J Antimicrob Chemother 2015; **70**: 23–40
doi:10.1093/jac/dku356 Advance Access publication 26 September 2014

Journal of Antimicrobial Chemotherapy

The spread of carbapenemase-producing bacteria in Africa: a systematic review

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Received 25 April 2014; returned 7 June 2014; revised 31 July 2014; accepted 13 August 2014

Background: Carbapenems are the last line of defence against ever more prevalent MDR Gram-negative bacteria, but their efficacy is threatened worldwide by bacteria that produce carbapenemase enzymes. The epidemiology of bacteria producing carbapenemases has been described in considerable detail in Europe, North America and Asia; however, little is known about their spread and clinical relevance in Africa.

Methods: We systematically searched in PubMed, EBSCOhost, Web of Science, Scopus, Elsevier Masson Consulte and African Journals Online, international conference proceedings, published theses and dissertations for studies reporting on carbapenemase-producing bacteria in Africa. We included articles published in English or French up to 28 February 2014. We calculated the prevalence of carbapenemase producers only including studies where the total number of isolates tested was at least 30.

Results: Eighty-three studies were included and analysed. Most studies were conducted in North Africa (74%, 61/83), followed by Southern Africa (12%, 10/83), especially South Africa (90%, 9/10), West Africa (8%, 7/83) and East Africa (6%, 6/83). Carbapenemase-producing bacteria were isolated from humans, the hospital environment and community environmental water samples, but not from animals. The prevalence of carbapenemase-producing isolates in hospital settings ranged from 2.3% to 67.7% in North Africa and from 9% to 60% in sub-Saharan Africa.

Conclusions: Carbapenemase-producing bacteria have been described in many African countries; however, their prevalence is poorly defined and has not been systematically studied. Antibiotic stewardship and surveillance systems, including molecular detection and genotyping of resistant isolates, should be implemented to monitor and reduce the spread of carbapenemase-producing bacteria.

Keywords: antibiotic resistance, Gram-negative, β-lactamase, epidemiology

Introduction

MDR bacterial infections have emerged as one of the world's greatest threats due to limited availability of treatment options.[1,2] The spread of MDR Gram-negative (MDRGN) bacteria is increasingly reported in both hospital and community settings worldwide.[2] Carbapenem antibiotics are effective against MDRGN bacilli, particularly those producing extended-spectrum β-lactamase enzymes, as well as a broad range of Gram-positive bacteria. However, their usefulness is threatened by the emergence and spread of bacteria that produce carbapenemase enzymes.[3,4] Infections caused by carbapenemase-producing bacteria are associated with mortality rates as high as 67%, depending on the type of enzyme.[5–8] Bacteria that produce carbapenemases are therefore a major public health and clinical concern, and are increasingly reported worldwide, especially within the Enterobacteriaceae family.[9–12] As reported in 2012, the prevalence of carbapenemase-producing Enterobacteriaceae in Europe is high in Greece, Italy and Turkey, and very low in Nordic countries.[13]

Based on amino acid homology, carbapenemases can be assigned to three of the four classes of β-lactamases, namely, Ambler classes A, B and D.[11,14] These three classes of carbapenemases can also be differentiated based on the hydrolytic mechanism at their active sites. Class A and D carbapenemases are referred to as serine carbapenemases because they have serine (serine dependent) at their active sites, whereas class B carbapenemases

have zinc (zinc dependent) at their active site and are referred to as metallo-β-lactamases.[11] Ambler class A carbapenemases may be plasmid encoded or chromosomal, and are partially inhibited by clavulanic acid, a β-lactamase inhibitor.[11] The KPCs are the most frequently identified class A carbapenemases.[2] Class B metallo-β-lactamases are plasmid mediated, or in some cases chromosomal, and the most common enzymes among clinical isolates in this group include VIM, IMP and NDM.[11] NDM-1-producing Enterobacteriaceae have been identified as a major concern due to their rapid spread worldwide.[15–17] The plasmids harbouring bla_{NDM-1} gene are very diverse and may carry a number of other resistance determinants.[16,17] Class B enzymes are able to hydrolyse all β-lactams except for aztreonam, a monobactam, and their hydrolytic activity is reduced or inhibited by EDTA but not by clavulanic acid.[11] Class D enzymes, also referred to as OXA type, can be subdivided into five families, namely the OXA-23, -24/40, -48 and -58 carbapenemases, which are mainly plasmid encoded, and the OXA-51 carbapenemase, which is chromosomally encoded and intrinsic in *Acinetobacter baumannii*.[18] Class D enzymes are not inhibited by clavulanic acid or EDTA.[11]

Whilst the epidemiology of carbapenemase-producing organisms has been described in considerable detail in Europe, North America and Asia,[2,13,19] relatively little is known about their spread and clinical importance in Africa. We therefore did a systematic review of carbapenemase-producing bacteria in African countries, to determine their epidemiology in Africa and to identify areas for further research.

Methods

Literature search in databases

A comprehensive literature search of PubMed, EBSCOhost, Scopus and Web of Science was conducted using relevant keywords (Table S1, available as Supplementary data at *JAC* Online). Articles published in French were searched from Elsevier Masson Consulte database using the keywords: 'carbapenemase Afrique'. In addition, in order to retrieve articles published in journals that are not indexed in the above databases, the African Journals Online database was searched using the keywords 'β-lactamase AND Africa'.

Non-database literature search

A search of proceedings from international conferences (European Congress of Clinical Microbiology and Infectious Diseases, 2012, 2013; International Conference on Prevention and Infection Control, 2013; and International Congress on Infectious Diseases, 2012), published theses and dissertations was also performed to identify relevant articles.

Study selection criteria

We included peer-reviewed articles (in English or French) reporting any data on carbapenemase-producing bacteria from African countries. The last literature search was performed on 28 February 2014. We excluded studies conducted outside African Union countries or on islands administered by European countries (British, French, Spanish and Portuguese overseas territories); and those reporting non-carbapenem-resistant isolates from Africa. In addition, reviews, editorials and studies that did not give the details of the resistance mechanism of carbapenem-resistant isolates were excluded. Furthermore, we also excluded studies that used the same carbapenemase-producing isolates from published studies for other investigations. All studies describing carbapenemase-producing bacteria isolated from humans, animals or environmental samples from Africa were included.

Data extraction and synthesis

The data extracted include: the country in which the samples were collected, year of sampling, study design, type of sample, bacterial species identified, type of carbapenemase described, setting in which sampling was conducted and age group of the participants and the references. The data were extracted by two authors (R. I. M. and M. K.) and disagreements were resolved by discussion and consensus. A third author (H. J. Z. or M. P N.) was consulted where consensus could not be achieved. The study design was determined by two authors (R. I. M. and M. K.) for studies where this was not specified. In this review, children were defined as individuals of <12 years of age. We calculated the prevalence of carbapenemase producers only including studies where the total number of isolates tested was 30 or more.

Results

Literature search

A total of 2692 articles were identified through the electronic database searches. In addition, 15 articles were identified through non-database searches (Figure 1). After duplicate removal, 1986 articles were screened based on the titles and abstracts. Of these, 1686 were excluded as not meeting the specified inclusion criteria. Finally, 300 full-text articles were reviewed, of which 83 full-text articles fulfilled the criteria for inclusion in this systematic review. The reasons for excluding full-text articles are listed in Figure 1.

Characteristics of studies included in this systematic review

Tables 1 and 2 summarize the main characteristics of the 83 studies (from 15 countries) included in this systematic review. Most of the studies were based on laboratory-based surveillance. Prior to 2010, only seven studies reported carbapenemase-producing bacteria in Africa, but subsequently increasing numbers of studies (including outbreaks) were reported (Figure 2). Outbreaks reported in Africa involved OXA-48, OXA-58, OXA-23, VIM-2 or VIM-4 carbapenemase-producing bacteria (Tables 1 and 2).

Most of the studies reporting the identification of carbapenemase-producing bacteria were conducted in North Africa (74%, 61/83), followed by Southern Africa (12%, 10/83), especially South Africa (90%, 9/10), West Africa (8%, 7/83) and East Africa (6%, 6/83) (Tables 1 and 2).

Thirty-seven studies reported the age group of patients; 60% involved adults between the ages of 12 and 90 years old, 32% involved both adults and children and only three (8%) studies were specific to children (Tables 1 and 2). In addition, most studies (94%, 78/83) were performed in hospital settings with samples collected from hospitalized patients or the hospital environment (Tables 1 and 2). In humans, there were no reports of negative findings in studies that screened for carbapenemase producers. Carbapenemase-producing bacteria (OXA-23, OXA-24, OXA-58, VIM-2 or IMP-1) were isolated in all four studies that screened samples from hospital environments (ICU, toilet, mechanical ventilator).[20–23] In this systematic review, five out of 83 (6%) studies were conducted in a community setting: four studies included samples collected mainly from non-hospitalized patients from which both class B and D carbapenemase-producing bacteria were isolated.[10,24–27] One study tested environmental water samples from a Moroccan city, Marrakesh, and identified a

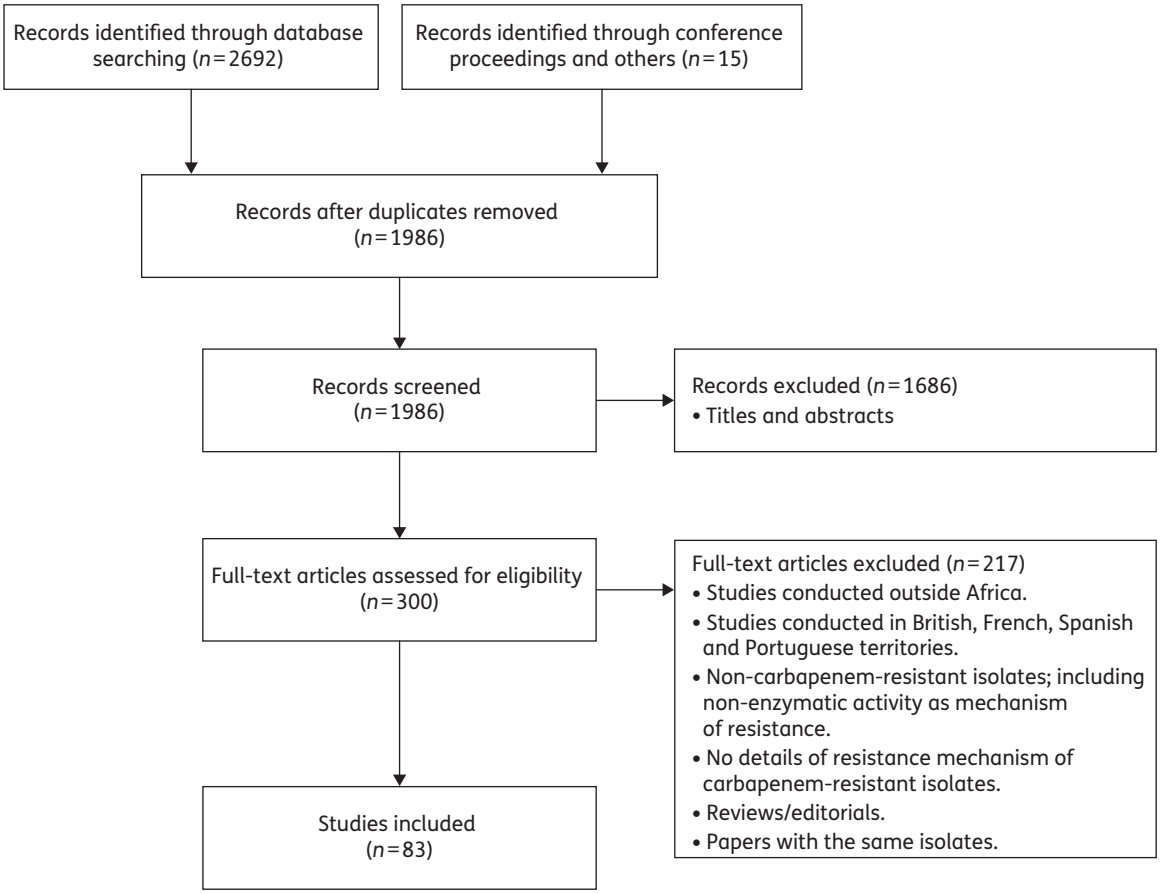

Figure 1. Flow diagram showing selection of studies reviewed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

class D (OXA-48) carbapenemase-producing *Serratia marcescens*.[10] In animals, only one study, conducted in Senegal, screened animal stool samples (donkeys, ducks, goats, cows, chickens, sheep, pigeons and a dog) to isolate carbapenemase-producing bacteria, but none of the samples tested positive for carbapenemases.[27]

Most studies (66%, 37/56) detecting carbapenemase producers followed the CLSI guidelines for susceptibility testing. Others used guidelines from the Antibiogram Committee of the French Microbiology Society (16%, 9/56), EUCAST (14%, 8/56) and BSAC (4%, 2/56). Depending on study design, the proportion of carbapenemase-producing isolates ranged from 0.2% to 100% (Tables 1 and 2). In studies included in this systematic review, the prevalence of carbapenemase-producing isolates in hospital settings ranged from 2.3% to 67.7% in North Africa,[20,21,28–36] and from 9% to 60% in sub-Saharan Africa.[37–40] In community settings, their prevalences were 0.2% and 5.4% in two studies conducted in Morocco.[25,26]

Carbapenemases among Enterobacteriaceae

Figures 3 and 4 show the number of reported carbapenemase-producing Enterobacteriaceae and their geographical distribution in Africa, respectively.

Ambler class A carbapenemases

In Africa, Ambler class A carbapenemases among Enterobacteriaceae were reported in only three studies, from Egypt, Tanzania and South Africa (Table 1). In Egypt, KPC-producing *Klebsiella pneumoniae* strains ($n=14$) were recovered from patients admitted to different wards at the Suez Canal University hospital.[33] The study in South Africa involved an adult patient infected with KPC-2-producing *K. pneumoniae* and *Enterobacter cloacae*.[41] The risk factors associated with the acquisition of KPC-2 producers were treatment with multiple antibiotic agents, prolonged hospital and ICU stay, use of invasive devices and immunosuppression.[41]

Ambler class B carbapenemases

Four metallo-β-lactamases (NDM, VIM, IMP and DIM) were reported among Enterobacteriaceae in Africa. NDM or VIM variants were reported in at least one country from each African region (Figure 4). IMP was only identified in Morocco, Tunisia and Tanzania,[20,25,26,42] whilst DIM-1 was found only in Sierra Leone.[43]

Most of the VIM-producing Enterobacteriaceae were recovered from adult patients hospitalized in ICUs or surgery wards.[24,28,44–47] In addition, VIM-4-producing *K. pneumoniae* isolates ($n=11$) were the cause of an outbreak in a Tunisian university hospital[45] (Table 1). Moreover, three studies showed an association of VIM-4 or VIM-19 enzymes with class 1 integrons.[44,45,48] VIM-1, VIM-4 and VIM-19 were identified in resistant Enterobacteriaceae (mainly *K. pneumoniae*, *Escherichia coli* and *E. cloacae*).[24,44–46,48,49] With the exception of a single report, from Tunisia, of VIM-2-producing *E. coli* isolates,[20] reports of VIM-2 enzymes were restricted to *Pseudomonas aeruginosa* isolates.[37,50–56]

Table 1. Studies reporting carbapenemase-producing Enterobacteriaceae in Africa

Country	Year of sampling	Type of study	Isolate source	Organisms	Number of isolates positive/ total tested (%)	Carbapenemase described (number of isolates)					Setting	Age group	Reference
						KPC	OXA	VIM	NDM	Others			
Algeria	2008	case report	urinary samples	*E. coli* *K. pneumoniae* *P. stuartii*	5/5 (100)			VIM-19 (2) VIM-19 (2) VIM-19 (1)			H	NA	48
Algeria	2011	case report	blood cultures	*K. pneumoniae*	NA		OXA-48 (1)				H	Ch	135
Cameroon[a]	NA	case report	rectal swab	*E. coli*	NA				NDM-4 (1)		H	NA	103
Egypt	2009–10	laboratory-based surveillance	stool, blood, pus, urine, throat swab, peritoneal fluid	*K. pneumoniae* *E. coli* *E. cloacae*	10/10 (100)		OXA-48 (1) OXA-48 (2) —	VIM-1 (2) VIM-1 (2) VIM-1 (4)			H	Ch & A	46
Egypt	2009–10	case report	blood culture, sputum	*K. pneumoniae*	NA		OXA-163 (2)				H	A	64
Egypt	2010–11	laboratory-based surveillance	NA	*E. cloacae*	2/3 (67)			VIM-4 (2)			H	NA	44
Egypt	2011	prospective study	urine, blood, respiratory tract specimens	*K. pneumoniae*	14/45 (31.1)	KPC (14)					H	NA	33
Egypt	2009–10	retrospective study	faecal, exudates, blood	*E. coli*	3/73 (4.1)		OXA-48 (2)	VIM-1 (1) VIM-29 (1)			H	Ch & A	28
Egypt	2012	case report	gastric fluid, blood	*K. pneumoniae*	NA		OXA-163 (1)		NDM-1 (1)		H	A	57
Kenya	2007–09	laboratory-based surveillance	urine, urethral pus	*K. pneumoniae*	7/7 (100)				NDM-1 (7)		H	A	58
Libya[a]	2011	cross-sectional	nostrils, tonsils and perineum specimens	*K. pneumoniae*	NA		OXA-48 (7)				H	NA	93
Libya[a]	2011	case report	blood	*K. pneumoniae*	NA		OXA-48 (1)				H	A	98
Libya[a]	2011	cross-sectional	rectal swabs	*K. pneumoniae*	NA		OXA-48 (1)				H	NA	99
Libya[a]	2011	case series	CSF, pleural fluid, catheter, urine, endotracheal	*K. pneumoniae*	6/6 (100)		OXA-48 (6)				H	NA	105
Libya[a]	2011	laboratory-based surveillance	NA	*K. pneumoniae*	NA		OXA-48 (13)				H	A	136
Morocco	2009–11	laboratory-based surveillance	blood, urine, bone, skin abscess, urinary tract catheter	*K. pneumoniae* *K. oxytoca* *E. cloacae*	21/21 (100)		OXA-48 (16) OXA-48 (1) OXA-48 (4)				H	Ch & A	95
Morocco	2009–11	laboratory-based surveillance	NA	*K. pneumoniae* *E. cloacae* *E. coli* *M. morganii*	9/17 (53)		OXA-48 (2) OXA-48 (1) OXA-48 (2) OXA-48 (1)			IMP-1 (1) IMP-1 (2)	C	NA	25

Morocco	2010–11	laboratory-based surveillance	NA	*E. coli*	2/47 (4)		OXA-48 (1)			IMP-1 (1)	C	Ch & A	26
Morocco	NA	case series	urine, blood, pancreatic abscess	*K. pneumoniae*	NA				NDM-1 (3)		H	A	59
Morocco	NA	cross-sectional	water (puddles)	*S. marcescens*	NA		OXA-48 (2)				C	NA	10
Morocco	2012	cross-sectional	rectal swabs	*K. pneumoniae*	10/37 (27)		OXA-48 (7)				H	NA	32
				E. cloacae			OXA-48 (3)						
Morocco	2011	cross-sectional	rectal swabs	*K. pneumoniae*	24/28 (86)		OXA-48 (14)		NDM-1 (5)		H	NA	63
				K. oxytoca			OXA-48 (1)						
				K. terrigena			OXA-48 (1)						
				E. cloacae			OXA-48 (2)						
				E. coli			OXA-48 (1)						
Morocco	NA	case report	urine	*K. pneumoniae*	NA		OXA-48 (1)	VIM-1 (1)	NDM-1 (1)		C	A	24
Morocco	2009–10	prospective	blood, pus, urine, catheter, subcutaneous fluid collection	*K. pneumoniae*	13/463 (2.8)		OXA-48 (6)		NDM-1 (3)		H	NA	36
				K. oxytoca			OXA-48 (1)						
				E. cloacae			OXA-48 (3)						
Morocco	2009	case report	NA	*K. pneumoniae*	NA		OXA-48 (1)				H	A	69
Morocco[a]	2010	case report	urine, rectal swab	*E. cloacae*	NA		OXA-48 (2)				H	NA	71
Morocco[a]	2010	case report	rectal swabs	*K. pneumoniae*	NA		OXA-48 (2)				H	NA	137
Morocco[a]	2010	case report	urine	*E. coli*	NA		OXA-48 (1)				H	A	138
South Africa	2011	case report	urine, blood, tracheal aspirate, central venous catheter	*K. pneumoniae*	NA	KPC-2 (3)			NDM-1 (1)		H	A	41
				E. cloacae		KPC-2 (1)			—				
South Africa	2011–12	case series	tissue, urine, tracheal aspirate	*K. pneumoniae*	NA		OXA-48 (3)				H	Ch & A	65
				—			OXA-181 (6)						
				S. marcescens			OXA-48 (1)						
South Africa	NA	case report	sputum	*E. cloacae*	NA				NDM-1 (1)		H	A	60
South Africa	2010	case report	pus	*K. pneumoniae*	NA			VIM-1 (1)			H	A	47
South Africa[a]	2012	case report	urine	*E. cloacae*	NA				NDM-1 (1)		H	A	61
Sierra Leone	2010–11	laboratory-based surveillance	NA	*E. cloacae*	13/20 (65)		OXA-58 (4)	VIM (3)		DIM-1 (3)	H	NA	43
				E. coli			OXA-58 (1)	VIM (1)		DIM-1 (1)			
				K. pneumoniae			OXA-58 (3)	VIM (4)					
				Enterobacter spp.			OXA-58 (1)	—					
				Providencia			OXA-58 (1)	VIM (1)					
				Enterobacteriaceae				VIM (1)					
Senegal	2008–09	case series	N/A	*K. pneumoniae*	11/11 (100)		OXA-48 (8)				H	NA	70
				E. coli			OXA-48 (1)						
				E. cloacae			OXA-48 (1)						
				Enterobacter sakazaki			OXA-48 (1)						

Continued

Table 1. *Continued*

Country	Year of sampling	Type of study	Isolate source	Organisms	Number of isolates positive/ total tested (%)	Carbapenemase described (number of isolates)					Setting	Age group	Reference
						KPC	OXA	VIM	NDM	Others			
Tanzania	2007–12	laboratory-based surveillance	pus, urine, blood, aspirate, sputum	*K. pneumoniae* *E. coli* *K. oxytoca* *C. freundii* *M. morganii* *S. marcescens* *Salmonella* spp.	NA	KPC (3) KPC (4)	OXA-48 (4) OXA-48 (3) OXA-48 (1) OXA-48 (1)	VIM (11) VIM (4) — VIM (1) — VIM (2) VIM (1)	NDM (2) NDM (2) NDM (1) — NDM (1)	IMP (9) IMP (19) IMP (3) IMP (2) — — IMP (1)	H	NA	42
Tunisia	2010	case report	urine	*K. pneumoniae*	NA		OXA-48 (2)				H	NA	96
Tunisia	2009–10	laboratory-based surveillance	NA	*K. pneumoniae*	21/153 (14)		OXA-48 (21)				H	NA	139
Tunisia	2005	laboratory-based surveillance[b]	urine, blood, wound, catheter, cerebral abscess, sputum	*K. pneumoniae*	11/11 (100)			VIM-4 (11)			H	A	45
Tunisia	2009	case report	sputum or blood	*K. pneumoniae*	NA		OXA-48 (1)				H	A	140
Tunisia	2011	laboratory-based surveillance[b]	rectal, nose, axilla, environmental swabs	*P. stuartii*	13/13 (100)		OXA-48 (13)				H	A	22
Tunisia	2010	cross-sectional	environmental swabs	*E. coli* *K. pneumoniae*	13/46 (28)			VIM-2 (4) —		IMP-1 (9)	H	NA	20
Tunisia	2012	case report	sternal pus	*K. pneumoniae*	NA				NDM-1 (1)		H	A	62
Tunisia	2009–11	laboratory-based surveillance	pus, urine, blood	*K. pneumoniae* *C. freundii*	NA		OXA-48 (4) OXA-48 (1)				H	Ch & A	94

NA, not available; H, hospital; C, community; Ch, children; A, adult.
For the 'Carbapenemase described' columns, blanks mean 'not detected'.
[a]Transferred or travel patient.
[b]Identified outbreak.

Table 2. Studies reporting carbapenemase-producing non-Enterobacteriaceae in Africa

Country	Year of sampling	Type of study	Isolate source	Organisms	Number of isolates positive/ total tested (%)	Carbapenemase described (number of isolates)					Setting	Age group	Reference
						KPC	OXA	VIM	NDM	Others			
Algeria	2010–11	laboratory-based surveillance	NA	*A. baumannii*	24/ 24 (100)		OXA-23 (23) OXA-58 (2)				H	Ch & A	141
Algeria	2008	laboratory-based surveillance[a]	rectal, urine, bronchial, environmental samples	*A. baumannii*	16/ 16 (100)		OXA-58 (16)				H	NA	23
Algeria	2010–11	laboratory-based surveillance	bronchial samples	*A. baumannii*	14/23 (61)		OXA-23 (14)				H	Ch & A	142
Algeria	NA	NA	NA	*A. baumannii*	NA		OXA-23 (43) OXA-24 (6)				H	NA	143
Algeria	2004	laboratory-based surveillance	NA	*A. baumannii*	NA		OXA-23 (2)				H	NA	144
Algeria	2008–12	laboratory-based surveillance	rectal swab, tracheal aspirate, urine, wound, environment	*A. baumannii* — *A. nosocomialis* *A. radioresistens*	57/ 113 (50)		OXA-23 (39) OXA-24 (16) OXA-23 (1) OXA-24 (1)		NDM-1 (5)		H	NA	21
Algeria	2010–11	laboratory-based surveillance	tracheal swabs, other specimens	*A. baumannii*	34/71 (48)		OXA-23 (31) OXA-72 (5)				H	NA	29
Algeria	2010–11	laboratory-based surveillance	blood, urine, bronchial aspirate, urinary catheter, wound	*P. aeruginosa*	14/17 (82)			VIM-2 (14)			H	Ch & A	56
Algeria	2009–12	laboratory-based surveillance	tracheal suction samples	*P. aeruginosa*	2/89 (2.2)			VIM-2 (2)			H	A	35
Algeria[b]	2011	case report	blood catheter, rectal swabs	*A. baumannii*	NA				NDM-1 (1)		H	A	102
Algeria[b]	2011	case report	rectal swab	*A. baumannii*	NA				NDM-1 (1)		H	NA	106
Côte d'Ivoire	2009–11	laboratory-based surveillance[a]	NA	*P. aeruginosa*	7/12 (58)			VIM-2 (7)			H	NA	54
Egypt	2005	laboratory-based surveillance	sputum	*A. baumannii*	NA		OXA-23 (1)				H	NA	144
Egypt	NA	laboratory-based surveillance	NA	*P. aeruginosa*	35/50 (70)			VIM-2 (35)			H	NA	50
Egypt	NA	case report	catheter tip	*A. baumannii*	NA		OXA-58 (1)				H	NA	145
Egypt	2011–12	laboratory-based surveillance	NA	*A. baumannii*	39/ 39 (100)		OXA-23 (39)	VIM (1)			H	NA	30

Continued

Table 2. *Continued*

Country	Year of sampling	Type of study	Isolate source	Organisms	Number of isolates positive/ total tested (%)	Carbapenemase described (number of isolates)					Setting	Age group	Reference
						KPC	OXA	VIM	NDM	Others			
Egypt	2010–11	laboratory-based surveillance	wound, blood, catheter tip, central venous port, urine, stool, sputum, BAL, ear swab	*A. baumannii*	23/34 (68)		OXA-23 (19) OXA-58 (5) OXA-40 (1)				H	NA	31
Egypt	2012	laboratory-based surveillance	NA	*A. baumannii*	25/40 (63)		OXA-23 (20) OXA-24 (3) OXA-58 (2)				H	NA	146
Egypt	2011–12	laboratory-based surveillance	wound, blood, urine, sputum, ear, CSF, abscess, catheter, tissue	*P. aeruginosa*	31/ 122 (25.4)			VIM-2 (28)	NDM (2)	IMP (1)	H	NA	147
Egypt[b]	2011	case report	BAL, oral cavity swabs, airways	*A. baumannii*	NA				NDM-1 (2)		H	NA	104
Egypt[b]	2011	case report	central venous line catheter	*A. baumannii*	NA				NDM-2 (1)		H	Ch	148
Ghana[b]	2006	case report	NA	*P. aeruginosa*	NA			VIM-2 (1)			H	NA	149
Kenya	2006–07	laboratory-based surveillance	urine, blood, wounds, respiratory tract specimens	*P. aeruginosa*	57/ 57 (100)			VIM-2 (57)			H	NA	37
Kenya	2009–10	laboratory-based surveillance	tracheal aspirate, bone marrow aspirate, CSF, catheter tip, axillary swab, nasal swab, urine, blood, and debrided tissue	*A. baumannii*	16/ 16 (100)		OXA-23 (16)		NDM-1 (1)		H	NA	150
Libya	2004	laboratory-based surveillance	NA	*A. baumannii*	NA		OXA-23 (1)				H	NA	144
Libya[b]	2011	cross-sectional	nostrils, tonsils and perineum specimens	*A. baumannii*	NA		OXA-23 (3)		NDM-1 (1)		H	NA	93
Libya[b]	2011	laboratory-based surveillance	NA	*A. baumannii*	NA		OXA-23 (4)		NDM-1 (2)		H	A	136
Madagascar	2006–09	laboratory-based surveillance	skin wound, urine, blood, respiratory tract secretions	*A. baumannii*	53/ 53 (100)		OXA-23 (53)				H	NA	40
Nigeria	2012	prospective study	NA	*A. baumannii*	3/5 (60)		OXA-23 (3)				H	NA	151
South Africa	2002	laboratory-based surveillance	NA	*A. baumannii*	49/ 49 (100)		OXA-23 (49)				H	NA	152
South Africa	2006	laboratory-based surveillance	urine	*A. baumannii*	NA		OXA-23 (1)				H	NA	144

South Africa	2008	laboratory-based surveillance	NA	*A. baumannii*	58/97 (59)		OXA-23 (58) OXA-58 (3)	VIM (1)			H	NA	39
South Africa	2010–11	laboratory-based surveillance[a]	blood, stool, bile, urine, catheter tip	*P. aeruginosa*	11/15 (73)			VIM-2 (11)			H	NA	53
Sierra Leone	2010–11	laboratory-based surveillance	NA	*C. testosteroni* *Pseudomonas* *Burkholderia* *D. acidovorans* Peudomonadaceae	6/20 (30)		OXA-58 (1) OXA-58 (1) OXA-58 (2) OXA-58 (1) OXA-58 (1)	— VIM (1) — — VIM (1)		DIM-1 (1) DIM-1 (1) — DIM-1 (1)	H	NA	43
Senegal	2008–10	prospective	stool, head lice	*A. baumannii*	NA		OXA-23 (9)[c]				C	Ch & A	27
Senegal	2011	case-series	blood, BAL	*A. baumannii*	NA		OXA-23 (3)				H	Ch & A	153
Tanzania	2010–11	laboratory-based surveillance	pus, blood, urine	*P. aeruginosa*	8/90 (8.9)			VIM (8)			H	Ch	38
Tanzania	2007–12	laboratory-based surveillance	pus, urine, blood, aspirate	*P. aeruginosa* *A. baumannii*	NA	KPC (1)	OXA-48 (2)	VIM (9)	NDM (1)	IMP (12) IMP (3)	H	NA	42
Tunisia	2008	laboratory-based surveillance[a]	urine, cutaneous pus, blood	*P. aeruginosa*	16/24 (67)			VIM-2 (16)			H	A	52
Tunisia	2001–05	laboratory-based surveillance	blood, pus	*A. baumannii*	19/39 (49)		OXA-97 (19)				H	NA	34
Tunisia	2003–07	laboratory-based surveillance[a]	blood, urine, catheter	*P. aeruginosa*	5/75 (6.7)			VIM-2 (5)			H	A	55
Tunisia	2002–06	laboratory-based surveillance	pus, blood, urine, catheter, bronchial secretions	*P. aeruginosa*	35/73 (48)			VIM-2 (35)			H	Ch & A	51
Tunisia	2007	laboratory-based surveillance[a]	blood, pus, urine, pulmonary specimens, materials	*A. baumannii*	41/50 (82)		OXA-23 (41)				H	NA	72
Tunisia	2007	case report	tracheal protection culture	*A. baumannii*	NA		OXA-23 (1)				H	A	154
Tunisia	2007	laboratory-based surveillance	NA	*P. aeruginosa*	30/30 (100)			VIM-2 (30)			H	NA	155
Tunisia	2005–07	laboratory-based surveillance[a]	blood, pus, urine, tracheal aspirate	*A. baumannii*	13/99 (13)		OXA-23 (13)				H	A	73

BAL, bronchoalveolar lavage; Ch, children; A, adult; H, hospital; C, community; NA, not available.
For the 'Carbapenemase described' columns, blanks mean 'not detected'.
[a]Identified outbreak.
[b]Transferred or travel patient.
[c]Three isolates from human head lice.

With the exception of one *K. pneumoniae* strain recovered from the urine of a non-hospitalized patient, NDM-producing Enterobacteriaceae (mainly *K. pneumoniae*) were identified in hospital settings, mostly among adult patients hospitalized in ICUs or medical or surgical wards.[24,41,57–62] NDM-producing Enterobacteriaceae were mostly isolated from rectal swabs, urine, catheter tips or pus.[24,36,41,58,59,62,63] NDM-1-producing Enterobacteriaceae were mainly *K. pneumoniae* isolates (Table 1). One *K. pneumoniae* isolate from a urine sample of a non-hospitalized (elderly male) patient from Taza, Morocco, was found to harbour OXA-48, VIM-1 and NDM-1 enzymes.[24] NDM-1 was also identified in *E. cloacae* isolates in South Africa;[60,61] one such isolate was cultured from the urine sample of a patient who had been hospitalized in India before travelling to South Africa.[61] In Africa, NDM-1 was first identified in Kenya among seven clonally related *K. pneumoniae* isolates from urine or urethral pus of seven adult patients hospitalized in different wards (four in a medical ward, two in ICU and one in a maternity ward) at the Aga Khan University Hospital between 2007 and 2009.[58]

Only three studies reported the detection of IMP-1 in Africa: two from Morocco and one from Tunisia. In Tunisia, IMP-1-producing *K. pneumoniae* isolates ($n=9$) were isolated from swabs taken from the hospital environmental (ICU and toilet).[20] In Morocco, four IMP-1 carbapenemase producers (one uropathogenic *E. coli*, one *K. pneumoniae* and two *E. cloacae*) were isolated from community-acquired urinary tract infections.[25,26] Three of these four isolates (one *K. pneumoniae* and two *E. cloacae*) were from Casablanca.[25] The origin of the IMP-1-producing uropathogenic *E. coli* isolate was not mentioned.[26]

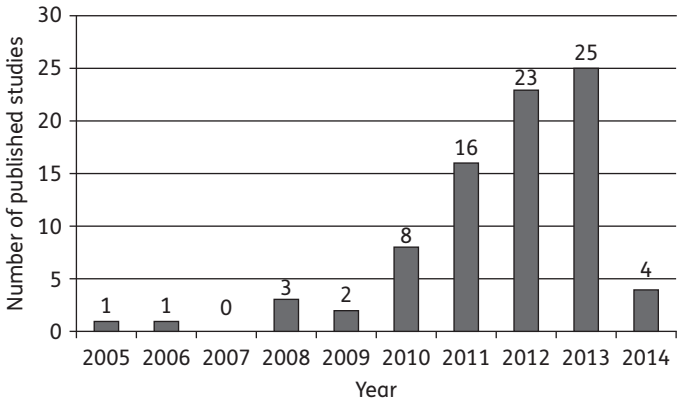

Figure 2. Number of studies reporting carbapenemase-producing bacteria in Africa per year (until February 2014).

Ambler class D carbapenemases

OXA-48-like producing Enterobacteriaceae were isolated from both hospital and community settings (Table 1). Most of the OXA-48-like producers were isolated from pus, wounds, rectal swabs, blood or urine samples collected from adults or children hospitalized in surgical wards or ICUs.[24,32,36,57,62–65] Several reports indicated that OXA-48-producing Enterobacteriaceae are endemic in North African countries, such as in Morocco and Tunisia.[2,66–71] OXA-48-producing *Providencia stuartii* isolates were reported as the cause of an outbreak in a Tunisian hospital.[22] OXA-181, a point mutant analogue of OXA-48, was reported in South Africa from *K. pneumoniae* isolates recovered in tracheal aspirate and urine samples of hospitalized adult patients.[65] In addition to OXA-181, OXA-163, an OXA-48 variant that has an increased activity against extended spectrum β-lactams was identified among *K. pneumoniae* strains in Egypt.[57,64] Of note, the OXA-51-like and OXA-58 carbapenemases which are known to be *Acinetobacter*-related, were identified among Enterobacteriaceae species in a study conducted in Sierra Leone[43] (Table 1).

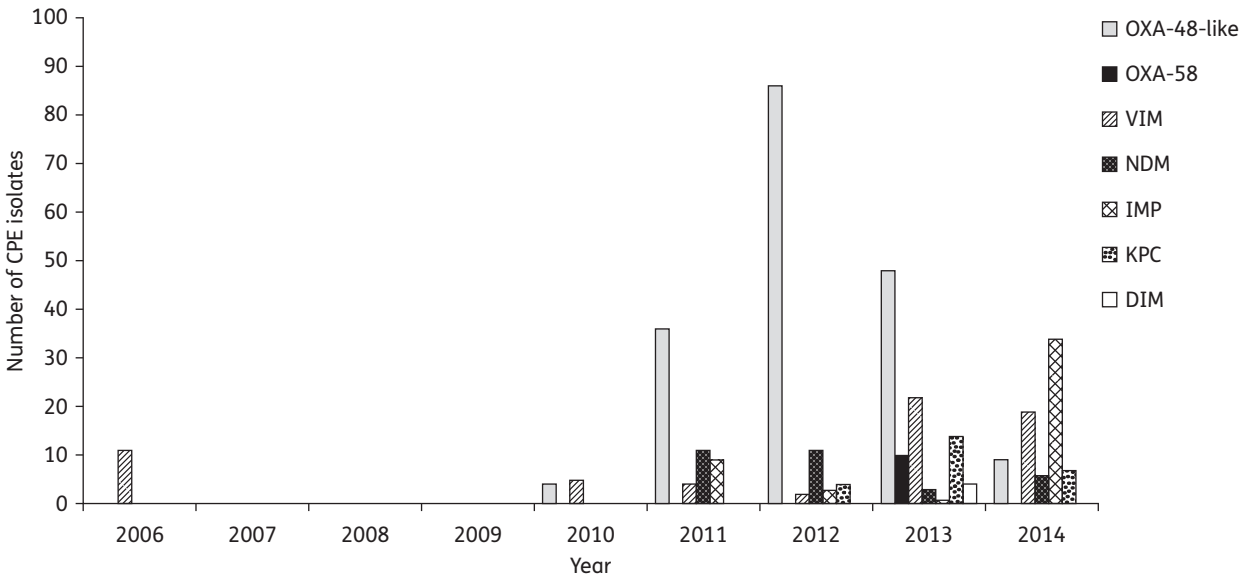

Figure 3. Number of reported carbapenemase-producing Enterobacteriaceae (CPE) isolates in Africa (until February 2014).

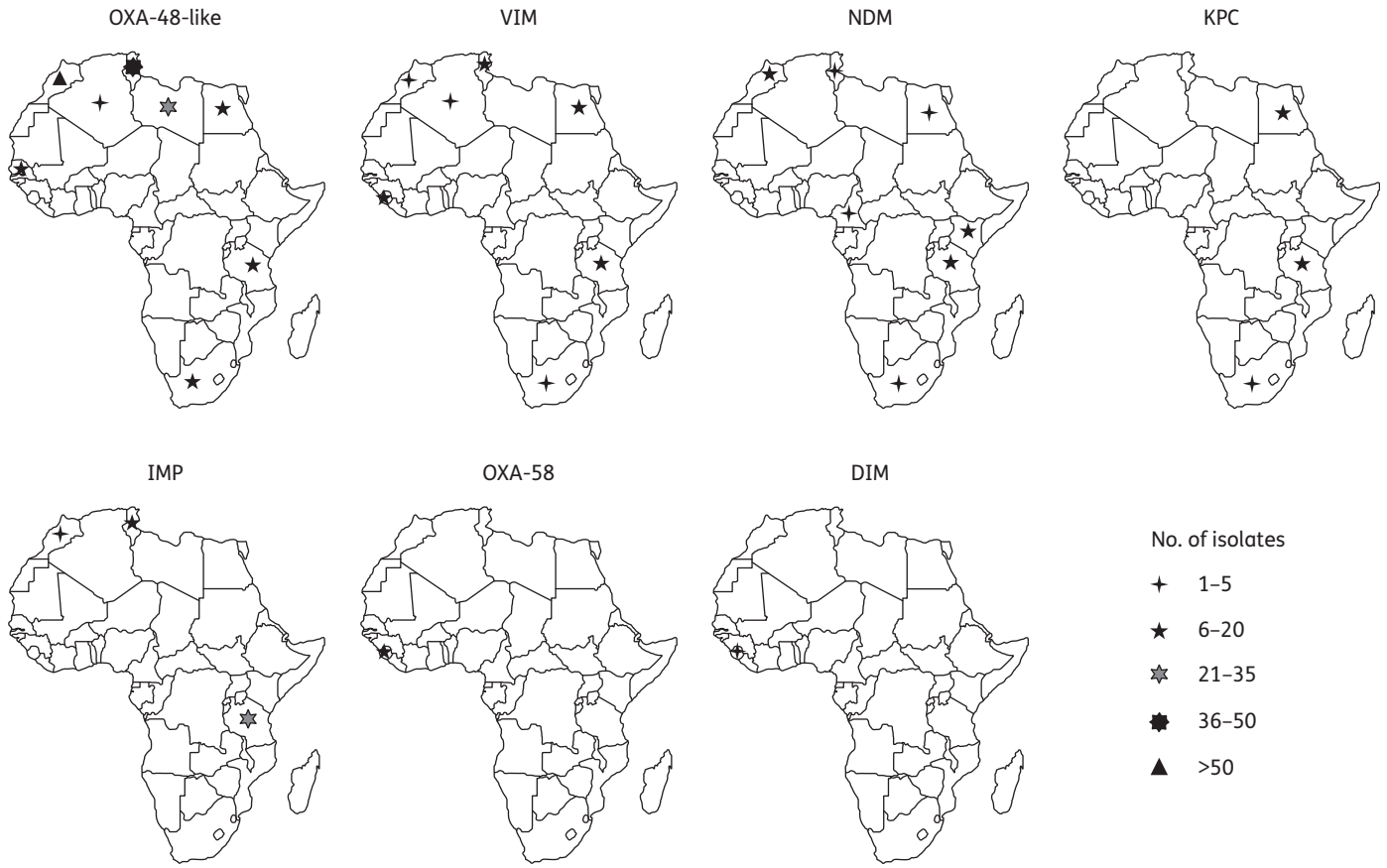

Figure 4. Geographical distribution of carbapenemase-producing Enterobacteriaceae isolates in Africa (until February 2014).

Carbapenemases among non-Enterobacteriaceae

Figures 5 and 6 show the number of reported carbapenemase-producing non-Enterobacteriaceae isolates and their geographical distribution in Africa, respectively.

Ambler class A carbapenemases

Class A carbapenemases were only reported in Tanzania. The KPC enzyme, known to be prevalent among Enterobacteriaceae, was identified in a *P. aeruginosa* isolate from a clinical specimen from a tertiary hospital in northwestern, Tanzania.[42]

Ambler class B carbapenemases

A variety of metallo-β-lactamases were reported among non-Enterobacteriaceae isolates (Figure 6). VIM-2 and NDM variants (NDM-1 and NDM-2) were reported among *P. aeruginosa* and *A. baumannii*, respectively. VIM-2-producing *P. aeruginosa* were involved in outbreaks in Tunisia, Côte d'Ivoire and South Africa,[52–55] (Table 2). Four studies showed an association of VIM-2 enzyme with class 1 integrons that also contained gene cassettes that render isolates resistant to different classes of antimicrobial agents.[51,54–56] NDM-producing *A. baumannii* isolates were identified in patients from North and East Africa, with no obvious link with the Indian subcontinent (Figure 6 and Table 2).

Ambler class D carbapenemases

Carbapenem-hydrolysing class D β-lactamases were identified in many African countries (Figure 6). The OXA-23-like carbapenemase subgroup was mainly reported in *A. baumannii* strains from North Africa (Figure 6). OXA-23-producing *A. baumannii* strains were reported as the cause of an outbreak in Tunisian hospitals.[72,73] OXA-24-like enzymes were reported in Algeria and Egypt, among resistant *A. baumannii* isolates (Figure 6). OXA-58-like enzymes were less common and, like OXA-23 and OXA-24, they were more consistently associated with resistant *Acinetobacter* species (Table 2). Interestingly, the OXA-48 enzyme, which is widespread among Enterobacteriaceae, was identified in two *P. aeruginosa* clinical isolates in Tanzania.[42]

Discussion

The burden of antibiotic resistance is a public health concern and may contribute to increased mortality, prolonged hospital stay and increased costs of healthcare, especially in developing countries.[74–78] In Africa, data on antibiotic resistance are very limited.[79] Lack of systematically collected data on the African continent contributes to a poor understanding of antimicrobial resistance and limits an effective response to the problem.[79]

Carbapenemase-producing bacteria, particularly KPC, VIM, IMP, NDM and OXA types, are increasingly reported worldwide;

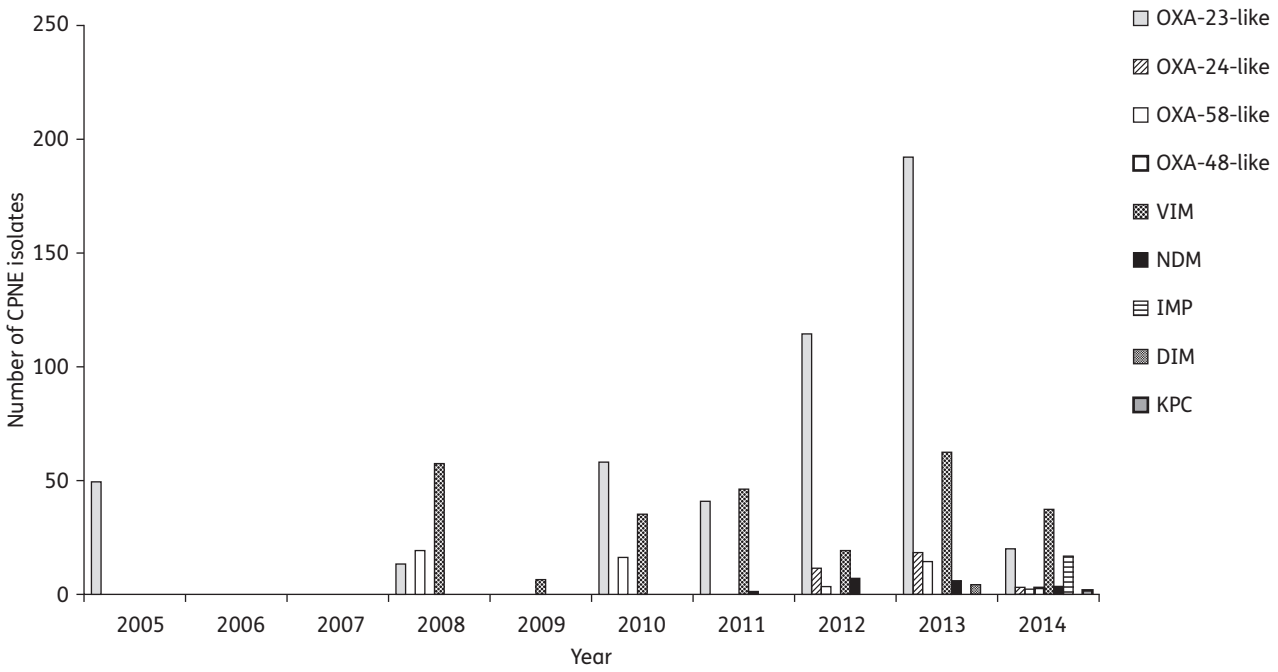

Figure 5. Number of reported carbapenemase-producing non-Enterobacteriaceae (CPNE) isolates in Africa (until February 2014).

however, most reports are from Europe, North America and Asia.[2,11,80] The KPC enzyme was first identified from a *K. pneumoniae* isolate in the USA in 1996.[12] Since then, KPC-producing bacteria have spread worldwide, including Africa.[81–85] VIM-producing isolates are endemic in Greece;[86,87] however, outbreaks as well as isolated cases have been reported throughout the world.[2,13,52,88,89] IMP producers, which are endemic in Japan and Taiwan, were reported worldwide.[84,87,90] NDM enzymes are mostly described in Enterobacteriaceae, especially *E. coli* and *K. pneumoniae*, and they are widespread in India and Pakistan but are increasingly reported worldwide.[13,16,58,91,92] Class D, OXA-48-producing *K. pneumoniae* are widespread in Turkey, the Middle East and North Africa.[2,66–71]

This systematic review showed that there is a rapid increase in the number of reports of carbapenemase-producing bacteria in Africa. Class D carbapenemases (especially OXA-48) are the most reported enzymes among Enterobacteriaceae in Africa, particularly in North African countries. This enzyme was described in various Enterobacteriaceae, including *K. pneumoniae*, *E. coli*, *E. cloacae*, *P. stuartii* and *Citrobacter freundii* isolates from North African countries.[22,32,46,63,93,94] Data from these countries show that OXA-48-producing isolates are not from a single clone.[25,95,96] A study conducted by Poirel *et al.*[71] also showed differing pulsotypes (diverse clones) among four OXA-48-producing *E. cloacae* isolates, two from patients transferred from Morocco to France, and two from Turkey.[67,71] However, a common OXA-48-producing *K. pneumoniae* clone circulating in North African countries is also found in several European countries, especially in Turkey, France and the Netherlands.[2,9,13,25,95–97] There are cases of OXA-48-producing *K. pneumoniae* imported from Libya to Italy, Slovenia and Denmark, indicating that North Africa harbours OXA-48-producing Enterobacteriaceae.[93,98,99] OXA-23 (also known as ARI-1) was first identified in 1985 from an *A. baumannii* strain from a patient in Edinburgh, UK.[100,101] The relatedness of strains circulating in Africa is not clear; however, many strains of OXA-23-producing *A. baumannii* from Madagascar and Tunisia were reported to be of the same clone.[40,73]

This systematic review also indicates that metallo-β-lactamases are present in each African region. As in other parts of the world, the emergence, among Enterobacteriaceae, of NDM enzymes that are able to hydrolyse almost all β-lactam antibiotics is of great concern.[17,24,41,62,102,103] In addition to Enterobacteriaceae, NDM has been identified among *A. baumannii* isolates from North African countries, especially Algeria, Egypt and Libya.[21,93,102,104,105] There are also several reports of imported cases identified in Europe, in patients from North Africa with no obvious link to the Indian subcontinent.[102,104,106]

Several risk factors are associated with the acquisition of carbapenemase-producing bacteria in healthcare settings, such as recent antibiotic therapy, prolonged hospital stay, use of invasive devices and immunosuppression.[7,107–109] These risk factors were reported in a South African study.[41] In the community, risk factors are still uncertain; however, overuse and over-the-counter use of antibiotics, inadequate hygiene and global travel may enhance the spread of carbapenemase-producing bacteria.[2,79,110,111] Selection for such bacteria is not only associated with recent or prior carbapenem therapy but also with use of other antibiotics (such as aminoglycosides and fluoroquinolones),[81,112] as indicated by the detection of carbapenem-resistant (OXA-23) *A. baumannii* in Madagascar, where carbapenems were unavailable during the study period.[40] The uncontained spread of carbapenemase-producing bacteria may occur in Africa for several reasons. Firstly, there is substantial over-the-counter use of antibiotics in many African countries (reaching 40% in Nigeria and Uganda) with limited attention to antimicrobial stewardship.[79,110,111,113,114] Of concern is an increase in over-the-counter use of carbapenems in Africa, especially in Egypt.[78] Egypt is among the three countries (the other two being India and

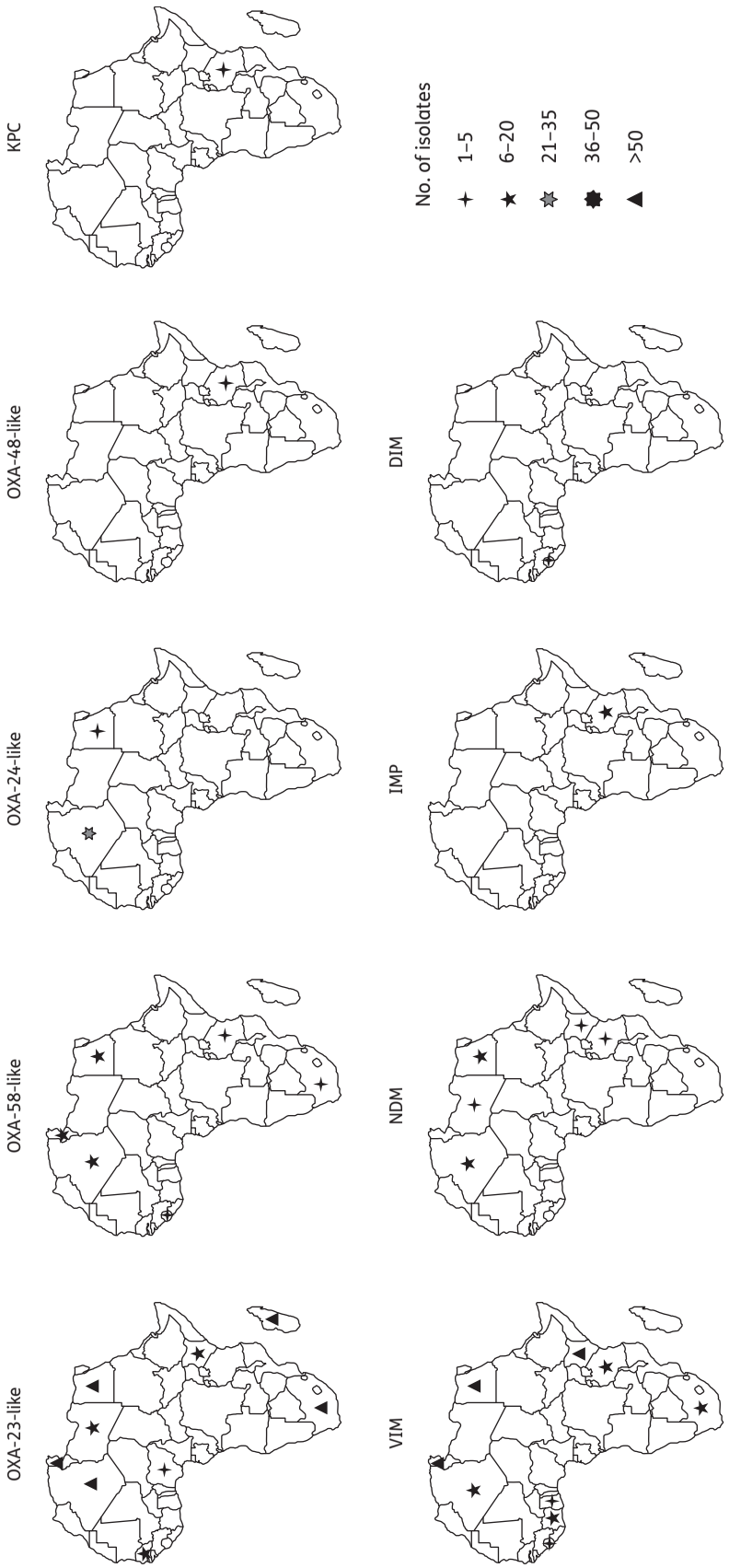

Figure 6. Geographical distribution of carbapenemase-producing non-Enterobacteriaceae isolates in Africa (until February 2014).

Pakistan) in the world where retail sales of carbapenems have drastically increased according to the report by The Lancet Infectious Diseases Commission.[78] This might be explained by, in addition to the quasi-absence of regulations governing antibiotic use, the availability of low-cost generic or counterfeit and low-quality carbapenems. Secondly, due to resource constraints, infection-control practices are often suboptimal, with limited opportunity for patient isolation or screening of high-risk individuals.[115] Finally, in the context of other pressing, more visible healthcare priorities, there may be limited political will or attention to the emerging problem of antimicrobial resistance.[116,117]

The occurrence, in Morocco, of OXA-48-producing *S. marcescens* isolates in environmental water is also of concern since such organisms can be spread through unsafe water and poor sanitation.[10] Carbapenemase-producing organisms have also been isolated from environmental water samples in Asia[118–121] and Europe.[122,123] Although no carbapenemase-producing bacteria were identified in a single study conducted in animal reservoirs in Africa,[27] there is a need for further studies. Of note, carbapenemase-producing bacteria have been found in animals (cattle, dogs, pigs and horses) in Western Europe.[124–128] Therefore, active surveillance is needed for the detection of bacteria resistant to carbapenems in the food chain as well as in livestock.

Detection of carbapenemase-producing bacteria is not straightforward, since there is no screening medium that is able to detect all types of carbapenemases,[129] and some carbapenemase producers demonstrate intermediate resistance or susceptibility to carbapenems on routine testing.[2] Most studies reviewed here used routine antibiotic susceptibility testing (either disc diffusion or automated systems) to screen for carbapenemase-producing bacteria.[30,52,55,56,66,130] Of note, automated systems are unreliable in detecting all types of carbapenemase-producing isolates.[131]

Limitations of this systematic review include the inability to determine the true prevalence of carbapenemase-producing bacteria as most studies were case reports or laboratory-based surveillance. In addition, there are few published data on carbapenemase-producing organisms from sub-Saharan Africa. There is also a lack of reports of negative findings in studies that screened for carbapenemase producers in humans; however, this may have been influenced by publication bias, with studies not detecting carbapenemase producers less likely to be reported. Many studies also had incomplete data regarding risk factors for the acquisition of carbapenemase-producing bacteria. In most studies there was no clear distinction between community-associated or hospital-associated infections.

Conclusions

Whilst data from Africa are still limited, this systematic review provides evidence that carbapenemase-producing bacteria occur widely in Africa. Infections due to MDRGN organisms are likely to cause a substantial burden of disease in Africa, and yet research into this area is not prioritized by grant funding organizations.[132] For example, neonatal infections were estimated to be responsible for more than 800 000 deaths in 2010, and yet the proportion of these caused by MDRGN organisms is unknown.[77] Therefore, to inform future policy decisions and guide appropriate antimicrobial therapy in Africa, data on antibiotic resistance should be systematically collected and appropriate screening methods used to identify carbapenemase-producing bacteria in Africa. These data should be supplemented by molecular detection and genotyping of resistant isolates and characterization of existing and novel carbapenemase genes.[133] NDM enzymes were already prevalent in India at the time when this enzyme was first detected.[134] Similarly, without strong surveillance systems in Africa, it is likely that the detection of emerging antimicrobial resistance will occur too late to prevent the widespread dissemination of resistant bacteria.

Acknowledgements

M. K. was a recipient of a Carnegie Corporation of New York (USA) fellowship.

Funding

This work was supported by a Bill and Melinda Gates Foundation Global Health Grant (OPP107641) and the National Research Foundation, South Africa. The funders had no role in the study design, data collection and analysis, decision to publish or preparation of the manuscript. R. I. M. is supported by the National Research Foundation of South Africa and the Drakenstein Child Health Study, Cape Town, South Africa. M. K. is supported by the Wellcome Trust, UK.

Transparency declarations

None to declare.

The corresponding author had full access to all of the data in the study and had final responsibility for the decision to submit the article for publication. All of the authors reviewed the final version of the manuscript prior to submission for publication.

Author contributions

M. K., H. J. Z. and M. P. N. initiated the project, and R. I. M. extracted the data and reviewed the article with M. K. All authors wrote the manuscript.

Supplementary data

Table S1 is available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

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