

Extended-spectrum β -lactamase-producing and carbapenemase-producing *Enterobacteriaceae*

Hayley Wilson^{1,*} and M. Estée Török^{1,2,3}

Abstract

Antimicrobial resistance (AMR) is a global public-health emergency, which threatens the advances made by modern medical care over the past century. The World Health Organization has recently published a global priority list of antibiotic-resistant bacteria, which includes extended-spectrum β -lactamase-producing *Enterobacteriaceae* and carbapenemase-producing *Enterobacteriaceae*. In this review, we highlight the mechanisms of resistance and the genomic epidemiology of these organisms, and the impact of AMR.

INTRODUCTION

The development and introduction of antimicrobials in the 20th century has transformed the delivery of modern medical care. Yet, this ‘antibiotic golden-age’ is ending, threatened by rising rates of antimicrobial resistance (AMR) globally. *Enterobacteriaceae*, a family encompassing many clinically important bacterial species, exhibits rising levels of AMR. Infection with either extended-spectrum β -lactamase-producing *Enterobacteriaceae* (ESBL-E) or carbapenemase-producing *Enterobacteriaceae* (CPE) is associated with increased mortality rates, time to effective therapy, length of stay and overall healthcare costs [1–8]. The impact of the continued spread of AMR could have repercussions in multiple sectors. In the healthcare sector itself, patient deaths resulting from AMR are projected to reach 10 million annually by 2050, but AMR will also cause losses in the trillions to global economic output [9]. ESBL-E and CPE have spread globally [10, 11], and technologies such as whole-genome sequencing (WGS) are providing detailed insights into their evolution and dissemination. The World Health Organization has recently published a global priority pathogens list to focus attention on the most significantly resistant pathogens. *Enterobacteriaceae* resistant to third-generation cephalosporins (which includes ESBL-E) and *Enterobacteriaceae* resistant to carbapenems (CRE) are included within the critical category of this list [12].

ESBL-E

The definition of multidrug resistance is variable [13], but *Enterobacteriaceae* exhibiting resistance to β -lactams, extended-spectrum β -lactams and third-generation cephalosporins are commonly recognized as ESBL-E [11, 14]. Extended-spectrum β -lactamase (ESBL) mechanisms themselves are classified based on their molecular structure or functional similarities [15, 16] (Table 1). Initially, ESBL-E were predominantly associated with nosocomial outbreaks, with resistance arising from point mutations in plasmid-mediated enzymes such as TEM-1, TEM-2, SHV-1 and OXA-10 [14]. CTX-M enzymes are now predominant. They arose via multiple escape events of chromosomal β -lactamase-encoding genes (*bla_{klb}*) from *Kluyvera* spp. [17–19], supported by the presence of transpositional units including *ISEcp1* in CTX-M groups 1, 2, 9 and 25 or *ISCR1* in groups 2 and 9 [20]. Following initial reports in Europe [21], South America [22] and Japan [23], CTX-M enzymes have disseminated globally [24]. The group 1 enzyme CTX-M-15 is the most frequently identified, and dominates in many countries in Europe [25–30], Asia [31, 32], Africa [33–35] and the USA [36, 37]. Additional CTX-M mechanisms predominate in other locations. For example, the group 9 enzyme CTX-M-14 is the leading mechanism in *Escherichia coli* in some areas of Korea [38] and South America [39]. Until recently, CTX-M-14 was the major mechanism across China [40–42], but a steady increase in CTX-M-15 has also occurred [43–45].

Received 27 September 2017; Accepted 19 June 2018

Author affiliations: ¹Department of Medicine, University of Cambridge, Addenbrooke's Hospital, Cambridge CB2 0QQ, UK; ²Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK; ³Clinical Microbiology and Public Health Laboratory, Public Health England, Cambridge, UK.

*Correspondence: Hayley Wilson, hjb60@medschl.cam.ac.uk

Keywords: ESBL; CPE; antimicrobial resistance; Gram-negative; *Enterobacteriaceae*.

Abbreviations: AMR, antimicrobial resistance; CPE, carbapenemase-producing *Enterobacteriaceae*; ESBL, extended-spectrum β -lactamase; ESBL-E, extended-spectrum β -lactamase-producing *Enterobacteriaceae*; FQR, fluoroquinolone resistance; KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo- β -lactamase; MDR, multidrug resistant; NDM, New Delhi metallo- β -lactamase; ST, sequence type; WGS, whole-genome sequencing; WHO, World Health Organization; XDR, extensively drug resistant.

Data statement: All supporting data, code and protocols have been provided within the article or through supplementary data files.

Genomic epidemiology demonstrates a number of widespread lineages including sequence type (ST)131, ST38, ST405 and ST10 in *E. coli* [46–49], and ST11, ST14 and ST15 in *Klebsiella pneumoniae* [32, 50, 51]. ST131, an extra-intestinal pathogenic *E. coli*, has undergone massive clonal expansion and is strongly associated with the global dissemination of the *bla*_{CTX-M-15} gene [47, 52, 53].

WGS has resolved ST131 into three clades, based upon the presence of marker alleles for the type 1 fimbriae, *fimH*. Clade A is associated with *H41*, clade B with *H22* and *H30* is associated with clade C [54–58]. A clade C sublineage is the main driving force in the widespread dissemination of CTX-M-15 and fluoroquinolone resistance (FQR) in ST131 [55, 56, 59]. Clade C is identifiable by FQR mutations in *gyrA* (*gyrA1AB*) and *parC* (*parC1aAB*) genes, whereas clades A and B are predominantly fluoroquinolone susceptible [55]. Further segregation of clade C into C1 and C2 occurs depending upon the presence of *bla*_{CTX-M-15} [56, 59]. Prior to the emergence of C1 and C2, acquisition of elements including the GI-*pheV* genomic island [54] and the *H30* allele [60] helped to prime ST131 for global success. C1 and C2 divergence and the development of FQR mutations is estimated to have occurred in the late 1980s, consistent with the introduction of fluoroquinolones for clinical use [54]. CTX-M-14, CTX-M-27, CTX-M-19, CTX-M-24 and CTX-M-55 have been identified in clade C [59]; however, CTX-M-15 is almost entirely restricted to C2 [55, 56, 59]. Bayesian analysis based upon CTX-M variant distribution also suggests *bla*_{CTX-M-15} emerged in ST131 following the introduction of extended-spectrum cephalosporins into clinical practice [59].

Plasmid movement between different species and lineages represents a major source of AMR. *bla*_{CTX-M-15} in ST131 is invariably associated with plasmids of incompatibility group F (IncF) [25, 59, 61–63], although presence on IncN [64], IncX [65] and IncI [66] plasmids has also been reported.

IMPACT STATEMENT

The World Health Organization (WHO) has published a global priority pathogens list of antibiotic-resistant bacteria, in order to increase the significance of and galvanize research into new treatments for particular antibiotic-resistant pathogens. Of critical importance on this list are carbapenem-resistant *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacteriaceae*. Pathogens of this nature cause high morbidity and mortality and increased healthcare costs. Carbapenem-resistant *Enterobacteriaceae* encompasses a number of genera, many of which harbour acquired multidrug-resistance plasmids, which can carry and transmit antimicrobial-resistance genes on an intra- and inter-species level. This complicates surveillance, outbreak investigations and actions by infection control professionals. The spread of multidrug resistance is a globally important problem, with several countries currently reporting endemicity of highly resistant pathogens such as carbapenem-resistant *Klebsiella pneumoniae*. We have reviewed the current literature on carbapenem and third-generation cephalosporin-resistant *Enterobacteriaceae*. Our review highlights the continued increasing trend of resistance in *Enterobacteriaceae* and discusses the mechanisms by which this occurs. We aim to provide valuable collated information as part of a series of reviews on the WHO priority pathogens and enhance the current understanding in this area.

Specific IncF plasmids have been associated with C2 isolates. This includes those with dual replicons, which complicates plasmid typing and broadens the plasmid host range [67, 68], additional AMR genes, gene cassettes, toxin/

Table 1. Classification of β -lactamases

Adapted from Bush and Jacoby, 2010 [16].

Ambler molecular class	Bush-Jacoby group	Preferred substrate	Inhibited	Representative enzyme
A (serine penicillinases)	2a	Penicillins	+	PC1 from <i>S. aureus</i>
	2b	Penicillins, narrow-spectrum cephalosporins	+	TEM-1, TEM-2, SHV-1
	2be	Penicillins, narrow-spectrum and extended-spectrum cephalosporins	+	SHV-2 to SHV-6, TEM-3 to TEM-26, CTX-Ms, BEL-1, VEB-1, PER-1
	2br	Penicillins	–	TEM-30, SHV-72, SHV-19
	2c	Penicillins, carbenicillin	+	PSE-1
	2e	Extended-spectrum cephalosporins	+	FEC-1, CepA
B (MBLs)	2f	Penicillins, cephalosporins, carbapenems	+/-	KPC-2, SME-1, NMC-A
	3	Most β -lactams including carbapenems	–	IMP-1, VIM-1, NDM-1, CcrA and BcII, CphA, LI
C (cephalosporinases)	1	Cephalosporins	–	AmpC, CMY-2, ACT-1
D (oxacillinases)	2	Penicillins, cloxacillin	+/-	OXA-1, OXA-10
	2de	Extended-spectrum cephalosporins	+/-	OXA-11, OXA-15
	2df	Carbapenems	+/-	OXA-23, OXA-48

antitoxin systems and stability mechanisms, all of which may have influenced plasmid and clade success [57, 59, 69]. Architecture of the ST131 accessory genome, including plasmids, further supports clade-specific adaptations that have likely contributed to the success of ST131 [70]. Multiple clusters of variable accessory genome content within clade C suggest that clonal expansions of stabilized accessory gene profiles occur frequently, allowing generalization of this highly structured clone [59, 70].

CPE

Rising ESBL-E prevalence correlates with increased carbapenem consumption [71, 72]; and appears to have driven the emergence and spread of carbapenem resistance, especially in *Enterobacteriaceae* [73]. Carbapenem resistance may be caused by different mechanisms, including inducible overexpression of chromosomal cephalosporinases, such as AmpC, combined with porin loss [74]. More problematic, however, is acquisition of carbapenemase genes via mobile genetic elements. The most frequently identified mechanism is the Ambler class A *K. pneumoniae* carbapenemase (KPC), followed by class B metallo- β -lactamases (MBLs) such as New Delhi MBL (NDM), and the class D OXA-type genes [75] (Table 2, Fig. 1).

Since its identification in the USA in 1996 [76], KPC has disseminated globally, has been reported to be present in more than 50 % of CPE in many countries, and in some cases 100 % of carbapenem-resistant *K. pneumoniae* [77–84]. The majority of KPC-encoding genes are seen in *K. pneumoniae* clonal group (CG)258, which includes the successful lineages ST258 and ST11 [85–87]. An example of this rapid dissemination can be seen in Greece. Following the first KPC isolation in 2007 [88], KPC had spread to most acute-care facilities within 2 years [89–92]. Most infections remain hospital-related, and associated with high mortality rates [6, 93–95]. Many early cases were epidemiologically linked to travel to high prevalence locations [96–101]; however, complex local transmission networks now signify endemicity [102, 103]. More than 20 KPC variants have been recognized, with *bla*_{KPC2} and *bla*_{KPC3} being the most abundant [79, 83, 85, 104–106]. The gene is located in isoforms of the 10 kb Tn4401 transposon [107], of the Tn3 transposon family [108, 109], and is associated with diverse plasmids including IncFIIK [87], IncI [110], IncN [111], IncL/M [112] and IncX [113].

Carbapenem-resistant lineages exhibit less diversity when compared to carbapenem-susceptible *Enterobacteriaceae* [114, 115] and lineages such as ST258 [112, 116, 117] and ST11 [84, 106] demonstrate clonal spread. However, in contrast to the clonality of ESBL lineages and predominance of a small number of globally disseminated epidemic lineages, carbapenemase genes and plasmids show increased transferability within and between species, lineages, STs and patients. This genetic mobility complicates the investigation of outbreaks [114, 118–120]. This has been observed more frequently in *E. coli* than other *Enterobacteriaceae*. The

spread of carbapenem resistance displays increased diversity across STs, such as the large ST10 complex, rather than strong association with existing global epidemic lineages like ST131 [114, 121–123].

Non-clonal dissemination is also highly apparent in MBLs, especially NDM. These class B enzymes, which include NDM, GES, VIM and IMP, have also disseminated globally [124]. MBLs hydrolyse all β -lactams, are not inhibited by β -lactamase inhibitors, and their host bacteria often carry additional resistance mechanisms such as ESBLs [125–128]. First identified in a Swedish patient repatriated from a New Delhi hospital [129], most early cases had epidemiological links to the Indian subcontinent [130–143]. Epidemic spread and environmental contamination is evident in India, Pakistan and Bangladesh [144, 145], whilst sporadic cases or regional spread now occur on all continents [75, 84, 146, 147]. Clonal spread may occur during outbreaks [148, 149], but the high resolution of WGS enables tracking of varying *bla*_{NDM}-positive plasmids including IncA/C, IncF, IncH, IncL/M, IncN and IncX types [113, 150–153], and fluctuating genomic contexts flanking the *bla*_{NDM} gene among non-clonal isolates [128, 151, 154–156]. The *bla*_{NDM} gene is chimeric following fusion with the aminoglycoside gene *aphA6* and lies downstream of either entire, truncated or remnants of the IS*Aba125* element [157].

*bla*_{VIM} genes were originally described in Italian *Pseudomonas aeruginosa* in the mid-1990s [158] and *Enterobacteriaceae* carrying *bla*_{VIM} are predominantly reported in Europe as occurring sporadically or in single hospital outbreaks [147]. Sporadic cases are also seen in Africa, Taiwan, Mexico, Saudi Arabia and the USA [159]. Since 2015, Hungary, Italy and Spain have reported inter-regional spread; however, as with other CPE mechanisms, *bla*_{VIM} is endemic in Greece [147]. More than 48 variants have been identified with *bla*_{VIM-1} and *bla*_{VIM-2} showing global dissemination [159]. *bla*_{VIM} genes are carried on variable class 1 integrons within multiple plasmid Inc types [159–161].

*bla*_{IMP} was the first described case of a transmissible carbapenemase gene [162]; however, large-scale epidemiological studies are lacking. The majority of *bla*_{IMP} isolates originate in the South Pacific [163] and Asia [164]. *bla*_{IMP} is found predominantly in *K. pneumoniae*, *E. coli* and *Enterobacter* spp. on class 1 integrons [165]. Integrons and their gene cassette combinations are variable and may show geographical correlations [164]. Despite being named due to imipenem resistance, certain variants of *bla*_{IMP}, particularly *bla*_{IMP-6}, actually exhibit low levels of imipenem resistance, which may lead to misidentification, and contribute to the lower detection rates of this mechanism [166, 167]. Genomic evidence is now emerging of this mechanism moving into epidemic *Enterobacteriaceae* such as *E. coli* ST131 [168, 169].

Finally, OXA-48 carbapenemases, first identified in 2001 in Turkey, are also a public-health threat [170–172]. Owing to their variable levels of carbapenem resistance, the spread of

Table 2. Carbapenem-resistance genes identified in *Enterobacteriaceae*

bla_{SME-1}, *Serratia marcescens* enzyme; *bla_{IMI}*, imipenem-hydrolysing- β -lactamase; *bla_{KPC}*, *K. pneumoniae* carbapenemase; *bla_{IMP}*, active on imipenem; *bla_{NDM}*, New Delhi MBL; *bla_{VIM}*, Verona integron-encoded; *bla_{GIM}*, German imipenemase; *bla_{KHM}*, Kyorin Health Science MBL.

Gene	Species of origin*	Geographical origin† (year)	Active site	Ambler class	Location	Plasmid	No. of variants	Case
<i>bla_{SME-1}</i>	<i>Serratia marcescens</i>	London, UK (1982)	Serine	A	Chromosomally encoded, SmarGII novel genomic island [250]		5	Mataseje <i>et al.</i> [250] – characterization of a novel genomic island
<i>bla_{IMI}</i>	<i>Enterobacter cloacae</i>	California, USA (1984)	Serine	A	Chromosomally encoded in <i>Enterobacter cloacae</i> , IncF plasmid in <i>Klebsiella variicola</i> [251] and <i>Escherichia coli</i> [252]	IncF types [251, 252]	12	Rasmussen <i>et al.</i> [253] – characterization of first clinical IMI isolate
<i>bla_{KPC}</i>	<i>Klebsiella pneumoniae</i>	North Carolina, USA (1996)	Serine	A	Tn4401 [107]	Multiple [107, 254]	24	Munoz-price <i>et al.</i> [105] – description of an ongoing UK outbreak
<i>bla_{OXA-48}</i>	<i>Klebsiella pneumoniae</i>	Istanbul, Turkey (2001)	Serine	D	Tn1999 [185]	IncL/M [185]	OXA-181, OXA-204, OXA-232, OXA-163	Potron <i>et al.</i> [175] – description of a clonal multi-country outbreak
<i>bla_{IMP}</i>	<i>Serratia marcescens</i>	Aichi Prefecture, Japan (1991)	Zinc	B	Variable – chromosomal, class I integron [255]	IncA/C, IncH, IncL/M [255]	>52	Peleg <i>et al.</i> [256] – multi-genera dissemination of <i>bla_{IMP}</i> in Australia
<i>bla_{NDM}</i>	<i>Klebsiella pneumoniae</i>	New Delhi, India (2008)	Zinc	B	Tn125 [151]	Multiple [126, 151, 153]	16	Walsh <i>et al.</i> [145] – environmental spread of <i>bla_{NDM}</i>
<i>bla_{VIM}</i>	<i>Pseudomonas aeruginosa</i>	Verona, Italy (1997)	Zinc	B	Class I integrons, In2-Tn402 [257]	IncHI2, IncI [257], IncN [258]	>46	Luzzaro <i>et al.</i> [259] – <i>bla_{VIM}</i> in multiple genera from one patient
<i>bla_{GIM}</i>	<i>Pseudomonas aeruginosa</i>	North Rhine-Westphalia, Germany (2004)	Zinc	B	Not determined	Not determined		Rieber <i>et al.</i> [260] – emergence of <i>bla_{GIM}</i> in clinical samples
<i>bla_{KHM}</i>	<i>Citrobacter freundii</i>	Tokyo, Japan (1997)	Zinc	B	Not determined	Not determined		Sekiguchi <i>et al.</i> [261] – first identification of <i>bla_{KHM}</i>

*First species known to be reported in.

†First location reported in the literature.

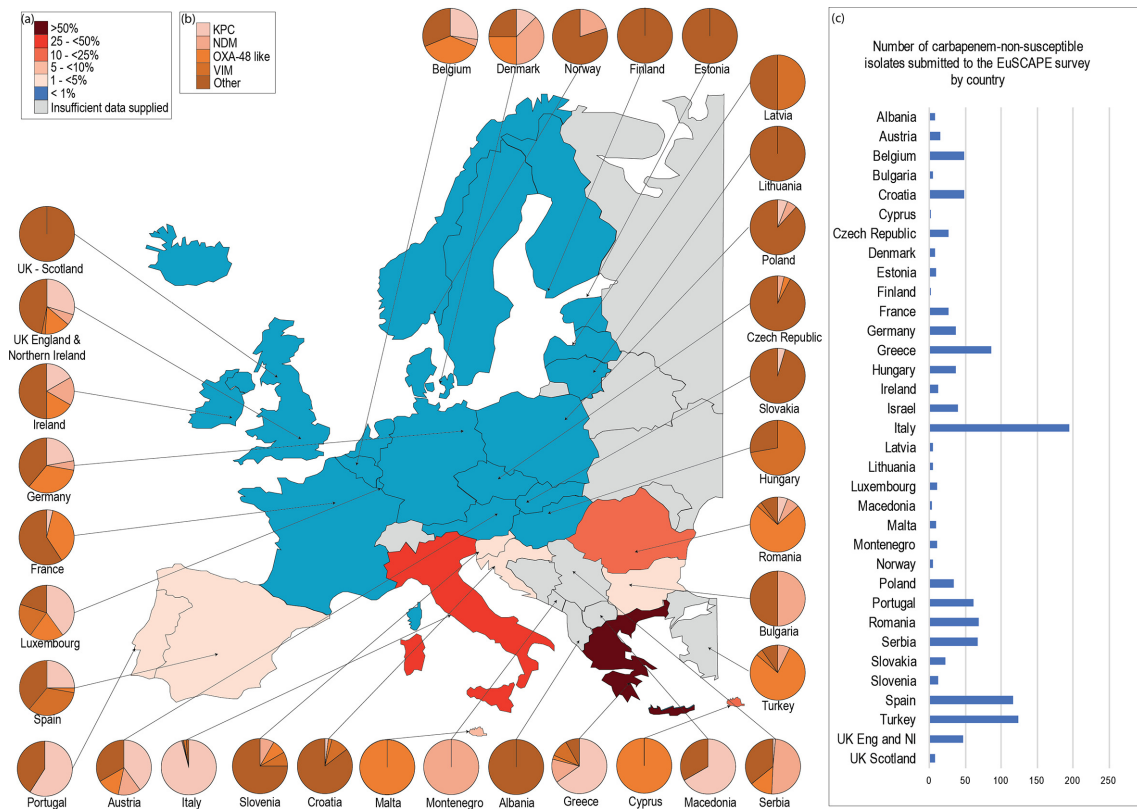


Fig. 1. Composite figure demonstrating the prevalence and characteristics of carbapenem resistance in Europe. (a) Percentage of invasive isolates resistant to carbapenem antibiotics as determined by the European Centre for Disease Prevention and Control in the *Antimicrobial Resistance Surveillance in Europe 2015* report [11]. Each country is coloured according to the percentage of submitted *K. pneumoniae* isolates that were non-susceptible to doripenem, imipenem or meropenem. (b) Pie charts indicating the distribution of carbapenem-resistance mechanisms in *K. pneumoniae* isolates submitted to the EuSCAPE study [52]. Mechanisms are coloured according to the key. 'Other' mechanisms: no KPC, NDM, OXA-48 or VIM genes detected. (c) Overall number of *K. pneumoniae* isolates submitted by each participating country in the EuSCAPE study.

bla_{OXA-48} has been initially underestimated [173–175]. In parallel to bla_{NDM} and its Indian origins, bla_{OXA-48} was initially geographically linked to Turkey [171, 176]. However, since 2015, multiple countries have inter-regional spread and bla_{OXA-48} is endemic in Malta and Turkey [147]. Further afield, extensively drug resistant (XDR) strains co-harboring bla_{NDM} and bla_{OXA-48} have been identified in the Middle East [177, 178], and bla_{OXA-48} strains have emerged in Canada [173], Algeria [179] and Korea [180]. *Shewanella* spp. may be the natural progenitors of bla_{OXA-48} genes [181], which now predominantly appear in *K. pneumoniae*, *E. coli* and *Enterobacter* spp. [173, 182, 183]. bla_{OXA-48} is associated with the Tn1999 transposon, which is composed of two copies of IS1999 bracketing the gene [184, 185]. The majority of bla_{OXA-48} genes are associated with Tn1999 or the variants Tn1999.2 [171], Tn1999.3 [186] and Tn1999.4 [187]. Tn1999.4 is a mosaic of Tn1999 and a second transposon, Tn2015, which additionally carries $bla_{CTX-M-15}$ [187]. In contrast to other CPE genes, dissemination of bla_{OXA-48} is associated with a single, successful

IncL/M plasmid into which the Tn1999 transposon has inserted [173, 174, 178, 185, 187–193].

A variant of bla_{OXA-48} , $bla_{OXA-181}$, has also begun to disseminate among *Enterobacteriaceae* and appears to be establishing in the Indian subcontinent, South Africa and Singapore, or in patients epidemiologically linked to these areas [194–199]. Recently, the first cases of likely patient-to-patient transmission have also been reported [200, 201]. $bla_{OXA-181}$ has been identified on a non-self-conjugative ColE2 plasmid in association with *ISEcp1* and the Tn2013 transposon [198]. Additionally, $bla_{OXA-181}$ has been identified in the same strains as bla_{NDM} genes, reflecting its prevalence in India [201, 202], and now in a conjugative plasmid [202], suggesting widespread dissemination may occur in the future.

THE CONTINUED THREAT OF AMR

The impact of antibiotic consumption is reflected in geographical variations of CPE and ESBL-E prevalence. Countries with high antibiotic consumption rates, such as

Turkey, Tunisia, Algeria, Greece and Romania [71], have particularly high rates of multidrug-resistant (MDR) bacteria [11, 147]. Overuse of particular antibiotic classes also affects MDR organisms, such as in Greece where high cephalosporin use [203] is paralleled by high levels of ESBL-E [11]. Travel to endemic regions also may be having a global impact following acquisition of MDR pathogens by travellers [204–208].

A particularly concerning issue, especially in Asia, is transferable colistin resistance [209]. Increased carbapenem resistance has resulted in an increase in the use of polymyxins (e.g. colistin) to treat XDR pathogens [71, 210]. We are now faced with the dissemination of genes conferring resistance to these drugs, which are frequently co-located with additional resistance genes, leaving some infections almost untreatable [211–214]. Following the first publication of the transferable colistin-resistance gene, *mcr-1* [209], screening has demonstrated global existence of *mcr-1* in food, animal and human samples [215, 216]. Following the association of *mcr-1* with IS*Apl-1* of the IS30 family and formation of the composite transposon Tn6330, *mcr-1* and its genetic environment has stabilized [217–219]. It is now beginning to spread across multiple plasmid types [214, 220–224]. The ancestral mobilizable state of *mcr-1* is more frequently identified in agricultural isolates than human isolates, particularly those in China, supporting the theory of an animal origin [209, 225–227]. Colistin is ubiquitous in food-animal production [228], but its use as a growth promoter has been banned in the European Union since 2006 and in China since 2016 [229, 230]. This may begin to ease the antibiotic selection pressure; however, it is difficult to speculate how this may affect the human situation as stabilization and dissemination of the gene into conjugative plasmids has already occurred.

CONCLUSION

Antimicrobial stewardship as a strategy to reduce AMR is high on policy agendas in many countries [231–235] and a positive impact on the prevalence of MDR pathogens is beginning to show [236, 237]. Continued strategy development is still required; accepted international definitions and guidelines are yet to be adopted, particularly those suitable for low-to-middle income countries [238]. With the inception of the ‘One Health’ initiative [233, 239, 240], consideration should also be given to antimicrobial prescription in primary care [30, 210, 241, 242], poorly regulated community antimicrobial use [243–246] and agricultural antimicrobial use [239, 247–249].

The ability of CPE and ESBL-E to evolve and adapt rapidly due to antibiotic selective pressures is one of the biggest threats to medical care. An international, multi-disciplinary approach is urgently required to tackle this global threat. Pressing issues include improving surveillance to recognize the importance of mobile AMR elements and increasing the drive to move rapid, high-resolution diagnostics, such as WGS, from the research environment into routine clinical

practice. A proactive approach involving all users of antimicrobials is imperative to prevent a return to the pre-antibiotic era.

Funding information

This work was supported by the Academy of Medical Sciences, the Health Foundation, and by the NIHR Cambridge Biomedical Research Centre.

Acknowledgements

M. E. T. is a Clinician Scientist Fellow funded by the Academy of Medical Sciences, the Health Foundation, and supported by the NIHR Cambridge Biomedical Research Centre.

Conflicts of interest

The authors declare that there are no conflicts of interest.

References

1. Ray S, Anand D, Purwar S, Samanta A, Upadhye KV *et al.* Association of high mortality with extended-spectrum β -lactamase (ESBL) positive cultures in community acquired infections. *J Crit Care* 2018;44:255–260.
2. Schwaber MJ, Carmeli Y. Mortality and delay in effective therapy associated with extended-spectrum β -lactamase production in *Enterobacteriaceae* bacteraemia: a systematic review and meta-analysis. *J Antimicrob Chemother* 2007;60:913–920.
3. Giske CG, Monnet DL, Cars O, Carmeli Y, ReAct-Action on Antibiotic Resistance. Clinical and economic impact of common multidrug-resistant Gram-negative bacilli. *Antimicrob Agents Chemother* 2008;52:813–821.
4. Tumbarello M, Spanu T, di Bidino R, Marchetti M, Ruggeri M *et al.* Costs of bloodstream infections caused by *Escherichia coli* and influence of extended-spectrum- β -lactamase production and inadequate initial antibiotic therapy. *Antimicrob Agents Chemother* 2010;54:4085–4091.
5. Melzer M, Petersen I. Mortality following bacteraemic infection caused by extended spectrum β -lactamase (ESBL) producing *E. coli* compared to non-ESBL producing *E. coli*. *J Infect* 2007;55: 254–259.
6. Fraenkel-Wandel Y, Raveh-Brawer D, Wiener-Well Y, Yinnon AM, Assous MV. Mortality due to *bla*_{KPC} *Klebsiella pneumoniae* bacteraemia. *J Antimicrob Chemother* 2016;71:1083–1087.
7. Mcconville TH, Sullivan SB, Gomez-Simmonds A, Whittier S, Uhlemann AC. Carbapenem-resistant *Enterobacteriaceae* colonization (CRE) and subsequent risk of infection and 90-day mortality in critically ill patients, an observational study. *PLoS One* 2017;12:e0186195.
8. Xu L, Sun X, Ma X. Systematic review and meta-analysis of mortality of patients infected with carbapenem-resistant *Klebsiella pneumoniae*. *Ann Clin Microbiol Antimicrob* 2017;16:18.
9. O'Neill J. *The Review on Antimicrobial Resistance*. London: Wellcome Trust and HM Government; 2016.
10. World Health Organization. *Antimicrobial Resistance: Global Report on Surveillance*. Geneva: World Health Organization; 2014.
11. European Centre for Disease Prevention and Control. *Antimicrobial Resistance Surveillance in Europe 2015. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net)*. Stockholm: European Centre for Disease Prevention and Control; 2017.
12. World Health Organization. *Global Priority List of Antibiotic-Resistant Bacteria to Guide Research, Discovery, and Development of New Antibiotics*. Geneva: World Health Organization; 2017.
13. Drees M, Pineles L, Harris AD, Morgan DJ. Variation in definitions and isolation procedures for multidrug-resistant Gram-negative bacteria: a survey of the society for healthcare epidemiology of america research network. *Infect Control Hosp Epidemiol* 2014;35:362–366.

14. Paterson DL, Bonomo RA. Extended-spectrum β -lactamases: a clinical update. *Clin Microbiol Rev* 2005;18:657–686.
15. Ambler RP. The structure of β -lactamases. *Philos Trans R Soc Lond B Biol Sci* 1980;289:321–331.
16. Bush K, Jacoby GA. Updated functional classification of β -lactamases. *Antimicrob Agents Chemother* 2010;54:969–976.
17. Decusserer JW, Poirel L, Nordmann P. Characterization of a chromosomally encoded extended-spectrum class A β -lactamase from *Kluyvera cryocrescens*. *Antimicrob Agents Chemother* 2001;45:3595–3598.
18. Humeniuk C, Arlet G, Gautier V, Grimont P, Labia R *et al.* β -lactamases of *Kluyvera ascorbata*, probable progenitors of some plasmid-encoded CTX-M types. *Antimicrob Agents Chemother* 2002;46:3045–3049.
19. Poirel L, Kämpfer P, Nordmann P. Chromosome-encoded Ambler class A β -lactamase of *Kluyvera georgiana*, a probable progenitor of a subgroup of CTX-M extended-spectrum β -lactamases. *Antimicrob Agents Chemother* 2002;46:4038–4040.
20. Naseer U, Sundsfjord A. The CTX-M conundrum: dissemination of plasmids and *Escherichia coli* clones. *Microb Drug Resist* 2011;17:83–97.
21. Bauernfeind A, Schweighart S, Grimm H. A new plasmidic cefotaximase in a clinical isolate of *Escherichia coli*. *Infection* 1990;18:294–298.
22. Bauernfeind A, Casellas JM, Goldberg M, Holley M, Jungwirth R *et al.* A new plasmidic cefotaximase from patients infected with *Salmonella typhimurium*. *Infection* 1992;20:158–163.
23. Ishii Y, Ohno A, Taguchi H, Imajo S, Ishiguro M *et al.* Cloning and sequence of the gene encoding a cefotaxime-hydrolyzing class A β -lactamase isolated from *Escherichia coli*. *Antimicrob Agents Chemother* 1995;39:2269–2275.
24. Cantón R, González-Alba JM, Galán JC. CTX-M enzymes: origin and diffusion. *Front Microbiol* 2012;3:110.
25. Robin F, Beyrouthy R, Bonacorsi S, Aissa N, Bret L *et al.* Inventory of extended-spectrum- β -lactamase-producing *Enterobacteriaceae* in France as assessed by a multicenter study. *Antimicrob Agents Chemother* 2017;61:e01911–16.
26. Rios E, Lopez MC, Rodriguez-Avial I, Culebras E, Picazo JJ. Detection of *Escherichia coli* ST131 clonal complex (ST705) and *Klebsiella pneumoniae* ST15 among faecal carriage of extended-spectrum β -lactamase- and carbapenemase-producing *Enterobacteriaceae*. *J Med Microbiol* 2017;66:169–174.
27. Pietsch M, Eller C, Wendt C, Holfelder M, Falgenhauer L *et al.* Molecular characterisation of extended-spectrum β -lactamase (ESBL)-producing *Escherichia coli* isolates from hospital and ambulatory patients in Germany. *Vet Microbiol* 2017;200:130–137.
28. Burke L, Humphreys H, Fitzgerald-Hughes D. The molecular epidemiology of resistance in cefotaximase-producing *Escherichia coli* clinical isolates from Dublin, Ireland. *Microb Drug Resist* 2016;22:552–558.
29. Willemsen I, Oome S, Verhulst C, Pettersson A, Verduin K *et al.* Trends in extended spectrum β -lactamase (ESBL) producing *Enterobacteriaceae* and ESBL genes in a Dutch teaching hospital, measured in 5 yearly point prevalence surveys (2010–2014). *PLoS One* 2015;10:e0141765.
30. Public Health England. *English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) Report 2017*. London: Public Health England; 2017.
31. Runcharoen C, Raven KE, Reuter S, Kallonen T, Paksanont S *et al.* Whole genome sequencing of ESBL-producing *Escherichia coli* isolated from patients, farm waste and canals in Thailand. *Genome Med* 2017;9:81.
32. Lee MY, Ko KS, Kang CI, Chung DR, Peck KR *et al.* High prevalence of CTX-M-15-producing *Klebsiella pneumoniae* isolates in Asian countries: diverse clones and clonal dissemination. *Int J Antimicrob Agents* 2011;38:160–163.
33. Musicha P, Feasey NA, Cain AK, Kallonen T, Chaguzo C *et al.* Genomic landscape of extended-spectrum β -lactamase resistance in *Escherichia coli* from an urban African setting. *J Antimicrob Chemother* 2017;72:1602–1609.
34. Dziri R, Klibi N, Alonso CA, Said LB, Bellaaj R *et al.* Characterization of extended-spectrum β -lactamase (ESBL)-producing *Klebsiella*, *Enterobacter*, and *Citrobacter* obtained in environmental samples of a Tunisian hospital. *Diagn Microbiol Infect Dis* 2016;86:190–193.
35. Eibach D, Belmar Campos C, Krumkamp R, Al-Emran HM, Dekker D *et al.* Extended spectrum β -lactamase producing *Enterobacteriaceae* causing bloodstream infections in rural Ghana, 2007–2012. *Int J Med Microbiol* 2016;306:249–254.
36. Johnson JR, Johnston B, Clabots C, Kuskowski MA, Castanheira M. *Escherichia coli* sequence type ST131 as the major cause of serious multidrug-resistant *E. coli* infections in the United States. *Clin Infect Dis* 2010;51:286–294.
37. Doi Y, Park YS, Rivera JI, Adams-Haduch JM, Hingwe A *et al.* Community-associated extended-spectrum β -lactamase-producing *Escherichia coli* infection in the United States. *Clin Infect Dis* 2013;56:641–648.
38. Kim S, Sung JY, Cho HH, Kwon KC, Koo SH. Characteristics of the molecular epidemiology of CTX-M-producing *Escherichia coli* isolated from a tertiary hospital in Daejeon, Korea. *J Microbiol Biotechnol* 2016;26:1643–1649.
39. Pallecchi L, Bartoloni A, Fiorelli C, Mantella A, di Maggio T *et al.* Rapid dissemination and diversity of CTX-M extended-spectrum β -lactamase genes in commensal *Escherichia coli* isolates from healthy children from low-resource settings in Latin America. *Antimicrob Agents Chemother* 2007;51:2720–2725.
40. Munday CJ, Xiong J, Li C, Shen D, Hawkey PM. Dissemination of CTX-M type β -lactamases in *Enterobacteriaceae* isolates in the People's Republic of China. *Int J Antimicrob Agents* 2004;23:175–180.
41. Liu W, Chen L, Li H, Duan H, Zhang Y *et al.* Novel CTX-M β -lactamase genotype distribution and spread into multiple species of *Enterobacteriaceae* in Changsha, Southern China. *J Antimicrob Chemother* 2009;63:895–900.
42. Zhang J, Zheng B, Zhao L, Wei Z, Ji J *et al.* Nationwide high prevalence of CTX-M and an increase of CTX-M-55 in *Escherichia coli* isolated from patients with community-onset infections in Chinese county hospitals. *BMC Infect Dis* 2014;14:659.
43. Zhong YM, Liu WE, Liang XH, Li YM, Jian ZJ *et al.* Emergence and spread of O16-ST131 and O25b-ST131 clones among faecal CTX-M-producing *Escherichia coli* in healthy individuals in Hunan Province, China. *J Antimicrob Chemother* 2015;70:2223–2227.
44. Quan J, Zhao D, Liu L, Chen Y, Zhou J *et al.* High prevalence of ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* in community-onset bloodstream infections in China. *J Antimicrob Chemother* 2017;72:273–280.
45. Li B, Lu Y, Lan F, He Q, Li C *et al.* Prevalence and characteristics of ST131 clone among unselected clinical *Escherichia coli* in a Chinese university hospital. *Antimicrob Resist Infect Control* 2017;6:118.
46. Chen LF, Freeman JT, Nicholson B, Keiger A, Lancaster S *et al.* Widespread dissemination of CTX-M-15 genotype extended-spectrum- β -lactamase-producing *Enterobacteriaceae* among patients presenting to community hospitals in the southeastern United States. *Antimicrob Agents Chemother* 2014;58:1200–1202.
47. Nicolas-Chanoine MH, Blanco J, Leflon-Guibout V, Demarty R, Alonso MP *et al.* Intercontinental emergence of *Escherichia coli* clone O25:H4-ST131 producing CTX-M-15. *J Antimicrob Chemother* 2008;61:273–281.
48. Algoribi MF, Gibreel TM, Farnham G, Al Johani SM, Balkhy HH *et al.* Antibiotic-resistant ST38, ST131 and ST405 strains are the leading uropathogenic *Escherichia coli* clones in Riyadh, Saudi Arabia. *J Antimicrob Chemother* 2015;70:2757–2762.

49. Peirano G, van der Bij AK, Gregson DB, Pitout JD. Molecular epidemiology over an 11-year period (2000 to 2010) of extended-spectrum β -lactamase-producing *Escherichia coli* causing bacteremia in a centralized Canadian region. *J Clin Microbiol* 2012;50:294–299.
50. Oteo J, Cuevas O, Lopez-Rodriguez I, Banderas-Florida A, Vindel A *et al*. Emergence of CTX-M-15-producing *Klebsiella pneumoniae* of multilocus sequence types 1, 11, 14, 17, 20, 35 and 36 as pathogens and colonizers in newborns and adults. *J Antimicrob Chemother* 2009;64:524–528.
51. Ks K, Lee JY, Baek JY, Suh JY, Lee MY *et al*. Predominance of an ST11 extended-spectrum β -lactamase-producing *Klebsiella pneumoniae* clone causing bacteraemia and urinary tract infections in Korea. *J Med Microbiol* 2010;59:822–828.
52. Coque TM, Novais A, Carattoli A, Poirel L, Pitout J *et al*. Dissemination of clonally related *Escherichia coli* strains expressing extended-spectrum β -lactamase CTX-M-15. *Emerg Infect Dis* 2008;14:195–200.
53. Rogers BA, Sidjabat HE, Paterson DL. *Escherichia coli* O25b-ST131: a pandemic, multiresistant, community-associated strain. *J Antimicrob Chemother* 2011;66:1–14.
54. Ben Zakour NL, Alsheikh-Hussain AS, Ashcroft MM, Khanh Nhu NT, Roberts LW *et al*. Sequential acquisition of virulence and fluoroquinolone resistance has shaped the evolution of *Escherichia coli* ST131. *mBio* 2016;7.
55. Petty NK, Ben Zakour NL, Stanton-Cook M, Skippington E, Totsika M *et al*. Global dissemination of a multidrug resistant *Escherichia coli* clone. *Proc Natl Acad Sci USA* 2014;111:5694–5699.
56. Price LB, Johnson JR, Aziz M, Clabots C, Johnston B *et al*. The epidemic of extended-spectrum- β -lactamase-producing *Escherichia coli* ST131 is driven by a single highly pathogenic subclone, H30-Rx. *MBio* 2013;4:e00377-13.
57. Schembri MA, Zakour NL, Phan MD, Forde BM, Stanton-Cook M *et al*. Molecular characterization of the multidrug resistant *Escherichia coli* ST131 clone. *Pathogens* 2015;4:422–430.
58. Peirano G, van der Bij AK, Freeman JL, Poirel L, Nordmann P *et al*. Characteristics of *Escherichia coli* sequence type 131 isolates that produce extended-spectrum β -lactamases: global distribution of the H30-Rx sublineage. *Antimicrob Agents Chemother* 2014;58:3762–3767.
59. Stoesser N, Sheppard AE, Pankhurst L, De Maio N, Moore CE *et al*. Evolutionary history of the global emergence of the *Escherichia coli* epidemic clone ST131. *MBio* 2016;7:e02162-15.
60. Paul S, Linardopoulou EV, Billig M, Tchesnokova V, Price LB *et al*. Role of homologous recombination in adaptive diversification of extraintestinal *Escherichia coli*. *J Bacteriol* 2013;195:231–242.
61. Ciesielczuk H, Doumith M, Hope R, Woodford N, Wareham DW. Characterization of the extra-intestinal pathogenic *Escherichia coli* ST131 clone among isolates recovered from urinary and bloodstream infections in the United Kingdom. *J Med Microbiol* 2015;64:1496–1503.
62. Day MJ, Rodríguez I, van Essen-Zandbergen A, Dierikx C, Kadlec K *et al*. Diversity of STs, plasmids and ESBL genes among *Escherichia coli* from humans, animals and food in Germany, the Netherlands and the UK. *J Antimicrob Chemother* 2016;71:1178–1182.
63. Doumith M, Dhanji H, Ellington MJ, Hawkey P, Woodford N. Characterization of plasmids encoding extended-spectrum β -lactamases and their addiction systems circulating among *Escherichia coli* clinical isolates in the UK. *J Antimicrob Chemother* 2012;67:878–885.
64. Chen L, Hu H, Chavda KD, Zhao S, Liu R *et al*. Complete sequence of a KPC-producing IncN multidrug-resistant plasmid from an epidemic *Escherichia coli* sequence type 131 strain in China. *Antimicrob Agents Chemother* 2014;58:2422–2425.
65. Partridge SR, Ellem JA, Tetu SG, Zong Z, Paulsen IT *et al*. Complete sequence of pJIE143, a pir-type plasmid carrying ISEcp1-*bla*_{CTX-M-15} from an *Escherichia coli* ST131 isolate. *Antimicrob Agents Chemother* 2011;55:5933–5935.
66. Woodford N, Carattoli A, Karisik E, Underwood A, Ellington MJ *et al*. Complete nucleotide sequences of plasmids pEK204, pEK499, and pEK516, encoding CTX-M enzymes in three major *Escherichia coli* lineages from the United Kingdom, all belonging to the international O25:H4-ST131 clone. *Antimicrob Agents Chemother* 2009;53:4472–4482.
67. Osborn AM, da Silva Tatley FM, Steyn LM, Pickup RW, Saunders JR. Mosaic plasmids and mosaic replicons: evolutionary lessons from the analysis of genetic diversity in IncFII-related replicons. *Microbiology* 2000;146:2267–2275.
68. Villa L, García-Fernández A, Fortini D, Carattoli A. Replicon sequence typing of IncF plasmids carrying virulence and resistance determinants. *J Antimicrob Chemother* 2010;65:2518–2529.
69. Phan MD, Forde BM, Peters KM, Sarkar S, Hancock S *et al*. Molecular characterization of a multidrug resistance IncF plasmid from the globally disseminated *Escherichia coli* ST131 clone. *PLoS One* 2015;10:e0122369.
70. McNally A, Oren Y, Kelly D, Pascoe B, Dunn S *et al*. Combined analysis of variation in core, accessory and regulatory genome regions provides a super-resolution view into the evolution of bacterial populations. *PLoS Genet* 2016;12:e1006280.
71. Klein EY, van Boeckel TP, Martinez EM, Pant S, Gandra S *et al*. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. *Proc Natl Acad Sci USA* 2018; 115:E3463–E3470.
72. Meyer E, Schwab F, Schroeren-Boersch B, Gastmeier P. Dramatic increase of third-generation cephalosporin-resistant *E. coli* in German intensive care units: secular trends in antibiotic drug use and bacterial resistance, 2001 to 2008. *Crit Care* 2010;14:R113.
73. McLaughlin M, Advincula MR, Malczynski M, Qi C, Bolon M *et al*. Correlations of antibiotic use and carbapenem resistance in *Enterobacteriaceae*. *Antimicrob Agents Chemother* 2013;57:5131–5133.
74. Nordmann P, Dortet L, Poirel L. Carbapenem resistance in *Enterobacteriaceae*: here is the storm!. *Trends Mol Med* 2012;18: 263–272.
75. Logan LK, Weinstein RA. The epidemiology of carbapenem-resistant *Enterobacteriaceae*: the impact and evolution of a global menace. *J Infect Dis* 2017;215S28–S36.
76. Yigit H, Queenan AM, Anderson GJ, Domenech-Sanchez A, Biddle JW *et al*. Novel carbapenem-hydrolyzing β -lactamase, KPC-1, from a carbapenem-resistant strain of *Klebsiella pneumoniae*. *Antimicrob Agents Chemother* 2001;45:1151–1161.
77. Tavares CP, Pereira PS, Marques EA, Faria C, de Souza MP *et al*. Molecular epidemiology of KPC-2-producing *Enterobacteriaceae* (non-*Klebsiella pneumoniae*) isolated from Brazil. *Diagn Microbiol Infect Dis* 2015;82:326–330.
78. Bradford PA, Bratu S, Urban C, Visalli M, Mariano N *et al*. Emergence of carbapenem-resistant *Klebsiella* species possessing the class A carbapenem-hydrolyzing KPC-2 and inhibitor-resistant TEM-30 β -lactamases in New York City. *Clin Infect Dis* 2004;39:55–60.
79. Castanheira M, Costello AJ, Deshpande LM, Jones RN. Expansion of clonal complex 258 KPC-2-producing *Klebsiella pneumoniae* in Latin American hospitals: report of the SENTRY antimicrobial surveillance program. *Antimicrob Agents Chemother* 2012;56:1668–1669.
80. Castanheira M, Farrell SE, Deshpande LM, Mendes RE, Jones RN. Prevalence of β -lactamase-encoding genes among *Enterobacteriaceae* bacteremia isolates collected in 26 U.S. hospitals: report from the SENTRY antimicrobial surveillance program (2010). *Antimicrob Agents Chemother* 2013;57:3012–3020.

81. Chiang T, Mariano N, Urban C, Colon-Urban R, Grenner L *et al*. Identification of carbapenem-resistant *Klebsiella pneumoniae* harboring KPC enzymes in New Jersey. *Microb Drug Resist* 2007;13:235–240.
82. Giakkoupi P, Papagiannitsis CC, Miriagou V, Pappa O, Polemis M *et al*. An update of the evolving epidemic of blaKPC-2-carrying *Klebsiella pneumoniae* in Greece (2009–10). *J Antimicrob Chemother* 2011;66:1510–1513.
83. Richter SN, Frasson I, Franchin E, Bergo C, Lavezzo E *et al*. KPC-mediated resistance in *Klebsiella pneumoniae* in two hospitals in Padua, Italy, June 2009–December 2011: massive spreading of a KPC-3-encoding plasmid and involvement of non-intensive care units. *Gut Pathog* 2012;4:7.
84. Zhang R, Liu L, Zhou H, Chan EW, Li J *et al*. Nationwide surveillance of clinical carbapenem-resistant *Enterobacteriaceae* (CRE) strains in China. *EBioMedicine* 2017;19:98–106.
85. Kitchel B, Rasheed JK, Patel JB, Srinivasan A, Navon-Venezia S *et al*. Molecular epidemiology of KPC-producing *Klebsiella pneumoniae* isolates in the United States: clonal expansion of multi-locus sequence type 258. *Antimicrob Agents Chemother* 2009;53:3365–3370.
86. Breurec S, Guessennd N, Timinouni M, Le TA, Cao V *et al*. *Klebsiella pneumoniae* resistant to third-generation cephalosporins in five African and two Vietnamese major towns: multiclonal population structure with two major international clonal groups, CG15 and CG258. *Clin Microbiol Infect* 2013;19:349–355.
87. Chen L, Mathema B, Chavda KD, Deleo FR, Bonomo RA *et al*. Carbapenemase-producing *Klebsiella pneumoniae*: molecular and genetic decoding. *Trends Microbiol* 2014;22:686–696.
88. Tegmark-Wisell K, Haeggman S, Gezelius L, Thompson O, Gustafsson I *et al*. Identification of *Klebsiella pneumoniae* carbapenemase in Sweden. *Euro Surveill* 2007;12:3333.
89. Maltezos HC, Giakkoupi P, Maragos A, Bolikas M, Raftopoulos V *et al*. Outbreak of infections due to KPC-2-producing *Klebsiella pneumoniae* in a hospital in Crete (Greece). *J Infect* 2009;58:213–219.
90. Pournaras S, Protonotariou E, Voulgari E, Kristo I, Dimitroulia E *et al*. Clonal spread of KPC-2 carbapenemase-producing *Klebsiella pneumoniae* strains in Greece. *J Antimicrob Chemother* 2009;64:348–352.
91. Souli M, Galani I, Antoniadou A, Papadomichelakis E, Poulakou G *et al*. An outbreak of infection due to β -lactamase *Klebsiella pneumoniae* carbapenemase 2-producing *K. pneumoniae* in a Greek University Hospital: molecular characterization, epidemiology, and outcomes. *Clin Infect Dis* 2010;50:364–373.
92. Kontopoulou K, Protonotariou E, Vasilakos K, Kriti M, Koteli A *et al*. Hospital outbreak caused by *Klebsiella pneumoniae* producing KPC-2 β -lactamase resistant to colistin. *J Hosp Infect* 2010;76:70–73.
93. Tumbarello M, Trearichi EM, De Rosa FG, Giannella M, Giacobbe DR *et al*. Infections caused by KPC-producing *Klebsiella pneumoniae*: differences in therapy and mortality in a multi-centre study. *J Antimicrob Chemother* 2015;70:2133–2143.
94. Zarkotou O, Pournaras S, Tselioti P, Dragoumanos V, Pitiriga V *et al*. Predictors of mortality in patients with bloodstream infections caused by KPC-producing *Klebsiella pneumoniae* and impact of appropriate antimicrobial treatment. *Clin Microbiol Infect* 2011;17:1798–1803.
95. Lübbert C, Becker-Rux D, Rodloff AC, Laudi S, Busch T *et al*. Colonization of liver transplant recipients with KPC-producing *Klebsiella pneumoniae* is associated with high infection rates and excess mortality: a case-control analysis. *Infection* 2014;42:309–316.
96. Bogaerts P, Montesinos I, Rodriguez-Villalobos H, Blairon L, Deplano A *et al*. Emergence of clonally related *Klebsiella pneumoniae* isolates of sequence type 258 producing KPC-2 carbapenemase in Belgium. *J Antimicrob Chemother* 2010;65:361–362.
97. Chua KY, Grayson ML, Burgess AN, Lee JY, Howden BP. The growing burden of multidrug-resistant infections among returned Australian travellers. *Med J Aust* 2014;200:116–118.
98. Lopez JA, Correa A, Navon-Venezia S, Correa AL, Torres JA *et al*. Intercontinental spread from Israel to Colombia of a KPC-3-producing *Klebsiella pneumoniae* strain. *Clin Microbiol Infect* 2011;17:52–56.
99. Naas T, Nordmann P, Vedel G, Poyart C. Plasmid-mediated carbapenem-hydrolyzing β -lactamase KPC in a *Klebsiella pneumoniae* isolate from France. *Antimicrob Agents Chemother* 2005;49:4423–4424.
100. Samuelsen O, Naseer U, Tofteland S, Skutlaberg DH, Onken A *et al*. Emergence of clonally related *Klebsiella pneumoniae* isolates of sequence type 258 producing plasmid-mediated KPC carbapenemase in Norway and Sweden. *J Antimicrob Chemother* 2009;63:654–658.
101. Wendt C, Schütt S, Dalpke AH, Konrad M, Mieth M *et al*. First outbreak of *Klebsiella pneumoniae* carbapenemase (KPC)-producing *K. pneumoniae* in Germany. *Eur J Clin Microbiol Infect Dis* 2010;29:563–570.
102. Kanerva M, Skogberg K, Ryyänänen K, Pahkamäki A, Jalava J *et al*. Coincidental detection of the first outbreak of carbapenemase-producing *Klebsiella pneumoniae* colonisation in a primary care hospital, Finland, 2013. *Euro Surveill* 2015;20:21172.
103. Kwong JC, Lane CR, Romanes F, Gonçalves da Silva A, Easton M *et al*. Translating genomics into practice for real-time surveillance and response to carbapenemase-producing *Enterobacteriaceae*: evidence from a complex multi-institutional KPC outbreak. *PeerJ* 2018;6:e4210.
104. Chen S, Hu F, Xu X, Liu Y, Wu W *et al*. High prevalence of KPC-2-type carbapenemase coupled with CTX-M-type extended-spectrum β -lactamases in carbapenem-resistant *Klebsiella pneumoniae* in a teaching hospital in China. *Antimicrob Agents Chemother* 2011;55:2493–2494.
105. Munoz-Price LS, Poirel L, Bonomo RA, Schwaber MJ, Daikos GL *et al*. Clinical epidemiology of the global expansion of *Klebsiella pneumoniae* carbapenemases. *Lancet Infect Dis* 2013;13:785–796.
106. Qi Y, Wei Z, Ji S, Du X, Shen P *et al*. ST11, the dominant clone of KPC-producing *Klebsiella pneumoniae* in China. *J Antimicrob Chemother* 2011;66:307–312.
107. Stoesser N, Sheppard AE, Peirano G, Anson LW, Pankhurst L *et al*. Genomic epidemiology of global *Klebsiella pneumoniae* carbapenemase (KPC)-producing *Escherichia coli*. *Sci Rep* 2017;7:5917.
108. Cuzon G, Naas T, Nordmann P. Functional characterization of Tn4401, a Tn3-based transposon involved in bla_{KPC} gene mobilization. *Antimicrob Agents Chemother* 2011;55:5370–5373.
109. Naas T, Cuzon G, Villegas MV, Lartigue MF, Quinn JP *et al*. Genetic structures at the origin of acquisition of the β -lactamase bla_{KPC} gene. *Antimicrob Agents Chemother* 2008;52:1257–1263.
110. Chen L, Chavda KD, Al Laham N, Melano RG, Jacobs MR *et al*. Complete nucleotide sequence of a bla_{KPC}-harboring IncI2 plasmid and its dissemination in New Jersey and New York hospitals. *Antimicrob Agents Chemother* 2013;57:5019–5025.
111. Chmelnitsky I, Shklyar M, Leavitt A, Sadovsky E, Navon-Venezia S *et al*. Mix and match of KPC-2 encoding plasmids in *Enterobacteriaceae*-comparative genomics. *Diagn Microbiol Infect Dis* 2014;79:255–260.
112. Andrade LN, Curiao T, Ferreira JC, Longo JM, Clímaco EC *et al*. Dissemination of bla_{KPC-2} by the spread of *Klebsiella pneumoniae* clonal complex 258 clones (ST258, ST11, ST437) and plasmids (IncFII, IncN, IncL/M) among *Enterobacteriaceae* species in Brazil. *Antimicrob Agents Chemother* 2011;55:3579–3583.
113. Ho PL, Cheung YY, Lo WU, Li Z, Chow KH *et al*. Molecular characterization of an atypical IncX3 plasmid pKPC-NY79 carrying

- blaKPC-2* in a *Klebsiella pneumoniae*. *Curr Microbiol* 2013;67:493–498.
114. Cerqueira GC, Earl AM, Ernst CM, Grad YH, Dekker JP *et al*. Multi-institute analysis of carbapenem resistance reveals remarkable diversity, unexplained mechanisms, and limited clonal outbreaks. *Proc Natl Acad Sci USA* 2017;114:1135–1140.
 115. Esteban-Cantos A, Aracil B, Bautista V, Ortega A, Lara N *et al*. The carbapenemase-producing *Klebsiella pneumoniae* population is distinct and more clonal than the carbapenem-susceptible population. *Antimicrob Agents Chemother* 2017;61:e02520-16.
 116. Gomez SA, Pasteran FG, Faccione D, Tijet N, Rapoport M *et al*. Clonal dissemination of *Klebsiella pneumoniae* ST258 harbouring KPC-2 in Argentina. *Clin Microbiol Infect* 2011;17:1520–1524.
 117. Weterings V, Zhou K, Rossen JW, van Stenis D, Thewessen E *et al*. An outbreak of colistin-resistant *Klebsiella pneumoniae* carbapenemase-producing *Klebsiella pneumoniae* in the Netherlands (July to December 2013), with inter-institutional spread. *Eur J Clin Microbiol Infect Dis* 2015;34:1647–1655.
 118. Sheppard AE, Stoesser N, Wilson DJ, Sebra R, Kasarskis A *et al*. Nested russian doll-like genetic mobility drives rapid dissemination of the carbapenem resistance gene *blaKPC*. *Antimicrob Agents Chemother* 2016;60:3767–3778.
 119. Kanamori HPC, Juliano JJ, van Duin D, Cairns BA, Weber DJ *et al*. A prolonged outbreak of KPC-3-producing *Enterobacter cloacae* and *Klebsiella pneumoniae* driven by multiple mechanisms of resistance transmission at a large academic burn center. *Antimicrob Agents Chemother* 2016;61:e01516-16.
 120. Mathers AJ, Stoesser N, Sheppard AE, Pankhurst L, Giess A *et al*. *Klebsiella pneumoniae* carbapenemase (KPC)-producing *K. pneumoniae* at a single institution: insights into endemicity from whole-genome sequencing. *Antimicrob Agents Chemother* 2015;59:1656–1663.
 121. Zong Z, Yu F, Connor C, Fenn S, McNally A. Complete genomic characterisation of two *Escherichia coli* lineages responsible for a cluster of carbapenem resistant infections in a Chinese hospital. *bioRxiv* 2018.
 122. Pl H, Cheung YY, Wang Y, Wu L, Lai EL *et al*. Characterization of carbapenem-resistant *Escherichia coli* and *Klebsiella pneumoniae* from a healthcare region in Hong Kong. *European J Clin Microbiol Infect Dis* 2016;35:379–385.
 123. Chavda KD, Chen L, Jacobs MR, Bonomo RA, Kreiswirth BN. Molecular diversity and plasmid analysis of KPC-producing *Escherichia coli*. *Antimicrob Agents Chemother* 2016;60:4073–4081.
 124. Kazmierczak KM, Rabine S, Hackel M, McLaughlin RE, Biedenbach DJ *et al*. Multiyear, multinational survey of the incidence and global distribution of metallo- β -lactamase-producing *Enterobacteriaceae* and *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother* 2016;60:1067–1078.
 125. Bathoorn E, Rossen JW, Lokate M, Friedrich AW, Hammerum AM. Isolation of an NDM-5-producing ST16 *Klebsiella pneumoniae* from a Dutch patient without travel history abroad, August 2015. *Euro Surveill* 2015;20:30040.
 126. Huang TW, Wang JT, Lauderdale TL, Liao TL, Lai JF *et al*. Complete sequences of two plasmids in a *bla*_{NDM-1}-positive *Klebsiella oxytoca* isolate from Taiwan. *Antimicrob Agents Chemother* 2013;57:4072–4076.
 127. Stoesser N, Giess A, Batty EM, Sheppard AE, Walker AS *et al*. Genome sequencing of an extended series of NDM-producing *Klebsiella pneumoniae* isolates from neonatal infections in a Nepali hospital characterizes the extent of community- versus hospital-associated transmission in an endemic setting. *Antimicrob Agents Chemother* 2014;58:7347–7357.
 128. Wailan AM, Paterson DL, Kennedy K, Ingram PR, Bursle E *et al*. Genomic characteristics of NDM-producing *Enterobacteriaceae* isolates in Australia and their *bla*_{NDM} genetic contexts. *Antimicrob Agents Chemother* 2016;60:136–141.
 129. Yong D, Toleman MA, Giske CG, Cho HS, Sundman K *et al*. Characterization of a new metallo- β -lactamase gene, *bla*_{NDM-1}, and a novel erythromycin esterase gene carried on a unique genetic structure in *Klebsiella pneumoniae* sequence type 14 from India. *Antimicrob Agents Chemother* 2009;60:5046–5054.
 130. Chihara S, Okuzumi K, Yamamoto Y, Oikawa S, Hishinuma A. First case of New Delhi metallo- β -lactamase 1-producing *Escherichia coli* infection in Japan. *Clin Infect Dis* 2011;52:153–154.
 131. Gaibani P, Ambretti S, Berlinger A, Cordovana M, Farruggia P *et al*. Outbreak of NDM-1-producing *Enterobacteriaceae* in northern Italy, July to August 2011. *Euro Surveill* 2011;16:20027.
 132. McDermott H, Morris D, McArdle E, O'Mahony G, Kelly S *et al*. Isolation of NDM-1-producing *Klebsiella pneumoniae* in Ireland, July 2011. *Euro Surveill* 2012;17:20087.
 133. Nielsen JB, Hansen F, Littauer P, Schonning K, Hammerum AM. An NDM-1-producing *Escherichia coli* obtained in Denmark has a genetic profile similar to an NDM-1-producing *E. coli* isolate from the UK. *J Antimicrob Chemother* 2012;67:2049–2051.
 134. Osterblad M, Kirveskari J, Hakanen AJ, Tissari P, Vaara M *et al*. Carbapenemase-producing *Enterobacteriaceae* in Finland: the first years (2008–11). *J Antimicrob Chemother* 2012;67:2860–2864.
 135. Oteo J, Domingo-Garcia D, Fernandez-Romero S, Saez D, Guiu A *et al*. Abdominal abscess due to NDM-1-producing *Klebsiella pneumoniae* in Spain. *J Med Microbiol* 2012;61:864–867.
 136. Peirano G, Ahmed-Bentley J, Woodford N, Pitout JD. New Delhi metallo- β -lactamase from traveler returning to Canada. *Emerg Infect Dis* 2011;17:242–244.
 137. Pfeifer Y, Witte W, Holfelder M, Busch J, Nordmann P *et al*. NDM-1-producing *Escherichia coli* in Germany. *Antimicrob Agents Chemother* 2011;55:1318–1319.
 138. Poirel L, Lagrutta E, Taylor P, Pham J, Nordmann P. Emergence of metallo- β -lactamase NDM-1-producing multidrug-resistant *Escherichia coli* in Australia. *Antimicrob Agents Chemother* 2010;54:4914–4916.
 139. Samuelsen Ø, Thilesen CM, Heggelund L, Vada AN, Kümme A *et al*. Identification of NDM-1-producing *Enterobacteriaceae* in Norway. *J Antimicrob Chemother* 2011;66:670–672.
 140. Tijet N, Alexander DC, Richardson D, Lastovetska O, Low DE *et al*. New Delhi metallo-beta-lactamase, Ontario, Canada. *Emerg Infect Dis* 2011;17:306–307.
 141. Williamson DA, Sidjabat HE, Freeman JT, Roberts SA, Silvey A *et al*. Identification and molecular characterisation of New Delhi metallo- β -lactamase-1 (NDM-1)- and NDM-6-producing *Enterobacteriaceae* from New Zealand hospitals. *Int J Antimicrob Agents* 2012;39:529–533.
 142. Wu HS, Chen T-L, Chen IC-J, Huang M-S, Wang F-D *et al*. First identification of a patient colonized with *Klebsiella pneumoniae* carrying *bla*_{NDM-1} in Taiwan. *J Chin Med Assoc* 2010;73:596–598.
 143. Zarfel G, Hoenigl M, Leitner E, Salzer HJ, Feierl G *et al*. Emergence of New Delhi metallo- β -lactamase, Austria. *Emerg Infect Dis* 2011;17:129–130.
 144. Kumarasamy KK, Toleman MA, Walsh TR, Bagaria J, Butt F *et al*. Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. *Lancet Infect Dis* 2010;10:597–602.
 145. 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;11:355–362.
 146. Dortet L, Poirel L, Nordmann P. Worldwide dissemination of the NDM-type carbapenemases in Gram-negative bacteria. *Biomed Res Int* 2014;2014:249856.
 147. Albiger B, Glasner C, Struelens MJ, Grundmann H, Monnet DL *et al*. Carbapenemase-producing *Enterobacteriaceae* in Europe: assessment by national experts from 38 countries, May 2015. *Euro Surveill* 2015;20:30062.

148. Phan HTT, Stoesser N, Maciucă IE, Toma F, Szekely E *et al.* Illumina short-read and MinION long-read WGS to characterize the molecular epidemiology of an NDM-1 *Serratia marcescens* outbreak in Romania. *J Antimicrob Chemother* 2018;73:672–679.
149. Bosch T, Lutgens SPM, Hermans MHA, Wever PC, Schneeberger PM *et al.* Outbreak of NDM-1-producing *Klebsiella pneumoniae* in a Dutch hospital, with interspecies transfer of the resistance plasmid and unexpected occurrence in unrelated health care centers. *J Clin Microbiol* 2017;55:2380–2390.
150. Nordmann P, Poirel L. The difficult-to-control spread of carbapenemase producers among *Enterobacteriaceae* worldwide. *Clin Microbiol Infect* 2014;20:821–830.
151. Sekizuka T, Matsui M, Yamane K, Takeuchi F, Ohnishi M *et al.* Complete sequencing of the *bla*_{NDM-1}-positive IncA/C plasmid from *Escherichia coli* ST38 isolate suggests a possible origin from plant pathogens. *PLoS One* 2011;6:e25334.
152. Villa L, Poirel L, Nordmann P, Carta C, Carattoli A. Complete sequencing of an IncH plasmid carrying the *bla*_{NDM-1}, *bla*_{CTX-M-15} and *qnrB1* genes. *J Antimicrob Chemother* 2012;67:1645–1650.
153. Wailan AM, Sartor AL, Zowawi HM, Perry JD, Paterson DL *et al.* Genetic contexts of *bla*_{NDM-1} in patients carrying multiple NDM-producing strains. *Antimicrob Agents Chemother* 2015;59:7405–7410.
154. Giske CG, Fröding I, Hasan CM, Turlej-Rogacka A, Toleman M *et al.* Diverse sequence types of *Klebsiella pneumoniae* contribute to the dissemination of *bla*_{NDM-1} in India, Sweden, and the United Kingdom. *Antimicrob Agents Chemother* 2012;56:2735–2738.
155. Khong WX, Xia E, Marimuthu K, Xu W, Teo YY *et al.* Local transmission and global dissemination of New Delhi metallo- β -lactamase (NDM): a whole genome analysis. *BMC Genomics* 2016;17:452.
156. Wailan AM, Sidjabat HE, Yam WK, Alikhan NF, Petty NK *et al.* Mechanisms involved in acquisition of *bla*_{NDM} genes by IncA/C2 and IncFIIY plasmids. *Antimicrob Agents Chemother* 2016;60:4082–4088.
157. Toleman MA, Spencer J, Jones L, Walsh TR. *bla*_{NDM-1} is a chimera likely constructed in *Acinetobacter baumannii*. *Antimicrob Agents Chemother* 2012;56:2773–2776.
158. Lauretti L, Riccio M, Mazzariol A, Cornaglia G, Amicosante G *et al.* Cloning and characterization of *bla*_{VIM}, a new integron-borne metallo- β -lactamase gene from a *Pseudomonas aeruginosa* clinical isolate. *Antimicrob Agents Chemother* 1999;43:1584–1590.
159. Matsumura Y, Peirano G, Devinney R, Bradford PA, Motyl MR *et al.* Genomic epidemiology of global VIM-producing *Enterobacteriaceae*. *J Antimicrob Chemother* 2017;72:2249–2258.
160. Esposito EP, Gaiarsa S, Del Franco M, Crivaro V, Bernardo M *et al.* A novel IncA/C1 group conjugative plasmid, encoding VIM-1 metallo- β -lactamase, mediates the acquisition of carbapenem resistance in ST104 *Klebsiella pneumoniae* isolates from neonates in the intensive care unit of V. Monaldi Hospital in Naples. *Front Microbiol* 2017;8:2135.
161. Papagiannitsis CC, Izdebski R, Baraniak A, Fiett J, Herda M *et al.* Survey of metallo- β -lactamase-producing *Enterobacteriaceae* colonizing patients in European ICUs and rehabilitation units, 2008–11. *J Antimicrob Chemother* 2015;70:1981–1988.
162. Ito H, Arakawa Y, Ohsuka S, Wacharotayankun R, Kato N *et al.* Plasmid-mediated dissemination of the metallo- β -lactamase gene *bla*_{IMP} among clinically isolated strains of *Serratia marcescens*. *Antimicrob Agents Chemother* 1995;39:824–829.
163. Sidjabat HE, Townell N, Nimmo GR, George NM, Robson J *et al.* Dominance of IMP-4-producing *Enterobacter cloacae* among carbapenemase-producing *Enterobacteriaceae* in Australia. *Antimicrob Agents Chemother* 2015;59:4059–4066.
164. Matsumura Y, Peirano G, Motyl MR, Adams MD, Chen L *et al.* Global molecular epidemiology of IMP-producing *Enterobacteriaceae*. *Antimicrob Agents Chemother* 2017;61:e02729-16.
165. Yamazaki Y, Funaki T, Yasuhara T, Sugano E, Ugajin K *et al.* Molecular characteristics of a carbapenemase-producing *Enterobacter* species and *Klebsiella* species outbreak in a Japanese University Hospital. *Showa Univer J Med Sciences* 2017;29:163–172.
166. Yamamoto N, Asada R, Kawahara R, Hagiya H, Akeda Y *et al.* Prevalence of, and risk factors for, carriage of carbapenem-resistant *Enterobacteriaceae* among hospitalized patients in Japan. *J Hosp Infect* 2017;97:212–217.
167. Peleg AY, Franklin C, Bell JM, Spelman DW. Dissemination of the metallo- β -lactamase gene *bla*_{IMP-4} among Gram-negative pathogens in a clinical setting in Australia. *Clin Infect Dis* 2005;2005:1549–1556.
168. Sidjabat HE, Robson J, Paterson DL. Draft genome sequences of two IMP-4-producing *Escherichia coli* sequence type 131 isolates in Australia. *Genome Announc* 2015;3:e00983-15.
169. Stoesser N, Sheppard AE, Peirano G, Sebra RP, Lynch T *et al.* First report of *bla*_{IMP-14} on a plasmid harboring multiple drug resistance genes in *Escherichia coli* sequence type 131. *Antimicrob Agents Chemother* 2016;60:5068–5071.
170. Aktas Z, Kayacan CB, Schneider I, Can B, Midilli K *et al.* Carbapenem-hydrolyzing oxacillinase, OXA-48, persists in *Klebsiella pneumoniae* in Istanbul, Turkey. *Chemotherapy* 2008;54:101–106.
171. Carrèr A, Poirel L, Eraksoy H, Gagatay AA, Badur S *et al.* Spread of OXA-48-positive carbapenem-resistant *Klebsiella pneumoniae* isolates in Istanbul, Turkey. *Antimicrob Agents Chemother* 2008;52:2950–2954.
172. Poirel L, Héritier C, Tolün V, Nordmann P. Emergence of oxacillinase-mediated resistance to imipenem in *Klebsiella pneumoniae*. *Antimicrob Agents Chemother* 2004;48:15–22.
173. Mataseje LF, Boyd DA, Fuller J, Haldane D, Hoang L *et al.* Characterization of OXA-48-like carbapenemase producers in Canada, 2011–14. *J Antimicrob Chemother* 2018;73:626–633.
174. Potron A, Poirel L, Rondinaud E, Nordmann P. Intercontinental spread of OXA-48 β -lactamase-producing *Enterobacteriaceae* over a 11-year period, 2001 to 2011. *Euro Surveill* 2013;18:20549.
175. Potron A, Kalpoe J, Poirel L, Nordmann P. European dissemination of a single OXA-48-producing *Klebsiella pneumoniae* clone. *Clin Microbiol Infect* 2011;17:E24–E26.
176. Kilic A, Aktas Z, Bedir O, Gumral R, Bulut Y *et al.* Identification and characterization of OXA-48 producing, carbapenem-resistant *Enterobacteriaceae* isolates in Turkey. *Ann Clin Lab Sci* 2011;41:161–166.
177. Moubareck CA, Mouftah SF, Pál T, Ghazawi A, Halat DH *et al.* Clonal emergence of *Klebsiella pneumoniae* ST14 co-producing OXA-48-type and NDM carbapenemases with high rate of colistin resistance in Dubai, United Arab Emirates. *Int J Antimicrob Agents* 2018;52:90–95.
178. Solgi H, Giske CG, Badmasti F, Aghamohammad S, Havaei SA *et al.* Emergence of carbapenem resistant *Escherichia coli* isolates producing *bla*_{NDM} and *bla*_{OXA-48}-like carried on IncA/C and IncL/M plasmids at two Iranian university hospitals. *Infect Genet Evol* 2017;55:318–323.
179. Loucif L, Chelaghma W, Helis Y, Sebaa F, Baoune RD *et al.* First detection of OXA-48-producing *Klebsiella pneumoniae* in community-acquired urinary tract infection in Algeria. *J Glob Antimicrob Resist* 2018;12:115–116.
180. Jhang J, Wang HY, Yoo G, Hwang GY, Uh Y *et al.* NDM-5 and OXA-48 co-producing uropathogenic *Escherichia coli* isolate: first case in Korea. *Ann Lab Med* 2018;38:277–279.
181. Poirel L, Héritier C, Nordmann P. Chromosome-encoded ambler class D β -lactamase of *Shewanella oneidensis* as a progenitor of carbapenem-hydrolyzing oxacillinase. *Antimicrob Agents Chemother* 2004;48:348–351.
182. Lyman M, Walter M, Lonsway D, Rasheed K, Limbago B *et al.* Notes from the field: carbapenem-resistant *Enterobacteriaceae*

- producing OXA-48-like carbapenemases – United States, 2010–2015. *MMWR* 2015;64:1315–1316.
183. Poirel L, Potron A, Nordmann P. OXA-48-like carbapenemases: the phantom menace. *J Antimicrob Chemother* 2012;67:1597–1606.
 184. Aubert D, Naas T, Héritier C, Poirel L, Nordmann P. Functional characterization of IS1999, an IS4 family element involved in mobilization and expression of β -lactam resistance genes. *J Bacteriol* 2006;188:6506–6514.
 185. Poirel L, Bonnin RA, Nordmann P. Genetic features of the wide-spread plasmid coding for the carbapenemase OXA-48. *Antimicrob Agents Chemother* 2012;56:559–562.
 186. Giani T, Conte V, di Pilato V, Aschbacher R, Weber C *et al.* *Escherichia coli* from Italy producing OXA-48 carbapenemase encoded by a novel Tn1999 transposon derivative. *Antimicrob Agents Chemother* 2012;56:2211–2213.
 187. Potron A, Nordmann P, Rondinaud E, Jauregui F, Poirel L. A mosaic transposon encoding OXA-48 and CTX-M-15: towards pan-resistance. *J Antimicrob Chemother* 2013;68:476–477.
 188. Findlay J, Hopkins KL, Loy R, Doumith M, Meunier D *et al.* OXA-48-like carbapenemases in the UK: an analysis of isolates and cases from 2007 to 2014. *J Antimicrob Chemother* 2017;72:1340–1349.
 189. Gaibani P, Scaltriti E, Benni C, Pongolini S, Ambretti S *et al.* Characterization of an IncL/M plasmid carrying *bla*_{OXA-48} in a *Klebsiella pneumoniae* strain from Italy. *New Microbiologica* 2017;40:284–285.
 190. Izdebski R, Baraniak A, Zabicka D, Machulska M, Urbanowicz P *et al.* *Enterobacteriaceae* producing OXA-48-like carbapenemases in Poland, 2013–January 2017. *J Antimicrob Chemother* 2018;73:620–625.
 191. Lutgring JD, Zhu W, de Man TJB, Avillan JJ, Anderson KF *et al.* Phenotypic and genotypic characterization of *Enterobacteriaceae* producing oxacillinase-48-like carbapenemases, United States. *Emerg Infect Dis* 2018;24:700–709.
 192. Skalova A, Chudejova K, Rotova V, Medvecký M, Studentova V *et al.* Molecular characterization of OXA-48-like-producing *Enterobacteriaceae* in the Czech Republic and evidence for horizontal transfer of pOXA-48-like plasmids. *Antimicrob Agents Chemother* 2016;61: e01889-16.
 193. Yu F, Wang S, Lv J, Qi X, Guo Y *et al.* Coexistence of OXA-48-producing *Klebsiella pneumoniae* and *Escherichia coli* in a hospitalized patient who returned from Europe to China. *Antimicrob Agents Chemother* 2017;61: e02580-16.
 194. Balkan I, Aygün G, Aydin S, Mutcalı S, Kara Z *et al.* Blood stream infections due to OXA-48-like carbapenemase-producing *Enterobacteriaceae*: treatment and survival. *Int J Infect Dis* 2014; 26:51–56.
 195. Castanheira M, Deshpande LM, Mathai D, Bell JM, Jones RN *et al.* Early dissemination of NDM-1- and OXA-181-producing *Enterobacteriaceae* in Indian hospitals: report from the SENTRY antimicrobial surveillance program, 2006–2007. *Antimicrob Agents Chemother* 2011;55:1274–1278.
 196. Decousser JW, Poirel L, Desroches M, Jayol A, Denamur E *et al.* Failure to detect carbapenem-resistant *Escherichia coli* producing OXA-48-like using the Xpert Carba-R assay[®]. *Clin Microbiol Infect* 2015;21: e9–e10.
 197. Kalpoe JS, Al Naiemi N, Poirel L, Nordmann P. Detection of an Ambler class D OXA-48-type β -lactamase in a *Klebsiella pneumoniae* strain in The Netherlands. *J Med Microbiol* 2011;60:677–678.
 198. Potron A, Nordmann P, Lafeuille E, Al Maskari Z, Al Rashdi F *et al.* Characterization of OXA-181, a carbapenem-hydrolyzing class D β -lactamase from *Klebsiella pneumoniae*. *Antimicrob Agents Chemother* 2011;55:4896–4899.
 199. Williamson DA, Heffernan H, Sidjabat H, Roberts SA, Paterson DL *et al.* Intercontinental transfer of OXA-181-producing *Klebsiella pneumoniae* into New Zealand. *J Antimicrob Chemother* 2011;66:2888–2890.
 200. Cho SY, Huh HJ, Baek JY, Chung NY, Ryu JG *et al.* *Klebsiella pneumoniae* co-producing NDM-5 and OXA-181 carbapenemases, South Korea. *Emerg Infect Dis* 2015;21:1088–1089.
 201. Gamal D, Fernández-Martínez M, El-Defrawy I, Ocampo-Sosa AA, Martínez-Martínez L. First identification of NDM-5 associated with OXA-181 in *Escherichia coli* from Egypt. *Emerg Microbes Infect* 2016;5: e30.
 202. Overballe-Petersen S, Roer L, Ng K, Hansen F, Justesen US *et al.* Complete nucleotide sequence of an *Escherichia coli* sequence type 410 strain carrying *bla*_{NDM-5} on an IncF multidrug resistance plasmid and *bla*_{OXA-181} on an IncX3 Plasmid. *Genome Announc* 2018;6: e01542-17.
 203. Adriaenssens N, Coenen S, Versporten A, Muller A, Minalu G *et al.* European surveillance of antimicrobial consumption (ESAC): outpatient antibiotic use in Europe (1997–2009). *J Antimicrob Chemother* 2011;66: vi3–vi12.
 204. Arcilla MS, van Hattem JM, Haverkate MR, Bootsma MCJ, van Genderen PJJ *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.
 205. Bengtsson-Palme J, Angelin M, Huss M, Kjellqvist S, Kristiansson E *et al.* The human gut microbiome as a transporter of antibiotic resistance genes between continents. *Antimicrob Agents Chemother* 2015;59:6551–6560.
 206. Lübbert C, Straube L, Stein C, Makarewicz O, Schubert S *et al.* Colonization with extended-spectrum β -lactamase-producing and carbapenemase-producing *Enterobacteriaceae* in international travelers returning to Germany. *Int J Med Microbiol* 2015; 305:148–156.
 207. Ruppé E, Armand-Lefèvre L, Estellat C, Consigny PH, El Mniai A *et al.* High rate of acquisition but short duration of carriage of multidrug-resistant *Enterobacteriaceae* after travel to the tropics. *Clin Infect Dis* 2015;61:593–600.
 208. von Wintersdorff CJ, Penders J, Stobberingh EE, Oude Lashof AM, Hoebe CJ *et al.* High rates of antimicrobial drug resistance gene acquisition after international travel, The Netherlands. *Emerg Infect Dis* 2014;20:649–657.
 209. Liu YY, Wang Y, Walsh TR, Yi LX, Zhang R *et al.* Emergence of plasmid-mediated colistin resistance mechanism *MCR-1* in animals and human beings in China: a microbiological and molecular biological study. *Lancet Infect Dis* 2016;16:161–168.
 210. European Centre for Disease Prevention and Control. *Summary of the Latest Data on Antibiotic Consumption in the European Union*. Stockholm: European Centre for Disease Prevention and Control; 2017.
 211. Zheng B, Dong H, Xu H, Lv J, Zhang J *et al.* Coexistence of *MCR-1* and NDM-1 in clinical *Escherichia coli* isolates. *Clin Infect Dis* 2016;63:1393–1395.
 212. Newton-Foot M, Snyman Y, Maloba MRB, Whitelaw AC. Plasmid-mediated *mcr-1* colistin resistance in *Escherichia coli* and *Klebsiella* spp. clinical isolates from the Western Cape region of South Africa. *Antimicrob Resist Infect Control* 2017;6:78.
 213. Tian G-B, Doi Y, Shen J, Walsh TR, Wang Y *et al.* *MCR-1*-producing *Klebsiella pneumoniae* outbreak in China. *Lancet Infect Dis* 2017;17:577.
 214. Li A, Yang Y, Miao M, Chavda KD, Mediavilla JR *et al.* Complete sequences of *mcr-1*-harboring plasmids from extended-spectrum- β -lactamase- and carbapenemase-producing *Enterobacteriaceae*. *Antimicrob Agents Chemother* 2016;60:4351–4354.
 215. Skov RL, Monnet DL. Plasmid-mediated colistin resistance (*mcr-1* gene): three months later, the story unfolds. *Euro Surveill* 2016;21:30155.
 216. Schwarz S, Johnson AP. Transferable resistance to colistin: a new but old threat. *J Antimicrob Chemother* 2016;71:2066–2070.

217. Snesrud E, He S, Chandler M, Dekker JP, Hickman AB *et al*. A model for transposition of the colistin resistance gene *mcr-1* by IS*Apl1*. *Antimicrob Agents Chemother* 2016;60:6973–6976.
218. Poirel L, Kieffer N, Nordmann P. *In vitro* study of IS*Apl1*-mediated mobilization of the colistin resistance gene *mcr-1*. *Antimicrob Agents Chemother* 2017;61:e00127–17.
219. Snesrud E, McGann P, Chandler M. The birth and demise of the IS*Apl1-mcr-1*-IS*Apl1* composite transposon: the vehicle for transferable colistin resistance. *MBio* 2018;9:e02381–17.
220. Beyrouthy R, Robin F, Lessene A, Lacombat I, Dortet L *et al*. MCR-1 and OXA-48 *in vivo* acquisition in KPC-producing *Escherichia coli* after colistin treatment. *Antimicrob Agents Chemother* 2017;61:e02540–16.
221. McGann P, Snesrud E, Maybank R, Corey B, Ong AC *et al*. *Escherichia coli* harboring *mcr-1* and *bla*_{CTX-M} on a novel IncF plasmid: first report of *mcr-1* in the United States. *Antimicrob Agents Chemother* 2016;60:4420–4421.
222. Mediavilla JR, Patrawalla A, Chen L, Chavda KD, Mathema B *et al*. Colistin- and carbapenem-resistant *Escherichia coli* harboring *mcr-1* and *bla*_{NDM-5}, causing a complicated urinary tract infection in a patient from the United States. *MBio* 2016;7:e01191–16.
223. Wang Y, Tian GB, Zhang R, Shen Y, Tyrrell JM *et al*. Prevalence, risk factors, outcomes, and molecular epidemiology of *mcr-1*-positive *Enterobacteriaceae* in patients and healthy adults from China: an epidemiological and clinical study. *Lancet Infect Dis* 2017;17:390–399.
224. Yao X, Doi Y, Zeng L, Lv L, Liu JH. Carbapenem-resistant and colistin-resistant *Escherichia coli* co-producing NDM-9 and MCR-1. *Lancet Infect Dis* 2016;16:288–289.
225. Shen Z, Wang Y, Shen Y, Shen J, Wu C. Early emergence of *mcr-1* in *Escherichia coli* from food-producing animals. *Lancet Infect Dis* 2016;16:293.
226. Malhotra-Kumar S, Xavier BB, Das AJ, Lammens C, Hoang HT *et al*. Colistin-resistant *Escherichia coli* harbouring *mcr-1* isolated from food animals in Hanoi, Vietnam. *Lancet Infect Dis* 2016;16:286–287.
227. Wang R, van Dorp L, Shaw LP, Bradley P, Wang Q *et al*. The global distribution and spread of the mobilized colistin resistance gene *mcr-1*. *Nat Commun* 2018;9:1179.
228. European Medicines Agency. *European Surveillance of Veterinary Antimicrobial Consumption – Sales of Veterinary Antimicrobial Agents in 30 European Countries in 2015*. London: European Medicines Agency; 2017.
229. Walsh TR, Wu Y. China bans colistin as a feed additive for animals. *Lancet Infect Dis* 2016;16:1102–1103.
230. World Health Organization. United Nations meeting on antimicrobial resistance. *Bull World Health Organ* 2016;94:638–639.
231. United Nations General Assembly. *Political Declaration of the High-level Meeting of the General Assembly on Antimicrobial Resistance*. New York: United Nations; 2016.
232. Australian Government DoH, Department of Agriculture. *Responding to the Threat of Antimicrobial Resistance*. Canberra: Australian Government; 2015.
233. European Commission. *A European One Health Action Plan Against Antimicrobial Resistance (AMR)*. Brussels: European Commission; 2017.
234. UK Department of Health. *UK Five Year Antimicrobial Resistance Strategy 2013–2018*. London: UK Department of Health; 2013.
235. The White House. *National Strategy for Combating Antibiotic-Resistant Bacteria*. Washington, DC: The White House; 2014.
236. Giacobbe DR, Del Bono V, Mikulska M, Gustinetti G, Marchese A *et al*. Impact of a mixed educational and semi-restrictive antimicrobial stewardship project in a large teaching hospital in Northern Italy. *Infection* 2017;45:849–856.
237. Molina J, Peñalva G, Gil-Navarro MV, Praena J, Lepe JA *et al*. Long-term impact of an educational antimicrobial stewardship program on hospital-acquired candidemia and multidrug-resistant bloodstream infections: a quasi-experimental study of interrupted time-series analysis. *Clin Infect Dis* 2017;65:1992–1999.
238. Pulcini C, Binda F, Lamkang AS, Trett A, Charani E *et al*. Developing core elements and checklist items for global hospital antimicrobial stewardship programmes: a consensus approach. *Clin Microbiol Infect* 2018.
239. Robinson TP, Bu DP, Carrique-Mas J, Fèvre EM, Gilbert M *et al*. Antibiotic resistance is the quintessential One Health issue. *Trans R Soc Trop Med Hyg* 2016;110:377–380.
240. World Health Organization, Food and Agriculture Organization of the United Nations, World Organization for Animal Health. *Antimicrobial Resistance – A Manual for Developing National Action Plans*. Geneva: World Health Organization; 2016.
241. Pouwels KB, Dolk FCK, Smith DRM, Robotham JV, Smieszek T. Actual versus 'ideal' antibiotic prescribing for common conditions in English primary care. *J Antimicrob Chemother* 2018; 73:19–26.
242. Fleming-Dutra KE, Hersh AL, Shapiro DJ, Bartoces M, Enns EA *et al*. Prevalence of inappropriate antibiotic prescriptions among US ambulatory care visits, 2010–2011. *JAMA* 2016;315:1864–1873.
243. Bin Abdulhak AA, Altannir MA, Almansor MA, Almohaya MS, Onazi AS *et al*. Non prescribed sale of antibiotics in Riyadh, Saudi Arabia: a cross sectional study. *BMC Public Health* 2011; 11:538.
244. Kalungia AC, Burger J, Godman B, Costa JO, Simuwelu C. Non-prescription sale and dispensing of antibiotics in community pharmacies in Zambia. *Expert Rev Anti Infect Ther* 2016;14: 1215–1223.
245. Kotwani A, Wattal C, Joshi PC, Holloway K. Irrational use of antibiotics and role of the pharmacist: an insight from a qualitative study in New Delhi, India. *J Clin Pharm Ther* 2012;37:308–312.
246. Nga Dott, Chuc NT, Hoa NP, Hoa NQ, Nguyen NT *et al*. Antibiotic sales in rural and urban pharmacies in northern Vietnam: an observational study. *BMC Pharmacol Toxicol* 2014;15:6.
247. European Centre for Disease Prevention and Control. ECDC/EFSA/EMA second joint report on the integrated analysis of the consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals. *EFSA J* 2017;15:4872.
248. van Boeckel TP, Brower C, Gilbert M, Grenfell BT, Levin SA *et al*. Global trends in antimicrobial use in food animals. *Proc Natl Acad Sci USA* 2015;112:5649–5654.
249. US Food and Drug Administration. *2016 Summary Report on Antimicrobials Sold or Distributed of Use in Food-producing Animals*. Silver Spring, MD: US Food and Drug Administration; 2017.
250. Mataseje LF, Boyd DA, Delport J, Hoang L, Imperial M *et al*. *Serratia marcescens* harbouring SME-type class A carbapenemases in Canada and the presence of *bla*_{SME} on a novel genomic island, SmarG11-1. *J Antimicrob Chemother* 2014;69:1825–1829.
251. Hopkins KL, Findlay J, Doumith M, Mather B, Meunier D *et al*. IMI-2 carbapenemase in a clinical *Klebsiella variicola* isolated in the UK. *J Antimicrob Chemother* 2017;72:2129–2131.
252. Rojo-Bezares B, Martín C, López M, Torres C, Sáenz Y. First detection of *bla*_{IMI-2} gene in a clinical *Escherichia coli* strain. *Antimicrob Agents Chemother* 2012;56:1146–1147.
253. Rasmussen BA, Bush K, Keeney D, Yang Y, Hare R *et al*. Characterization of IMI-1 β -lactamase, a class A carbapenem-hydrolyzing enzyme from *Enterobacter cloacae*. *Antimicrob Agents Chemother* 1996;40:2080–2086.
254. Carattoli A. Plasmids and the spread of resistance. *Int J Med Microbiol* 2013;303:298–304.

255. Espedido BA, Partridge SR, Iredell JR. *bla*_{IMP-4} in different genetic contexts in *Enterobacteriaceae* isolates from Australia. *Antimicrob Agents Chemother* 2008;52:2984–2987.
256. Peleg AY, Franklin C, Bell JM, Spelman DW. Dissemination of the metallo- β -lactamase gene *bla*_{IMP-4} among gram-negative pathogens in a clinical setting in Australia. *Clin Infect Dis* 2005;41:1549–1556.
257. Tato M, Coque TM, Baquero F, Cantón R. Dispersal of carbapenemase *bla*_{VIM-1} gene associated with different Tn402 variants, mercury transposons, and conjugative plasmids in *Enterobacteriaceae* and *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother* 2010;54:320–327.
258. Loli A, Tzouvelekis LS, Tzelepi E, Carattoli A, Vatopoulos AC *et al*. Sources of diversity of carbapenem resistance levels in *Klebsiella pneumoniae* carrying *bla*_{VIM-1}. *J Antimicrob Chemother* 2006;58:669–672.
259. Luzzaro F, Docquier JD, Colinon C, Endimiani A, Lombardi G *et al*. Emergence in *Klebsiella pneumoniae* and *Enterobacter cloacae* clinical isolates of the VIM-4 metallo- β -lactamase encoded by a conjugative plasmid. *Antimicrob Agents Chemother* 2004;48:648–650.
260. Rieber H, Frontzek A, Pfeifer Y. Emergence of metallo- β -lactamase GIM-1 in a clinical isolate of *Serratia marcescens*. *Antimicrob Agents Chemother* 2012;56:4945–4947.
261. Sekiguchi J, Morita K, Kitao T, Watanabe N, Okazaki M *et al*. KHM-1, a novel plasmid-mediated metallo- β -lactamase from a *Citrobacter freundii* clinical isolate. *Antimicrob Agents Chemother* 2008;52:4194–4197.

Five reasons to publish your next article with a Microbiology Society journal

1. The Microbiology Society is a not-for-profit organization.
2. We offer fast and rigorous peer review – average time to first decision is 4–6 weeks.
3. Our journals have a global readership with subscriptions held in research institutions around the world.
4. 80% of our authors rate our submission process as 'excellent' or 'very good'.
5. Your article will be published on an interactive journal platform with advanced metrics.

Find out more and submit your article at microbiologyresearch.org.