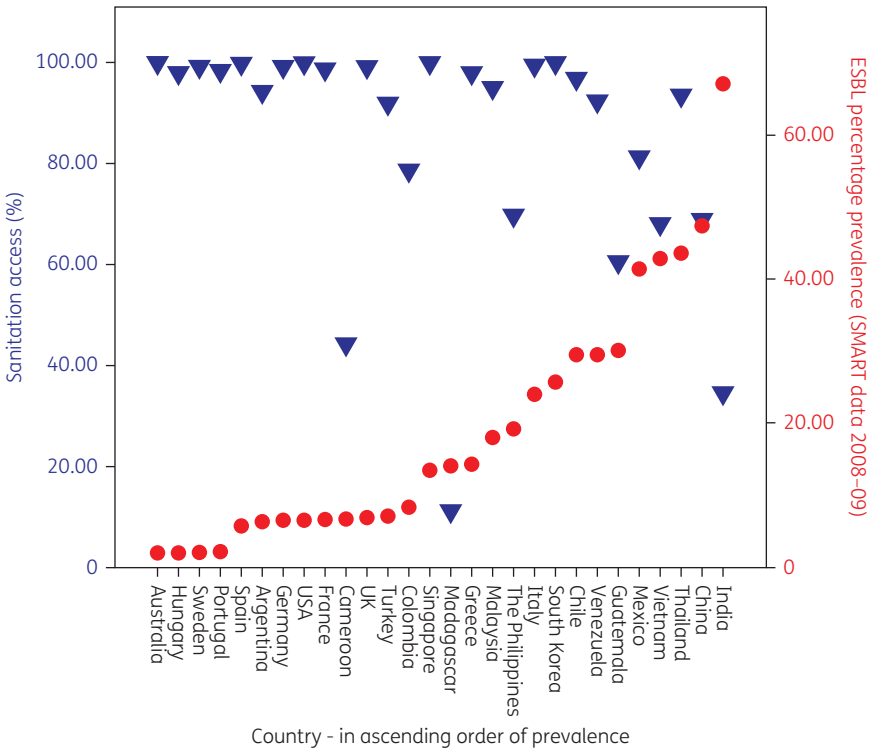

Figure 2. Sanitation access and ESBL prevalence. Sanitation access is access to improved sanitation facilities, 2008–09, as defined by WHO/UNICEF (data.worldbank.org/indicator/SH.STA.ACSN). ESBL prevalence is for 2008–09 and is derived from SMART study data.[111,147,148] This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

countries. However, the poor standards of sanitation and the contamination of drinking water supplies in the developing world allow increased cycling of CTX-M-producing *E. coli* between humans and the environment.[7] This explains our finding of a significant upward trend in ESBL community carriage rates in developing countries (Figure S2), notably in India, where ESBL carriage rates are amongst the highest in the world.[111] Moreover, the environmental–human exchange of AMR genes is highly relevant to the spread of other faecally carried genes, such as *mcr-1* and bla_{NDM-1}.[112]

The presence of resistance genes in an environment is closely related to anthropogenic activities. For example, the prevalence of class I integrons carrying resistance genes in sewage sludge, pig slurry and textile mill effluent is significantly higher than levels found in undisturbed soil. The common practice of using animal manure as fertilizer creates opportunities for species of Enterobacteriaceae to capture resistance genes on mobile genetic elements from soil bacteria.[9] More recently, a metagenomic approach was used to assess the AMR gene content across human, environmental and animal microbiomes in two developing regions in South America, and showed that mobile genetic elements played a significant role in the transfer of ESBLs between different resistomes.[8]

Environmental contamination with fluoroquinolones is especially worrisome, as these drugs are known to persist in rivers and soil, and have the ability to select bacteria bearing class I integrons which carry resistance cassettes, including *qnr* genes and bla_{CTX-M} genes.[9] In India, high levels of ciprofloxacin in the waste water effluents of pharmaceutical factories and in nearby sources of drinking water is a serious issue which is likely to be a contributory factor in the emergence and spread of bla_{CTX-M} in human populations and in the environment.[113]

ESBL rates, migration and access to basic sanitation

There is increasing community prevalence of ESBL-producing Enterobacteriaceae worldwide (Figure S1), especially CTX-M-15, which is reflected by much higher faecal carriage rates in Asia compared with Europe and North America.[5] Individuals with ethnic origins in the Middle East or South Asia (MESA) who reside in Europe have significantly higher carriage rates of CTX-M-15-producing *E. coli* compared with indigenous Europeans, which is likely to be due to the high frequency of travel by MESA people to these areas.[114] Prospective cohort studies have shown that travellers from Western countries visiting countries with a high prevalence of ESBLs become asymptomatic carriers: 75% of those travelling to Southern Asia acquired ESBL-producing bacteria.[115]

Access to improved sanitation facilities, as defined by WHO/UNICEF, is a key indicator of social and economic development, and is important in reducing the spread of diarrhoeal diseases.[116] We hypothesize that such access is also critical to controlling the spread of ESBLs. This has been identified by the O'Neill report as a key intervention in controlling resistance.[117]

Figure 2 shows access to improved sanitation facilities and ESBL community carriage by country. Despite gradual improvements in

India, access to basic sanitation still falls below 40%.[116] We hypothesize that poor access to latrines in India, combined with high population density and increasing human migration, have made this region a key epicentre of ESBL evolution, and a source for the worldwide spread of $bla_{CTX\text{-}M\text{-}15}$.

Accounting for prominent global trends in CTX-M epidemiology: the fall of $bla_{CTX\text{-}M\text{-}2}$ and the emergence of $bla_{CTX\text{-}M\text{-}27}$

The distribution of CTX-M genotypes in particular geographical regions is not easily attributed to human migration. Given cultural links between Spain/Portugal and South America, it follows that CTX-M genotypes in these regions should be similar, due to frequent migration between these areas. However, whereas $bla_{CTX\text{-}M\text{-}2}$ has been the main genotype in South America until the recent spread of $bla_{CTX\text{-}M\text{-}15}$, $bla_{CTX\text{-}M\text{-}2}$ has never gained a foothold in Spain or Portugal.[41] One explanation for this phenomenon is that $bla_{CTX\text{-}M\text{-}2}$ evolved in South America and was probably imported to Western Europe on multiple occasions, but lacked the successful evolutionary characteristics to compete with the dominant genotypes in Europe. Supporting this hypothesis, $bla_{CTX\text{-}M\text{-}2}$ was the only genotype in South America in the early 1990s,[118] whereas during the same period in Spain, only group 1 CTX-M producers were described.[119] Outside South America, the only regions showing a predominance of $bla_{CTX\text{-}M\text{-}2}$, before 2004, were Japan[120] and Israel.[85] It is clear that $bla_{CTX\text{-}M\text{-}2}$ is somehow evolutionarily less fit than its counterparts $bla_{CTX\text{-}M\text{-}14}$ and $bla_{CTX\text{-}M\text{-}15}$, as these two genotypes have started to overtake $bla_{CTX\text{-}M\text{-}2}$ in regions where it was previously the main CTX-M genotype (Figure 1).

There is increasing evidence to suggest that $bla_{CTX\text{-}M\text{-}27}$, a single-nucleotide variant of $bla_{CTX\text{-}M\text{-}14}$, has begun to out-compete other $bla_{CTX\text{-}M}$ genotypes, although CTX-M-15 and -14 are still the most common CTX-M enzymes globally (Figure 1). First identified from clinical *E. coli* in France,[121] $bla_{CTX\text{-}M\text{-}27}$ is now found worldwide, recently gaining ground in Japan, China, South-East Asia, North America and Europe[74,86,122–128] (Figure 1). The cause of this rise is unclear: CTX-M-27 has a higher MIC of ceftazidime compared with CTX-M-14, so use of ceftazidime would theoretically select for $bla_{CTX\text{-}M\text{-}27}$.[129] *E. coli* clones producing CTX-M-27 may also be more transmissible in a nosocomial environment, when compared with CTX-M-15 producers.[130]

As discussed above, there is genetic exchange of $bla_{CTX\text{-}M}$ by HGT and/or clonal exchange of CTX-M-producing *E. coli* between humans, animals and the environment. The presence of $bla_{CTX\text{-}M\text{-}27}$ in food animal isolates from China in all three time periods (pre-2005; 2005–08; 2009–present) suggests a stable reservoir for $bla_{CTX\text{-}M\text{-}27}$ in this ecological niche (Figure S3). Indeed, $bla_{CTX\text{-}M\text{-}27}$ identified from *E. coli* from food animals in a Chinese study represented 12% of $bla_{CTX\text{-}M}$ genotypes detected,[89] and $bla_{CTX\text{-}M\text{-}27}$ also dominates ESBL-producing *Salmonella* serotypes in China.[131] In Vietnam as in China, where close proximity of animals and humans is common, $bla_{CTX\text{-}M\text{-}27}$ is the most common $bla_{CTX\text{-}M}$ genotype,[123] which could be due to human transmission from animal sources.

Clonal spread of *E. coli* ST131 in humans has certainly played a role in the dissemination of $bla_{CTX\text{-}M\text{-}27}$ in Japan,[84,132] China,[74] France,[133] Portugal,[134] Germany[135] and the Czech Republic.[126] Moreover, *E. coli* ST131 isolates producing CTX-M-27 have been reported from companion animals in Japan,[136] from wild birds in the Czech Republic[137] and from freshwater in Switzerland.[70]

However, ST131 CTX-M-27-producing isolates from South Korea and Japan did not belong to the *H*30-Rx sub-clone.[86,138] Rather, Matsumura *et al.*[86] found that $bla_{CTX\text{-}M\text{-}27}$ isolates were significantly associated with the *H*30-R sub-clone. They also suggested that although $bla_{CTX\text{-}M\text{-}27}$ is a single-nucleotide variant of $bla_{CTX\text{-}M\text{-}14}$, $bla_{CTX\text{-}M\text{-}27}$ is unlikely to have evolved by point mutation from $bla_{CTX\text{-}M\text{-}14}$ in Japan, as the genetic surroundings and virulence profiles of $bla_{CTX\text{-}M\text{-}27}$ versus $bla_{CTX\text{-}M\text{-}14}$ are quite different.[86] This suggests that separate importations to Japan and/or separate $bla_{CTX\text{-}M}$ capture events to *E. coli* clonal lineages occurred for $bla_{CTX\text{-}M\text{-}27}$ and $bla_{CTX\text{-}M\text{-}14}$.

The role of HGT in the spread of $bla_{CTX\text{-}M\text{-}27}$ has poor coverage in the literature. However, interestingly, published data suggest that in animal strains $bla_{CTX\text{-}M\text{-}27}$ is associated with a wide range of plasmid replicons in transconjugants, including N, FIB, FII, I1, HI2, A/C and P,[97,131,139] whereas in studies with human isolates $bla_{CTX\text{-}M\text{-}27}$ has been found in *E. coli* ST131 strains associated with F1A, FIB and FII replicons only.[95,138] Thus, one could speculate that $bla_{CTX\text{-}M\text{-}27}$ has undergone transposition onto an IncF plasmid residing in *E. coli* ST131, similar to the IS*26*-mediated capture of $bla_{CTX\text{-}M\text{-}15}$ described recently.[52] In addition, bacteriophage-mediated HGT is likely to play a role in $bla_{CTX\text{-}M\text{-}27}$ dissemination, as recently found in *Salmonella* spp. from pork samples in China.[57]

Conclusions

Infections with CTX-M-producing Enterobacteriaceae are of huge clinical importance, as increasing rates of ESBL producers drive carbapenem prescribing, which in turn promotes the spread of potentially untreatable carbapenemase-producing Enterobacteriaceae.[140] Dealing with this situation requires constant monitoring of the global epidemiology of CTX-M genotypes, allowing early anticipation of emerging ESBL genes. Moreover, improving the global surveillance of AMR has been identified as a key intervention in addressing the rise of resistant bacteria.[117]

This review has several limitations. Notably, in the early surveys of $bla_{CTX\text{-}M}$, sample sizes were often small and several studies undertook only CTX-M-grouping PCR. Furthermore, many studies did not report on the clonal relatedness of the strains they included, leading to bias by outbreaks. There is publication bias: e.g. in China many studies describe CTX-M prevalence, whereas in Africa there are few studies. Therefore the limited data from under-resourced countries are likely to represent the tip of the iceberg in terms of percentage ESBL prevalence in these regions, leading to late detection of new genes. We used WHO/UNICEF data on access to improved sanitation facilities; such a facility is defined as 'one that hygienically separates human excreta from human contact'.[116] This includes pit latrines and flushing latrines, and it must be noted that the fate of this human waste is not recorded in these data and therefore the presence or effectiveness of onward sewage processing is not recorded. Therefore human exposure to human sewage (and therefore ESBL-producing bacteria) in many underdeveloped regions is likely to occur, even if access to improved sanitation facilities is high, and such exposures are likely even with high standards of sewage treatment.[31]

We have shown that CTX-M community faecal carriage rates are rising (Figures S1 and S2), and this is more pronounced in developing countries, supporting previous studies.[18,141] Therefore, there exists a vast human reservoir of bla_{CTX-M}-producing strains, which provide a source of bacteria that often go on to cause antimicrobial-resistant infections. Equivalent ESBL reservoirs are present in the environment and in food-producing animals, which constantly exchange clones and mobile genetic elements with the human reservoir. Transfer of bla_{CTX-M} thus occurs by the spread of clonal lineages, epidemic plasmid spread, or via the movement of smaller genetic elements by transposition or transduction. Although these processes are usually studied in isolation, they do not occur in isolation. Rather, we should apply the concept of the 'selfish gene':[142] each individual bla_{CTX-M} gene is opportunistic, using every possible mechanism to propagate itself. Therefore the global success of bla_{CTX-M} is due to a combination of all the mechanisms discussed above.

There is little doubt, however, that a combination of human factors has increased the propagation of bla_{CTX-M}. Antibiotic overuse in humans and animals, increased global migration and population density, and contamination of the food chain and environment with human and animal waste promote AMR.[143] The evolution of highly successful lineages of CTX-M-producing bacteria is a critical factor. We have described the contribution of poor access to basic sanitation facilities in some countries as a risk factor for higher ESBL carriage. Poor sanitation access in these countries, combined with poor standards of animal husbandry, unregulated wet food markets, and antibiotic overuse in humans and animals is dangerous and provides opportunities for the evolution of novel AMR genes.

Where possible, attempts must be made to mitigate these risks through preventative strategies, such as improving access to latrines in developing countries, better antimicrobial stewardship in humans and animals, environmental controls and targeted evidence-based ESBL screening strategies.[117] This review will also support further research into novel interventions to reduce ESBL carriage, such as appropriate selective digestive decontamination or faecal microbiota transplantation.[144] Use of conjugation inhibitors[145] or plasmid curing[146] could be targeted at the gastrointestinal tract of humans or animals or the environmental resistome. Understanding the changing epidemiology and drivers of AMR also provides a baseline from which to measure the success of such interventions.

Bacteria carrying *mcr-1* and/or carbapenemase genes are found in similar habitats to Enterobacteriaceae producing CTX-M, such as the human gut. Therefore, explanations for the trends observed in bla_{CTX-M} epidemiology can be applied to these other faecally carried AMR genes.

This review has demonstrated a continued global rise in ESBL incidence. This has led to an inevitable rise in carbapenem use in humans, with an associated rise in resistance. We report dramatic regional shifts in the epidemiology of CTX-M-producing Enterobacteriaceae, but also remarkable stability in many regions. Both changes and stability in bla_{CTX-M} genotypes in specific regions of the world seem to favour the highly successful $bla_{CTX-M-15}$ and $bla_{CTX-M-14}$ genes. Understanding global temporal trends in these genotypes will help in the development of hypotheses as to why these changes occur, supporting strategies for reducing the spread of AMR in Gram-negative bacteria, averting excess mortality and preserving existing classes of antibiotics for future generations. edna

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A. M. J. works as an independent scientific consultant to a number of bodies and pharmaceutical companies including Becton Dickinson (Diagnostics), Novartis (Anti-Infectives), Astellas (Anti-Infectives), Smith & Nephew (Wound Care), Summit Pharmaceuticals and Synthetic Biologics. P. M. H. has received honoraria for educational presentations for AstraZeneca, Eumedica, Pfizer, Merck and Novartis, has received research funding from AstraZeneca, Pfizer and Eumedica, and has acted as a consultant for Pfizer, Roche, Novartis, Basilea, Novacta, Novolytics and Merck. E. R. B.: none to declare.

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Author contributions

E. R. B. performed literature searches, extracted and analysed data, formatted figures and wrote and edited the manuscript. A. M. J. produced and formatted figures and edited the manuscript. P. M. H. conceived the study and edited the manuscript.

Supplementary data

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

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