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β-Lactamase Production in Key Gram-Negative Pathogen Isolates from the Arabian Peninsula

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SUMMARY

Infections due to Gram-negative bacilli (GNB) are a leading cause of morbidity and mortality worldwide. The extent of antibiotic resistance in GNB in countries of the Gulf Cooperation Council (GCC), namely, Saudi Arabia, United Arab Emirates, Kuwait, Qatar, Oman, and Bahrain, has not been previously reviewed. These countries share a high prevalence of extended-spectrum-β-lactamase (ESBL)- and carbapenemase-producing GNB, most of which are associated with nosocomial infections. Well-known and widespread β-lactamases genes (such as those for CTX-M-15, OXA-48, and NDM-1) have found their way into isolates from the GCC states. However, less common and unique enzymes have also been identified. These include PER-7, GES-11, and PME-1. Several potential risk factors unique to the GCC states may have contributed to the emergence and spread of β-lactamases, including the unnecessary use of antibiotics and the large population of migrant workers, particularly from the Indian subcontinent. It is clear that active surveillance of antimicrobial resistance in the GCC states is urgently needed to address regional interventions that can contain the antimicrobial resistance issue.

INTRODUCTION

The words of Margaret Chan, Director of the WHO, at the 2012 European State meeting in Copenhagen echo the concerns of many: "Some experts say we are moving back to the preantibiotic era. No. This will be a postantibiotic era. In terms of new replace-

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ment antibiotics, the pipeline is virtually dry, especially for Gram-negative bacteria. The cupboard is nearly bare." An important cause of multidrug resistance (MDR) in Gram-negative bacilli (GNB) is the production of broad-spectrum β-lactamases. In the early 1980s, extended-spectrum β-lactamases (ESBLs) that hydrolyze penicillins and expanded-spectrum cephalosporins emerged (1). More recently, β-lactamases that hydrolyze carbapenems have become prominent, most notably, the *Klebsiella pneumoniae* carbapenemase (KPC) and metallo-β-lactamases (MBLs), such as the New Delhi metallo-β-lactamase (NDM) (2, 3).

This article reviews the prevalence of broad-spectrum-β-lactamase-producing GNB in the Middle East, with a primary focus on countries in the Arabian Peninsula, specifically, the Gulf Cooperation Council (GCC) states: Saudi Arabia, United Arab Emirates, Kuwait, Oman, Qatar, and Bahrain. PubMed and the abstracts of the 1st International Conference on Prevention and Infection Control (ICPIC), the 51st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), and the 22nd European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) were reviewed to determine the challenges and potential risk factors that may contribute to the transmission of ESBLs and carbapenemases in this region.

Although some of the cited studies identified *Acinetobacter* as *A. baumannii*, it is known that species identification using conventional methods may not be accurate (4, 5). For this reason, in this paper we will refer to *Acinetobacter* and not *A. baumannii*.

Additionally, we acknowledge that resistance to β-lactam antibiotics, including expanded-spectrum cephalosporins, is not solely due to ESBL production. Other β-lactamases, such as AmpC and carbapenemases, can confer phenotypic resistance to these agents. Moreover, resistance to β-lactam antibiotics (particularly carbapenem resistance in *Pseudomonas aeruginosa*) may be due to mechanisms other than β-lactamase production (for example, loss of outer membrane proteins or upregulated efflux pumps). However, we include all cited papers on resistance of Gram-negative bacilli to β-lactams in this review, and we specify where the precise mechanism of resistance is known.

KINGDOM OF SAUDI ARABIA

Extended-Spectrum and AmpC-Type β-Lactamases

Surveys from Saudi Arabia have studied the prevalence of antimicrobial resistance among GNB isolated from the community, medical wards, and intensive care units (ICUs). In 1988, a study reported that expanded-spectrum cephalosporins possessed activity against >90% of bacteria belonging to the *Enterobacteriaceae* family (6), but now resistance to expanded-spectrum cephalosporins (presumably due to ESBL production) ranges from 6% up to 38.5% (7–12) (Table 1). Substantial levels of resistance are now also evident in the community. Kader and Kamath screened 505 fecal samples from healthy individuals, of whom 12.3% were asymptomatic community carriers of ESBL-producing *Escherichia coli* and *K. pneumoniae* (13).

The prevalence of β-lactamases in ICUs in Saudi Arabia is high; clinical samples ($n = 106$) from ICU patients in Jeddah from 1994 to 1995 recorded ceftazidime and cefotaxime resistance at 32% and 37% for *K. pneumoniae*, respectively, while ESBL production was reported at 31% for *E. coli* and *K. pneumoniae* isolates (14) (Table 1). More recent ICU surveillance studies have not been reported, but it is unlikely that the situation has improved.

Limited studies in Saudi Arabia characterizing ESBL genotypes (Table 2) report that out of 100 ESBL phenotypes isolated from clinical samples from Al-Dhahran city (April to December 2006), 71 harbored $bla_{\text{CTX-M}}$-like genes. Moreover, 51% of *E. coli* isolates and 6.2% of *K. pneumoniae* isolates produced both CTX-M and TEM enzymes. bla_{SHV}-like genes were observed alone in 12.5% and simultaneously with $bla_{\text{CTX-M}}$-like genes in 6.3% of *K. pneumoniae* isolates (15). A 2007 study from two hospitals in Riyadh reported that 97.3% of *K. pneumoniae* isolates carried bla_{SHV}-like genes, followed by 84.1% carrying bla_{TEM} genes and 34.1% carrying $bla_{\text{CTX-M}}$-like genes. Further PCR screening revealed that 60% of the CTX-M-positive isolates carried $bla_{\text{CTX-M-1}}$-like genes and the other 40% carried $bla_{\text{CTX-M-9}}$-like genes (16). In April 2005, an outbreak occurring at a neonatal ward in Riyadh was due to an SHV-12-producing *K. pneumoniae* strain (17) (Table 3), which is prevalent in other parts of the world (18–20).

In the Al-Qassim area, 25.6% (110/430) of *K. pneumoniae* isolates from clinical specimens from inpatients at two major hospitals in Buraydah (January to June 2008) were found to be ESBL producers. Of note was that 60% of *K. pneumoniae* blood culture isolates were ESBL producers (21). Characterization of the resistance genes revealed the presence of SHV-12 (61.9%), SHV-5 (18.2%), CTX-M-15 (34.5%), and CTX-M-14 (1.9%). Some isolates possessed multiple ESBL genes, and most of the bacteria carried resistance genes on transmissible plasmids. The insertion sequence element IS*Ecp1* was detected in CTX-M-15-positive isolates (21).

Analysis of *P. aeruginosa* isolates from a burn unit of a hospital in Riyadh (January to April 2010) showed that 25 (16%) were ESBL producers, with 17 (68%) carrying bla_{VEB} genes and 5 (20%) carrying bla_{GES} genes. The OXA-10 enzyme, which weakly hydrolyzes cefotaxime, ceftriaxone, and aztreonam (22), was found in 14 isolates. Notably, some isolates coharbored $bla_{\text{OXA-10}}$ and bla_{VEB}, while a single isolate coharbored $bla_{\text{OXA-10}}$, bla_{VEB}, and bla_{GES} (23). Another study from Riyadh also reported bla_{GES} and bla_{VEB} in 5 (22%) and 20 (87%) of ESBL-positive *P. aeruginosa* isolates, respectively (24). Analysis of ESBL genes in 27 *Acinetobacter* isolates in Riyadh revealed that $bla_{\text{PER-1}}$ was found in 13, $bla_{\text{GES-1}}$ in six, $bla_{\text{GES-5}}$ in one, and $bla_{\text{GES-11}}$ in three (25) (Table 2).

Plasmid-encoded Ambler class C β-lactamases can mediate cephalosporin resistance (26). The first, and to our knowledge the only, plasmid-mediated bla_{AmpC} gene characterized in Saudi Arabia was the novel $bla_{\text{DHA-1}}$ carried in a *Salmonella enterica* serovar Enteritidis isolate from a stool sample of a patient with lung cancer admitted to a health care center in Al-Dhahran city (27, 28). The name DHA-1 derives from Al-Dhahran. Subsequently, $bla_{\text{DHA-1}}$ producers have been found worldwide (29–32).

Carbapenem Resistance in *Enterobacteriaceae*

Studies in the 2000s reported the emergence of carbapenem-resistant *Enterobacteriaceae* in Saudi Arabia but were limited to phenotypic descriptions only. A 2002-2003 study in the eastern province of Saudi Arabia reported that 14% of ESBL-producing *E. coli* and *K. pneumoniae* isolates had increased MICs to imipenem and meropenem, although mechanisms of increased carbapenem MICs were not explored (33). A 2004-2009 ICU study in Riyadh reported just a single carbapenem-resistant *K. pneumoniae* isolate out of 285 ESBL-positive isolates (34). The first, and to date the only, documented outbreak of carbapenem-resistant *K. pneu-*

TABLE 1 Summary of ESBL prevalence studies reported in the Gulf countries and frequencies of ESBL-producing *E. coli* and *Klebsiella* spp.[a]

Country and city	Hospital	Date	No. (%) of ESBL-producing isolates		Source	Reference
			E. coli	*Klebsiella*		
Saudi Arabia						
Jeddah	King Fahd Armed Forces Hospital	March-August 1994	14 (31)		Clinical specimens (ICU)	14
Riyadh	King Khalid University Hospital	January-September 1999	20 (29)	42 (64.6)	Clinical specimens	8
	Armed Forces Hospital	2003–2004	15 (7.7)	46 (22.3)	Blood	9
Dhahran	Saudi Aramco Health Center	2004–2005	109 (15.7)	34 (14.3)	Clinical specimens (inpatients)	10
		2004–2005	234 (4.8)	32 (3.2)	Clinical specimens (outpatients)	10
Al Kharaj	Armed Forces Hospital Tertiary	2004–2007	NA	34 (10.4)	Clinical specimens	7
Al Khobar	Almana General Hospital	2006–2007	87 (12)	4 (0.56)	Community (stool)	13
Riyadh	King Fahad National Guard Hospital	2004	ND (9)	ND (12)	Clinical specimens (ICU)	34
		2009	ND (16)	ND (21)	Clinical specimens (ICU)	34
	King Abdul Aziz Medical City	2007–2011	3,709 (18.3)	1,816 (19.9)	Clinical specimens	11
	ND	2006–2010	ND (8–10)	ND (6–9)	Various body sites	12
United Arab Emirates						
Abu-Dhabi and Al Ain	Three medical centers (Zayed Military Hospital, Alfalah Medical Center, and Alain Medical Center)	January-December 2008	240 (36)		Clinical specimens	56
Al Ain	Alain Medical Center	2003–2004	5 (11.3)	NA	Stool (with/without diarrhea)	52
ND	6 general hospital in UAE	2005–2006	32 (39)	21 (44.7)	Clinical specimens	51
Kuwait						
Kuwait	Infectious Disease Hospital	1995–2001	2 (0.3)	3 (1.5)	CA-UTI	69
	ND	2001–2004	0	4 (44.4)	Blood (inpatients)	71
	Mubarak Al-Kabeer Hospital	January-December 2003	119 (5.6)	58 (11.4)	Clinical specimens	70
	Al-Amiri Hospital	2005–2007	585 (12)	164 (17)	CA-UTI	72
			586 (26)	209 (28)	HA-UTI	72
	Ibn-Sina Hospital	2002–2005	376 (26.3)	428 (42.9)	Clinical specimens	73
	Mubarak Al-Kabeer Hospital	January-December 2006	142 (62)	96 (82.1)	Clinical specimens	74
	8 major hospitals	2006–2007	113 (12.9)	ND	Clinical specimens	75
Oman						
Muscat	Sultan Qaboos University Hospital	2005	13 (14.9)		Clinical specimens (pediatrics)	98
Qatar						
Doha	Hamad Medical Corporation	February-May 1998	0	4 (22)	Clinical specimens (ICU patients)	109
		2007–2008	27 (27.8)	7 (18)	Blood (inpatients)	110
Bahrain						
Manama	Salmaniya Medical Complex	1988	NA	2 (5)	Clinical pulmonary (ICU)	112
		1989	NA	28 (37)	Clinical pulmonary (ICU)	112
		1990	NA	64 (63)	Clinical pulmonary (ICU)	112
		1991	NA	30 (20)	Clinical pulmonary (ICU)	112
		1992	NA	5 (22.6)	Clinical pulmonary (ICU)	112
		2005–2006	2,695 (22.6)[b]		Clinical specimens	114
		2002–2004	46 (28.7)	40 (22)	Clinical specimens (NICU)	115
		2005–2007	49 (42.2)	49 (27.2)	Clinical specimens (NICU)	115

[a] All listed studies used phenotypic methods (for example, double-disk synergy test, ESBL Etest, or ESBL panel in semiautomated systems) to confirm ESBL production. NA, not applicable; ICU, intensive care unit; ND, no data; CA-UTI, community-acquired urinary tract infection; HA-UTI, hospital-acquired urinary tract infection; NICU, neonatal intensive care unit.

[b] Number (rate) in total tested *Enterobacteriaceae*.

moniae in Saudi Arabia was recently reported; it occurred in Riyadh from December 2009 to August 2010 and involved 20 patients. Clonal relatedness determined using pulsed-field gel-electrophoresis (PFGE) found a single dominant clone responsible for the outbreak (35). Molecular analysis showed that all isolates possessed altered outer membrane OMP36K, with five isolates harboring the insertion element IS*903* within *omp36*. Additionally, all isolates carried the carbapenemase gene $bla_{\text{OXA-48}}$

TABLE 2 Summary of ESBL enzymes and their rates identified in the GCC states[a]

Country and province or city	ESBL genotype	Producing organism(s)	No. (%) among ESBL producers	Time period	Reference
Saudi Arabia					
Eastern province	SHV-like	*E. coli*, *Klebsiella* spp.	8 (8)	April-December 2006	15
	TEM-like	*E. coli*, *Klebsiella* spp.	59 (59)	April-December 2006	15
	CTX-M-like	*E. coli*, *Klebsiella* spp.	71 (71)	April-December 2006	15
Riyadh	SHV-like	*K. pneumoniae*	214 (97.3)	2007	16
	SHV-1	*K. pneumoniae*	1 (incidental)	April 2005	17
	TEM-like	*K. pneumoniae*	185 (84.1)	2007	16
	TEM-like	*K. pneumoniae*	696 (60)	2006–2010	12
	CTX-M-like	*E. coli*	ND (5.1–25.3)	2007	12
	CTX-M-like	*K. pneumoniae*	75 (34.1)	2007	16
	CTX-M-like	*K. pneumoniae*	ND (6.4–7.4)	2006–2010	12
	CTX-M-1-like	*K. pneumoniae*	45 (20)	2007	16
	CTX-M-9-like	*K. pneumoniae*	30 (14)	2007	16
	PER-1	*Acinetobacter*	13 (57)	January-December 2010	25
	GES	*P. aeruginosa*	5 (20)	2010	23
	GES	*P. aeruginosa*	5 (22)	2010	24
	GES-1	*Acinetobacter*	6 (26)	January-December 2010	25
	GES-5	*Acinetobacter*	1 (4)	January-December 2010	25
	GES-11	*Acinetobacter*	3 (13)	January-December 2010	25
	VEB	*P. aeruginosa*	17 (68)	2010	23
	VEB	*P. aeruginosa*	20 (87)	2010	24
Al-Qassim	SHV-5	*K. pneumoniae*	20 (18.2)	January-June 2008	21
	SHV-12	*K. pneumoniae*	68 (61.9)	January-June 2008	21
	CTX-M-14	*K. pneumoniae*	2 (1.9)	January-June 2008	21
	CTX-M-15	*K. pneumoniae*	38 (34.5)	January-June 2008	21
United Arab Emirates					
Abu Dhabi	SHV-28	*K. pneumoniae*	29 (32.2)	January-December 2008	56
	CTX-M-15	*E. coli*	141 (94)	January-December 2008	56
	CTX-M-15	*Klebsiella* spp.	58 (64.4)	January-December 2008	56
Al Ain	TEM-like	*Salmonella* spp.	8 (12)	2003–2006	54
	TEM-1	*E. coli* (EAEC)	5 (100)	2003–2004	52
	CTX-M-15	*Salmonella* spp.	1 (1.4)	2003–2006	54
	CTX-M-15	*E. coli* (EAEC)	5 (100)	2003–2004	52
	PER-7	*Acinetobacter*	1 (incidental)	May and August 2008	58
Dubai	PME-1	*P. aeruginosa*	1 (incidental)	2008	57
Kuwait					
Kuwait	SHV-112	*K. pneumoniae*	10 (outbreak strain)	2005 and 2006	84
	SHV-122	*E. coli*	1 (incidental)	ND	80
	TEM-like	*Salmonella* spp.	21 (30)	2003–2006	54
	CTX-M-like	*E. coli*	88 (78)	2006–2007	75
	CTX-M-3	*E. coli* or *K. pneumoniae*	1 (6.3)	ND	190
	CTX-M-9	*E. coli*	1 (5)	2005–2006	76
	CTX-M-9	*K. pneumoniae*	1 (9)	2005–2006	76
	CTX-M-14	*E. coli*	1 (5)	2005–2006	76
	CTX-M-14	*E. coli*	7 (5.3)	January-May 2008	77
	CTX-M-14b	*E. coli*	6 (4.4)	January-May 2008	77
	CTX-M-15	*Salmonella* spp.	13 (19)	2003–2006	54
	CTX-M-15	*K. pneumoniae*	10 (outbreak strain)	2005 and 2006	84
	CTX-M-15	*K. pneumoniae*	10 (91)	2005–2006	76
	CTX-M-15	*E. coli*	19 (90)	2005–2006	76
	CTX-M-15	*E. coli*	89 (65)	January-May 2008	77
	CTX-M-15	*E. coli*, *K. pneumoniae*	14 (88)	ND	190
	CTX-M-15	*K. pneumoniae*	11 (69)	2010	81
	CTX-M-44	*E. coli*	4 (2.7)	January-May 2008	77
	CTX-M-55	*E. coli* or *K. pneumoniae*	1 (6.3)	ND	190
	VEB-1a	*P. aeruginosa*	1 (incidental)	January 1999	86
	VEB-1b	*P. aeruginosa*	1 (incidental)	June 1999	86

(Continued on following page)

TABLE 2 (Continued)

Country and province or city	ESBL genotype	Producing organism(s)	No. (%) among ESBL producers	Time period	Reference
Oman					
Muscat	SHV-2	*K. pneumoniae*	1 (4.5)[b]	2011	105
	SHV-12	*K. pneumoniae*	6 (27)[b]	2010–2011	105
	SHV-28	*K. pneumoniae*	1 (incidental)	2009	102
	CTX-M-14	*E. coli*	2 (9)[b]	2010	105
	CTX-M-14	*K. pneumoniae*	1 (4.5)[b]	2011	105
	CTX-M-15	*K. pneumoniae*	10 (45)[b]	2010–2011	105
	CTX-M-15	*E. coli*	2 (9)[b]	2011	105
	CTX-M-15	*K. pneumoniae*, *E. coli*, or *E. cloacae*	14 (78)	2010–2011	104
	CTX-M-24	*K. pneumoniae*, *E. coli*, or *E. cloacae*	3 (17)	2010–2011	104
	VEB-6	*P. mirabilis*	1 (incidental)	2007	99

[a] EAEC, enteroaggregative *E. coli*; ND, no data.
[b] Rate among carbapenemase producers.

(36, 37). This outbreak caused 40% mortality, mostly due to septic shock (70%) (35) (Table 3). A KPC-producing isolate has also been recently reported in Riyadh and was found to be resistant to tigecycline (38) (Table 4).

Carbapenem Resistance in *P. aeruginosa* and *Acinetobacter*

Rates of imipenem resistance in *P. aeruginosa* have typically been 5 to 20%, but isolated hospitals have reported much higher results. Resistance to imipenem in *P. aeruginosa* isolated from an ICU in Jeddah (1995 to 1996) was found in 14% of 37 isolates (39). Babay observed 6 to 9% imipenem resistance in *P. aeruginosa* between 2001 and 2005 (40). A national study conducted on nonfermentative GNB isolated in 2009 from 24 hospitals found that 15.9% out of 6,364 *P. aeruginosa* isolates were resistant to imipenem (Table 5) (41). The rate of carbapenem-susceptible *P. aeruginosa* isolated from the ICU of a tertiary hospital in Riyadh was 66% in 2004 but had declined to 26% by 2009 (34).

Metallo-β-lactamases have emerged as a common mechanism of carbapenem resistance in *P. aeruginosa* from Saudi Arabia. In France an HIV patient developed a urinary tract infection (UTI) caused by MBL-producing *P. aeruginosa* (bla_{VIM-2}), but before receiving treatment in France, the patient had been hospitalized in a Saudi hospital. It was believed that the patient was colonized with this strain before arriving in France (42). In 2007, Al-Agamy et al. screened 135 clinical isolates of *P. aeruginosa* from Riyadh and found that 16.29% harbored bla_{VIM}-like genes (43). Of 200 *P. aeruginosa* strains isolated in 2010 from Riyadh, 8% were MBL producing and carried bla_{VIM} (24). Another recent study found that 22.6% and 19.4% of 31 MBL-producing *P. aeruginosa* isolates from Makkah (Mecca) harbored bla_{IMP} and bla_{VIM}, respectively (44). All MBL-positive *P. aeruginosa* isolates ($n = 15$) obtained from the burn unit of a hospital in Riyadh carried bla_{VIM}, including five isolates that cocarried bla_{OXA-10} (23) (Table 4). These data suggest a high prevalence of MBLs among *P. aeruginosa* strains in Saudi Arabia, with VIM being the most prevalent MBL type.

TABLE 3 Most documented outbreaks caused by ESBL producers and carbapenem-resistant GNB in the GCC states[a]

Country and β-lactamase type	Hospital or cities	Outbreak	*n*	Ward(s)	Organism	No. (%) of deaths	Reference
Saudi Arabia							
ESBL	Armed Force Hospital	8 mo	9	Neonatal	*K. pneumoniae* (SHV-12)	2 (22)	17
CR	King AbdulAziz Medical City	2009–2010	20	ICU	*K. pneumoniae*	8 (40)	35
Kuwait							
ESBL	Mubarak Al-Kabeer Hospital	2 mo	14	ICU	*K. pneumoniae* (CTX-M-15)	3 (21.4)	82
ESBL	Al-Amiri Hospital	November-December 2007	13	3 wards and ICU	*K. pneumoniae* (SHV-112)	ND	83
ESBL	Al-Jahra Hospital	February-March 2006	7	NICU	*K. pneumoniae* (CTX-M-15, SHV-112)	ND	84
CR	Mubarak Al-Kabir Hospital	2006–2007	24	ICU	*Acinetobacter*	4 (16.7)	92
Qatar							
CR	Hamad Medical Corporation	6 mo	21	ICU	*Acinetobacter*	ND	111
Bahrain							
ESBL	Oxford, London	2 wk, 1991	6, 3	ICU	*K. pneumoniae*	1 (11)	113

[a] ESBL, extended-spectrum β-lactamase; CR, carbapenem resistant; ICU, intensive care unit; NICU, neonatal intensive care unit; ND, no data.

TABLE 4 Summary of carbapenemase enzymes observed in isolates from the Gulf states

Country and city or province	Carbapenemase genotype	Producing organism(s)	No. (%) among tested carbapenem-nonsusceptible isolates	Time period	Reference
Saudi Arabia					
ND[a]	VIM-2	*P. aeruginosa*	1 (incidental)	ND	42
Riyadh	KPC	*K. pneumoniae*	1 (incidental)	ND	38
	VIM-like	*P. aeruginosa*	22 (100)	2007	43
	VIM-like	*P. aeruginosa*	15 (60)	2010	23
	OXA-23	*Acinetobacter*[b]	14 (50)	2011	46
	OXA-23	*Acinetobacter*[b]	16 (60)	2010	25
	OXA-40	*Acinetobacter*[b]	1 (3.7)	2010	25
	OXA-48	*K. pneumoniae*	23 (outbreak strain)	2009–2010	36
Eastern province	OXA-23	*Acinetobacter*[b]	105 (78)	2010–2011	47
Makkah	IMP	*P. aeruginosa*	33 (18)	2009	44
	VIM	*P. aeruginosa*	29 (15)	2009	44
United Arab Emirates					
Abu Dhabi	VIM-4	*E. cloacae*	1 (3)	2011	61
	NDM	*Enterobacteriaceae* (*K. pneumoniae*, *E. coli*, *E. cloacae*)	22 (65) ($n = 6, 2, 1$)	ND	61
	NDM-1	*Enterobacteriaceae* (*K. pneumoniae*, *E. coli*, *C. freundii*, *E. cloacae*)	7 (22) ($n = 3, 2, 1, 1$)	2009–2011	62
	NDM-2	*Acinetobacter*[b]	2 (1.3)	2008–2010	65
	OXA-23	*Acinetobacter*[b]	5 (100)	2006	63
	OXA-48-like	*Enterobacteriaceae* (*K. pneumoniae*, *E. coli*)	11 (32) ($n = 8, 3$)	ND	61
Al Ain	OXA-23	*Acinetobacter*[b]	3 (100)	ND	64
Kuwait					
Kuwait	KPC	*E. coli* (ST131)	1 (incidental)	ND	80
	VIM	*E. coli* (ST131)	1 (incidental)	ND	80
	NDM-1	*K. pneumoniae*	2 (100)	2010–2011	87
	OXA-48	*K. pneumoniae*	1 (incidental)	2011	88
	OXA-58	*Acinetobacter*[b]	1 (incidental)	1996	94
	NDM-1	*K. pneumoniae*	2 (incidental)	March and June 2009	102
Oman					
Muscat	NDM-1	*K. pneumoniae*	11 (69)	2010–2011	105
	NDM-1	*K. pneumoniae*	10 (77)	2010–2011	104
	NDM-1	*E. coli*	1 (25)	2011	105
	OXA-48	*K. pneumoniae*	2 (13)	2011	105
	OXA-48	*E. coli*	3 (75)	2010–2011	105
	OXA-48	*E. coli*	3 (75)	2010–2011	104
	OXA-181	*K. pneumoniae*	1 (incidental)	March 2010	103
	OXA-181	*K. pneumoniae*	1 (6)	2011	105
	OXA-181	*K. pneumoniae*	2 (15)	2010–2011	104
Bahrain					
Manama	OXA-23	*Acinetobacter*	2 (25)	2007–2008	95
	OXA-58	*Acinetobacter*	1(13)	2007–2008	95
	OXA-72	*Acinetobacter*	5 (63)	2007–2008	95

[a] ND, no data.
[b] The intrinsic $bla_{\text{OXA-51-like}}$ gene was reported.

Studies on carbapenem resistance in *Acinetobacter* in Saudi Arabia report conflicting results. For example, in the ICU of a tertiary hospital in Riyadh, imipenem susceptibility in *Acinetobacter* declined from 55% in 2004 to just 10% in 2009 (34). Conversely, a national study from 24 hospitals in 2009 found that 94.6% of 2,228 *Acinetobacter* isolates were imipenem susceptible. This rate of susceptibility is significantly higher than other rates observed in studies from individual hospitals or from other GCC states (Table 5) (41).

A variety of β-lactamases have contributed to carbapenem resistance in *Acinetobacter* in Saudi Arabia. Carbapenem-resistant *Acinetobacter* isolates ($n = 20$) from patients with diabetes mellitus in Saudi Arabia (2006 to 2007) were PCR screened for OXA genes. Novel OXA-51-like-encoding genes ($bla_{\text{OXA-90}}$, $bla_{\text{OXA-130}}$, $bla_{\text{OXA-131}}$, and $bla_{\text{OXA-132}}$) were identified in nine *Acinetobacter* strains isolated from three different sites (45). More recent studies analyzed carbapenem-resistant *Acinetobacter* strains isolated from different sites in Riyadh (2010 to 2011) and found that 53.6% of

TABLE 5 Dramatic increase in rate of carbapenem-resistant GNB over the last decade[a]

Collection date	Country	City or province	Source	Organism(s)	No. (%) of imipenem-nonsusceptible isolates	Reference
1994	UAE	Al Ain	Clinical specimens	*E. coli*, *Klebsiella* spp.	0	48
1994–1995	Kuwait	Kuwait	ICU	All Gram-negative bacteria	0	14
			Burns	All Gram-negative bacteria	28 (3)	90
			Burns	*Acinetobacter*	0	90
			Blood from ICU	*Acinetobacter*	0	68
			Blood from ICU	*P. aeruginosa*	3 (19)	68
1996–1997	Kuwait	Kuwait	Clinical specimens	*P. aeruginosa*	37 (10.4)	89
March-August 1994	Saudi Arabia	Jeddah	ICU	*P. aeruginosa*	9 (32)	14
				Acinetobacter	0	14
1995–1996	Saudi Arabia	Jeddah	ICU	*P. aeruginosa*	5 (14)	39
1998	Qatar	Doha	Clinical specimens	*E. coli*	1 (6)	109
				Klebsiella spp.	1 (6)	109
				P. aeruginosa	6 (22)	109
				Acinetobacter	0	109
2001	Saudi Arabia	Riyadh	Clinical specimens	*P. aeruginosa*	46 (6)	40
2002	Saudi Arabia	Riyadh	Clinical specimens	*P. aeruginosa*	28 (4)	40
2003	Saudi Arabia	Riyadh	Clinical specimens	*P. aeruginosa*	61 (8)	40
2004	Saudi Arabia	Riyadh	Clinical specimens	*P. aeruginosa*	56 (9)	40
2005	Saudi Arabia	Riyadh	Clinical specimens	*P. aeruginosa*	51 (9)	40
2005	UAE	Al Ain	Clinical specimens	*E. coli*	109 (35.7)	48
				Klebsiella spp.	94 (29.8)	48
2006	Kuwait	Kuwait	Clinical specimens	*Acinetobacter*	63 (25.2)	91
					36 (64.3)	91
2004–2007	Oman	Dhahira	Blood	*E. coli*	6 (17.1)	101
				Klebsiella spp.	4 (14.3)	101
				P. aeruginosa	7 (63.3)	101
2007–2008	Qatar	Doha	Blood	*Acinetobacter*	5 (41.5)	110
				P. aeruginosa	3 (14.3)	110
2007–2009	Bahrain	Manama	Clinical specimens	*Acinetobacter*	262 (58)	95
January-December 2009	Saudi Arabia	>10 cities	Clinical specimens from 24 hospital	*P. aeruginosa*	1,010 (15.9)	41
				Acinetobacter	121 (5.4)	41
2009–2010	Saudi Arabia	Makkah	Clinical specimens	*P. aeruginosa*	186 (39)	44
2010	Saudi Arabia	Riyadh	Burns	*P. aeruginosa*	25 (16.2)	23
2010	Saudi Arabia	Riyadh	Clinical specimens	*Acinetobacter*	76 (90.5)	191
				P. aeruginosa	30 (91)	191
2010–2011	Saudi Arabia	Eastern province	Clinical specimens	*Acinetobacter*	90 (68)	47

[a] ICU, intensive care unit; UAE, United Arab Emirates.

the total 56 harbored the bla_{OXA-23} gene (25, 46) and a single isolate harbored bla_{OXA-40} (25). Of 132 *Acinetobacter* isolates from the eastern province, 79.5% carried bla_{OXA-23}, and notably, none of the isolates was reported to be positive for IMP and VIM (47) (Table 4).

UNITED ARAB EMIRATES

Extended-Spectrum and AmpC-Type β-Lactamases

Antibiotic resistance rates for different bacteria isolated from three hospitals in the United Arab Emirates (UAE) in 1994 were compared with the rates from 2005, and it was found that resistance of *E. coli* to ceftriaxone increased from 0 to 61%. *Klebsiella* spp. also displayed increased resistance to ceftriaxone in the three different hospitals (0 to 49.1%, 0 to 9.3%, and 2 to 20%) (48).

Community-acquired ESBL-producing *Enterobacteriaceae* are an emerging issue in the UAE. Overall, the resistance against expanded-spectrum cephalosporins in community-acquired uropathogens in children in UAE increased from 11 to 16.7% in 2003 to 2004 versus 2005 to 2006, respectively (49). This rate was slightly higher than that observed in isolates from community-acquired urinary tract infections (CA-UTIs) in Sharjah (2006 to 2007), where 7% and 11% of *E. coli* and *K. pneumoniae* isolates, respectively, were found to be resistant to ceftriaxone (50). Surveillance on *Enterobacteriaceae* isolated from inpatients found that 31% of reported ESBL-producing organisms were from urine (51).

CTX-M-type ESBLs appear to predominate in UAE. A study of *Enterobacteriaceae* ($n = 130$) isolates from inpatients from a hospital in Sharjah (2005 to 2006) showed that 41% ($n = 53$) were ESBL producers, and of these, 60% were *E. coli*, 36% *K. pneumoniae*, and 4% *Klebsiella oxytoca* (51) (Table 1). Sonnevend et al. found that 11.3% (5 of 44) enteroaggregative *E. coli* isolates from

2003 to 2004 were ESBL producers, and all produced CTX-M-15. This is the first report to describe CTX-M-15 in the GCC region (52) (Tables 1 and 2). Rotimi et al. evaluated resistance to cefotaxime among 122 nontyphoidal *Salmonella* sp. isolates in 2003 to 2004 from Al Ain (53). Nineteen isolates (15.4%) were ESBL positive, and molecular screening identified eight isolates harboring bla_{TEM}-like genes, while a single isolate coharbored $bla_{CTX\text{-}M\text{-}15}$ (54) (Table 2). Four percent of *Shigella* sp. isolates from patients with acute diarrhea (2003 to 2004) were ESBL positive. However, PCR amplification for the $bla_{CTX\text{-}M}$, bla_{SHV}, and bla_{TEM}-like genes did not show positive results, suggesting that other, less common ESBL genes may be responsible for such phenotypes (55).

Out of 662 combined *E. coli* and *K. pneumoniae* isolates from clinical specimens (January to December 2008) from three different hospitals, 36% were ESBL positive (Table 1). $bla_{CTX\text{-}M\text{-}15}$ was found in 94% of ESBL-positive *E. coli* and 64.4% of *K. pneumoniae* isolates. Additionally, 32.2% of ESBL-positive *K. pneumoniae* isolates harbored $bla_{SHV\text{-}28}$ (Table 2). Nine percent of ESBL-positive *E. coli* isolates did not show positive results for bla_{TEM}, bla_{SHV}, and $bla_{CTX\text{-}M}$-like genes (56), suggesting that a less common ESBL was present.

Recently, Tain et al. (57) defined a novel Ambler class A ESBL enzyme (PME-1) produced by *P. aeruginosa*, which was isolated from a patient who had prolonged hospitalization (6 months) in Dubai before being transferred to Pittsburgh, PA, in December 2008 (Table 2). The PME-1 enzyme shared 50%, 43%, and 41% amino acid similarity with the L2 β-lactamase of *Stenotrophomonas maltophilia*, CTX-M-9, and KPC-2, respectively. The PME-1 enzyme demonstrated hydrolytic activity against ceftazidime, cefotaxime, and aztreonam, although the enzyme was inhibited by clavulanic acid, sulbactam, and tazobactam. The original patient isolate producing PME-1 was resistant to ceftazidime (MIC, 64 μg/ml), cefepime (MIC, 64 μg/ml), and meropenem (MIC, 32 μg/ml), but a transformant harboring the PME-1-encoding plasmid had a cefepime MIC of 8 μg/ml and a meropenem MIC of 0.5 μg/ml. The $bla_{PME\text{-}1}$ gene was found on a plasmid that carried other antibiotic resistance genes and was flanked by the insertion sequence IS*CR24*, implying the use of rolling-circle transposition for its mobility (57).

Another lesser ESBL type being found in UAE is PER-7 from an *Acinetobacter* strain isolated from tracheal aspirates in Tawam Hospital. The strain was ceftazidime resistant, and the $bla_{PER\text{-}7}$ gene was found encoded in a large plasmid (58) (Table 2). However, the first identification of $bla_{PER\text{-}7}$ was in the chromosomal DNA of an *Acinetobacter* isolate from France (59). PER-7 is a derivative of PER-1, which is commonly produced by nosocomial *Acinetobacter* and *P. aeruginosa* isolated from Turkey (60).

The only reported plasmid-mediated AmpC from UAE was recently found in an *Enterobacter cloacae* strain that produced CMY-4 as well as CTX-M-15 and the carbapenemase VIM-4 (61).

Carbapenem Resistance in *Enterobacteriaceae*

Carbapenem resistance in *Enterobacteriaceae* in UAE is reportedly very rare, although isolated hospitals have had surprisingly high rates of resistance (48) (Table 5). A more recent concern has been the importation of carbapenemases. Recent studies investigated the dissemination of NDM-1-producing GNB in UAE. Seven out of 32 *Enterobacteriaceae* carried $bla_{NDM\text{-}1}$ on conjugative plasmids (Table 4). Of the seven isolates, three were recovered from patients from the Indian subcontinent and one from an Emirati patient who had a history of travel to India, but the other three patients were from Iraq, Oman, and Egypt and did not have histories of recent travel other than to the GCC countries (62). NDM-positive isolates have been found in 9 out of 34 carbapenem-nonsusceptible *Enterobacteriaceae*, while OXA-48-like was found in 11 isolates. From this collection, $bla_{VIM\text{-}4}$ was found in a plasmid carried by a single *E. cloacae* isolate from an Egyptian patient (61) (Table 4).

Carbapenem Resistance in *P. aeruginosa* and *Acinetobacter*

As with *Enterobacteriaceae*, the rate of imipenem-resistant nonfermenting GNB in UAE increased during the 2000s compared with rates from the 1990s. For example, 1.4 and 8% of *P. aeruginosa* strains isolated in 1994 from Al Ain were resistant to imipenem, while the rates in 2005 increased to 23 and 15.8% (48) (Table 5).

Five carbapenem-resistant *Acinetobacter* isolates from the ICU of a hospital in Abu Dhabi were found to produce OXA-23. Four of the isolates belonged to the same clone, which carried the $bla_{OXA\text{-}23}$ gene on the chromosome, and the fifth isolate carried the gene on a transferrable plasmid (63). This study indicates the presence of carbapenemases in UAE hospitals. Hence, further phenotypic surveillance combined with molecular analyses were carried out to identify the emergence of such MDR bacteria. Recently, Opazo et al. (64) identified three carbapenemase-producing *Acinetobacter* isolates from Al Ain. One was obtained from a catheter tip of an adult patient, and the other two were isolated from sputum of a pediatric patient a few weeks apart. These were identified by PFGE as the same clone, and all isolates carried the chromosomal $bla_{OXA\text{-}64}$ gene and the $bla_{OXA\text{-}23}$ gene on plasmids. Typically, the insertion sequence IS*Aba1* was found located upstream of the $bla_{OXA\text{-}23}$ gene (64).

Another study screened 155 carbapenem-nonsusceptible *Acinetobacter* isolates from Abu Dhabi hospitals (2008 to 2011). An isolate that produced NDM-2 was recovered from a urine sample from an Egyptian female patient (Table 4). Characteristically, the insertion element IS*Aba125* was found upstream of the $bla_{NDM\text{-}2}$ gene. The patient had received previous treatment in Egypt, Lebanon, and UAE (65).

KUWAIT

Extended-Spectrum and AmpC-Type β-Lactamases

Resistance to expanded-spectrum cephalosporins in community-acquired gastrointestinal pathogens was extremely rare in Kuwait in the 1990s. Two studies showed that 39% and 54% of *Salmonella* and *Shigella* sp. strains retrospectively isolated during and after the Gulf War (1990 to 1993 and 1996) were resistant to ampicillin, but all *Shigella* sp. isolates were susceptible to expanded-spectrum and broad-spectrum cephalosporins (66), and only 0.3% of *Salmonella* sp. isolates were resistant to cefotaxime (67). More recently, *Shigella* sp. isolates ($n = 42$) collected between 2003 and 2005 were all found to be susceptible to expanded-spectrum cephalosporins (55), while 1.6% of 247 nontyphoidal *Salmonella* isolates showed resistance to cefotaxime (53). In comparison, Rotimi et al. analyzed 101 Gram-negative bacteria isolated from ICU samples (1994 to 1995) and reported that resistance to ceftazidime was 70% in *Acinetobacter*, 12% in *P. aeruginosa*, and 44% in *E. cloacae*. However, no ESBL production was identified among *E. coli* and *K. pneumoniae* using the Etest (14). In the same ICU, 31% of *K.*

pneumoniae isolates (1996 to 1997) were resistant to cefotaxime and ceftazidime (68).

The prevalence of ESBLs in Kuwait appears to have increased (Table 1). Out of 1,094 uropathogens (1995 to 2001), 3 to 4% showed resistance to expanded-spectrum cephalosporins. ESBLs were found in only 3/196 (1.53%) *Klebsiella* sp. isolates and in 2/780 (0.3%) *E. coli* isolates (69). Jamal et al. reported the prevalence of ESBL-positive GNB collected from a tertiary hospital in 2003 and found using Etest that out of 2,107 *E. coli* isolates, 5.6% were ESBL positive, as were 11.4% of *K. pneumoniae* isolates (n = 509) and 3% of *Enterobacter* sp. isolates (n = 134) (70). Mokaddas et al. showed ESBL production in 5 out of 15 *Enterobacteriaceae* isolated between 2001 and 2004 (71). A larger study of 15,064 urine isolates (2005 to 2007) showed that 26% and 12% of *E. coli* isolates and 28% and 17% of *K. pneumoniae* isolates from hospital-acquired UTIs and CA-UTIs produced ESBLs, respectively (72). Isolates obtained from another hospital (2002 to 2005) showed similar trends, where 1,018 (31.7%) of 3,215 *Enterobacteriaceae* were ESBL producers. Of those, 42% were *K. pneumoniae* and 37% were *E. coli* (73). Even higher rates of ESBL production were found among *E. coli* (62% of 229) and *K. pneumoniae* (82.1% of 117) strains isolated in 2006 (74).

A Kuwaiti nationwide surveillance study (2006 to 2007) reported that most *E. coli* isolates that are resistant to expanded-spectrum cephalosporins carry $bla_{\text{CTX-M}}$-like genes, indicating that this is a major contributor of ESBLs in the region (Table 2). Notably, CTX-M genes have been commonly detected in *E. coli* isolates (75). Other ESBL types have been more dominant in other species. For example, 50 out of 248 (17.6%) *Salmonella* sp. isolates from stool samples (2003 to 2006) were found to be ESBL producers. Forty percent of these carried bla_{TEM}-like genes, while 26% harbored $bla_{\text{CTX-M-15}}$, including *S. enterica* serotype Typhi isolates. Nine of the *Salmonella* sp. isolates carried both CTX-M-15 genes and bla_{TEM} (54). The majority (72%) of *Salmonella* sp. isolates producing CTX-M-15-ESBL were obtained from non-Kuwaiti Arabs, while three of the CTX-M-15 producers were isolated from patients of Indian origin. Similarly, the majority of CTX-M-15-producing *E. coli* and *K. pneumoniae* isolates were found in patients from the Indian subcontinent and non-Kuwaiti Arabs with recent travel histories (76).

A Kuwaiti national screening study (eight hospitals in 2008) identifying dominant CTX-M types in 106 *E. coli* isolates showed that 84% were CTX-M-15 and 6.6% CTX-M-14. Less commonly, $bla_{\text{CTX-M-14b}}$ and $bla_{\text{CTX-M-44}}$ ($bla_{\text{TOHO-1}}$) were found, in 5.7% and 3.8%, respectively. Unsurprisingly, urine samples were the major source (78.9%) of the resistant bacteria. This study also showed that while the majority of CTX-M-producing *E. coli* isolates have been found among Kuwaiti nationals, patients belonging to other nationalities have also contributed significantly (77). Of 16 randomly selected ESBL-producing *K. pneumoniae* isolates and 27 *E. coli* isolates, CTX-M-15 was found in 10 out of 11 $bla_{\text{CTX-M}}$-positive *K. pneumoniae* and 19 out of 21 $bla_{\text{CTX-M}}$-positive *E. coli* strains isolated between 2005 and 2006. One *E. coli* isolate and another *K. pneumoniae* isolate produced CTX-M-9, while a single *E. coli* isolate was found to produce CTX-M-14 (76). An internationally prevalent *E. coli* clone (ST131) has been found to frequently produce CTX-M enzymes (78). While there has been no systematic evaluation of the prevalence of the ST131 *E. coli* clone in Kuwait, several reports describe the identification of the clone in this country (79, 80).

Recently, Vali et al. characterized 16 *K. pneumoniae* isolates (October to December 2010) and found that 11 harbored $bla_{\text{CTX-M-15}}$ (81). As an example of the increasing spread of ESBL-producing bacteria in Kuwaiti hospitals, an outbreak of CTX-M-15-producing *K. pneumoniae* was documented in an ICU at a major hospital in Kuwait, where 14 patients became infected by the single clone within 2 months, resulting in a 21.4% mortality rate (Table 3) (82).

The prevalence of ESBLs in *Enterobacteriaceae* in Kuwait may occasionally be due to the incidence of other ESBL variants (Table 2). Novel SHV-like enzymes have emerged, and some were first identified in Kuwait, for example, SHV-112 (83). Ten *K. pneumoniae* isolates caused outbreaks in a neonatal intensive care unit (NICU) and were found to be carrying $bla_{\text{TEM-1}}$, $bla_{\text{CTX-M-15}}$, and $bla_{\text{SHV-112}}$ (84). Another SHV-112-producing *K. pneumoniae* isolate caused an outbreak in 3 different wards and in an ICU at a single hospital in Kuwait during a period of 2 months in 2007 (Table 3). To date, no further data in the literature describe the detection of $bla_{\text{SHV-112}}$ from any other countries. Another novel SHV ESBL enzyme first identified in an MDR *E. coli* isolate from Al-Amiri Hospital was named SHV-122 (80). An SHV-122 variant was subsequently reported in a Brazilian hospital (85).

In 1999, two *P. aeruginosa* isolates, one associated with a respiratory tract infection in an infant admitted to the ICU of Ibn-Sina Hospital and the other associated with a UTI following catheterization in an elderly patient hospitalized in Mubarak Al-Kabeer Hospital, were found to be positive for bla_{VEB}-like ESBLs. Sequencing showed a 99% similarity to $bla_{\text{VEB-1}}$, and hence the enzymes were described as VEB-1a and VEB-1b. It is important to note that neither of the infected patients had a history of travel outside Kuwait (86).

Carbapenem Resistance in *Enterobacteriaceae*

The first documented case of carbapenem-resistant *Enterobacteriaceae* in Kuwait was reported in an *E. coli* strain that was highly resistant to meropenem and imipenem. The bacterium carried both bla_{KPC} and bla_{VIM}, along with the novel ESBL gene $bla_{\text{SHV-122}}$ (80). The second report describes the occurrence of two NDM-1-producing *K. pneumoniae* isolates: the first in an Indian patient with recent travel history admitted to the ICU of a tertiary care teaching hospital, and the second in an elderly Kuwaiti patient with previously known comorbidities admitted to the same ICU 2 weeks after the death of the first patient. The Kuwaiti patient had no travel history in the 2 years prior to the infection. Despite the facts that both isolates were resistant to aminoglycosides and carried a 50-kb transferable plasmid carrying $bla_{\text{NDM-1}}$, $bla_{\text{SHV-11}}$, and the AmpC $bla_{\text{CMY-6}}$ genes and were determined to be clonally related using PFGE, only the first isolate (from the Indian patient) showed resistance to colistin (MIC, 3 μg/ml) and tigecycline (MIC, 4 μg/ml) using Etest (87). In 2011, a Kuwaiti patient admitted to a hospital in France was found on surveillance cultures to have an OXA-48-producing *K. pneumoniae* strain. One month before travel to France, she had undergone surgery in Kuwait (Table 4) (88). These findings should alert other countries in the region to bacteria producing this emerging resistance mechanism.

Carbapenem Resistance in *P. aeruginosa* and *Acinetobacter*

Carbapenem resistance in Kuwaiti hospitals was uncommon until the mid-1990s. Of 357 *P. aeruginosa* isolates from different clinical specimens between 1996 and 1997, 5.9% were resistant to both

imipenem and meropenem (89). All GNB strains from ICU patients in a tertiary hospital (1994 to 1995) were susceptible to imipenem (14), and of 948 strains from the burn unit of Ibn-Sina Hospital during the same period, 3% had resistance to imipenem. Notably, 100% of *Acinetobacter* isolates from the burns unit (90) and from blood samples from an ICU were susceptible to imipenem (68) (Table 5). However, carbapenem resistance in *Acinetobacter* is now problematic in many Kuwaiti hospitals, and resistance to imipenem and meropenem has been found to be as high as 64.3% and 66.1%, respectively (74). A national surveillance study (2006) found that 25.2% and 37.2% of 205 *Acinetobacter* isolates were resistant to imipenem and meropenem, respectively (91) (Table 5).

Acinetobacter was associated from several outbreaks during 2006 to 2007 in an ICU and resulted in an overall mortality rate of 16.7% (Table 3). The majority of the isolates were blood cultures or endotracheal tube secretions, and the Etest showed positive MBL results with all carbapenem-resistant isolates, with two distinct clones being identified (92). However, the type of MBL was not determined.

The first report of a novel OXA carbapenemase, OXA-58, came from Kuwait (93, 94). Although this particular isolate was collected in 1996, only one further isolate has been identified in any Gulf state (Bahrain, 2008) (95). However, close to the GCC states, an outbreak in a Lebanese hospital had a high incidence of OXA-58-producing *Acinetobacter* (96).

SULTANATE OF OMAN

Extended-Spectrum and AmpC-Type β-Lactamases

Substantial proportions of *E. coli* and *Klebsiella* sp. isolates in Omani hospitals are ESBL producers. In one evaluation (2004 to 2005), 60% of ESBL producers were *E. coli* and 40% were *K. pneumoniae.* Unfortunately, the report failed to state the proportion of all *E. coli* and *K. pneumoniae* isolates which were ESBL producers. The majority of ESBL producers were from medical wards (29.6%), followed by samples from outpatients (24.3%), with urine specimens as the predominant source (70.4%), followed by blood cultures (16.5%) (97). The prevalence of ESBL producers isolated in 2005 from the pediatric wards of a tertiary hospital was found to be 9/87 (14.9%) for *E. coli* and *K. pneumoniae* isolates combined (98) (Table 1).

No molecular studies on ESBLs in Oman are reported prior to 2007, when an ESBL-related gene was first identified in *Proteus mirabilis* isolated from a bronchopulmonary secretion of an elderly hospitalized patient. Sequencing identified the gene as $bla_{\text{VEB-6}}$ (99) (Table 2).

To date, no plasmid-mediated AmpC from GNB isolated in hospitals in Oman has ever been reported.

Carbapenem Resistance in *Enterobacteriaceae*

Carbapenem resistance was not common over the past decade in Omani hospitals; for example, all ESBL producers isolated between 2004 and 2005 from a hospital in Muscat were found to be susceptible to carbapenems (97). The same result was found with ESBL-positive *E. coli* and *K. pneumoniae* isolates ($n = 301$) from the pediatric ward at the same hospital in 2005 (98). However, an imipenem-resistant *K. pneumoniae* strain was subsequently isolated from the hospital's pediatric oncology ward (100). Blood culture isolates collected from a regional hospital in Oman between 2004 and 2007 were tested using the disk diffusion method, and it was found that 4/28 *K. pneumoniae*, 2/7 *Enterobacter* sp., and 6/35 *of E. coli* isolates were resistant to imipenem (101) (Table 5).

Molecular characterization of carbapenemase-producing bacteria was not performed before the identification of the recently emergent NDM-1. $bla_{\text{NDM-1}}$ was detected in two different strains of *K. pneumoniae* isolated from different patients. The first patient was an Omani patient who received medical treatment in India in 2009 for pneumonia before being repatriated. $bla_{\text{NDM-1}}$ was shown to be on a transferable plasmid carrying the genes $bla_{\text{CTX-M-15}}$, $bla_{\text{SHV-28}}$, $bla_{\text{OXA-1}}$, $bla_{\text{OXA-9}}$, and $bla_{\text{TEM-1}}$ (Tables 2 and 4). Multilocus sequence typing (MLST) grouped this isolate to the ST14 clone, which matches *K. pneumoniae* carrying $bla_{\text{NDM-1}}$ from India (102).

The second patient was colonized by NDM-1-positive *K. pneumoniae* and had been admitted to the same ICU 3 months after the first patient was discharged. ICU admission was due to treatment of traumatic injury, and the patient had not traveled to India. NDM-1-producing *K. pneumoniae* was isolated from urine and also carried SHV-11 and OXA-1. This *K. pneumoniae* isolate grouped to the ST340 type and did not match the first isolate based on PFGE genotyping (102).

The detection of NDM-1 in Oman increased interest in identifying other carbapenem-hydrolyzing enzymes produced by clinical isolates in the sultanate. For example, Potron et al. characterized a *K. pneumoniae* isolate that produces a carbapenemase which was shown to be OXA-181, a close variant of OXA-48. The strain was isolated from a 54-year-old patient hospitalized in Muscat, who had previous hospitalization histories in Tanzania and Mumbai, India. The bacterium also carried other β-lactamase genes, including the $bla_{\text{CTX-M-15}}$, $bla_{\text{OXA-1}}$, $bla_{\text{TEM-1}}$, and $bla_{\text{SHV-11}}$ genes (103).

Between 2010 and 2011, carbapenem-resistant *K. pneumoniae* ($n = 13$), *E. coli* ($n = 4$), and *E. cloacae* ($n = 1$) strains were isolated from three different hospitals in Oman. All individuals were Omani, and only three of them had histories of travel to India or Pakistan prior to admission. $bla_{\text{OXA-48}}$ was found in all *E. coli* isolates and in a single *K. pneumoniae* isolates. Nine out of 10 *K. pneumoniae* isolates had $bla_{\text{NDM-1}}$, but the remaining isolate carried both $bla_{\text{OXA-181}}$ and $bla_{\text{NDM-1}}$. The OXA-181-encoding gene was also found in one *K. pneumoniae* isolate alone. PFGE analysis revealed that seven NDM-1-producing *K. pneumoniae* and three OXA-48-producing *E. coli* isolates were related, suggesting clonal dissemination of those strains in two hospitals (104).

A more recent study found that 10 *K. pneumoniae* isolates produced NDM-1, while three *E. coli* and two *K. pneumoniae* isolates produced OXA-48; an additional *K. pneumoniae* isolate simultaneously coproduced NDM-1 and OXA-181. Four of the patients had a history of travel to India. The *K. pneumoniae* isolates were MLST grouped; this found ST147 in 5/11 NDM-1-positive isolates, which was previously identified among NDM-1-producing isolates from Iraq (105).

Carbapenem Resistance in *P. aeruginosa* and *Acinetobacter*

The documented rates of carbapenem-resistant *P. aeruginosa* and *Acinetobacter* isolates from different sites in Omani hospitals were reportedly less than observed in other GCC states. For example, isolates from a hospital in Muscat (2007) showed that susceptibil-

ity to meropenem was 85% and 100% for *P. aeruginosa* and *Acinetobacter*, respectively (106) (Table 5).

QATAR

Extended-Spectrum and AmpC-Type β-Lactamases

Infections caused by *Salmonella* spp. are problematic in Qatar; however, similar to the case for other Gulf countries, no emerging resistance against extended-spectrum cephalosporins has been documented. For example, 24/100 *Salmonella* sp. isolates associated with bacteremia were MDR, but none were resistant to cefotaxime (107). Although some studies from the 1990s did not report ESBL producers from hospitalized patients (108), ICU studies illustrated a high prevalence of extended-spectrum cephalosporin resistance. In 1998, 108 samples were selected from patients after admission to a hospital in Doha. Four of 18 *Klebsiella* sp. isolates and 7/13 *Enterobacter* sp. isolates were ESBL confirmed using the double disk synergy test, but all *E. coli* isolates remained negative (109). More recent studies (2007 to 2008) of 425 blood culture isolates from the same hospital showed ESBL production, using Etest, in 27.8% of *E. coli* and 18% of *K. pneumoniae* isolates (110) (Table 1).

To date, no plasmid-mediated AmpC from GNB in Qatar has ever been reported.

Carbapenem Resistance in *Enterobacteriaceae*

Data on carbapenem resistance in *Enterobacteriaceae* are extremely limited. El Shafie et al. found that 6% of the reported isolates of both *E. coli* and *Klebsiella* spp. were resistant to imipenem but not to meropenem (109). Conversely, all *Enterobacter* sp., *Klebsiella* sp., and *E. coli* blood culture isolates (2007 to 2008) were found to be carbapenem susceptible (110).

Carbapenem Resistance in *P. aeruginosa* and *Acinetobacter*

Examination of ICU isolates collected in 1998 revealed that 21% of *P. aeruginosa* isolates were resistant to imipenem and meropenem but that all *Acinetobacter* isolates were carbapenem susceptible (109). In contrast, for blood culture isolates (2007 to 2008), carbapenem resistance was found in 41.5% of *Acinetobacter* and 14.3% *P. aeruginosa* isolates (110) (Table 5).

El Shafie et al. reported an outbreak, involving 21 ICU patients, caused by carbapenem-resistant *Acinetobacter*. The first isolate was obtained in January 2002. Subsequently, 20 patients admitted to the same ICU over a 6-month period were colonized or infected with the same *Acinetobacter* strain. The average length of stay was about 10 days before proven colonization or infection. Thirty-six percent of the environmental swabs ($n = 33$) (from bedrails, curtains, etc.) demonstrated contamination with the same strain (111) (Table 3).

KINGDOM OF BAHRAIN

Extended-Spectrum and AmpC-Type β-Lactamases

The first reported cases of ESBL-producing *K. pneumoniae* in the region were isolated from Manama (112). Extended-spectrum cephalosporins were introduced into Bahrain in 1987. In 1988, 5% of *K. pneumoniae* isolates had reported resistance to extended-spectrum cephalosporins, but by 1989, the rate increased to 37%. In 1990, nearly two-thirds of *K. pneumoniae* isolates were nonsusceptible to ceftazidime and/or ceftriaxone (112) (Table 1).

The emergence of ESBL-positive *K. pneumoniae* strains in the Manama hospital did affected not only patients in Bahrain but also patients in Europe, as cephalosporin-resistant *K. pneumoniae* outbreaks occurred in two British hospitals due to an intercontinental transfer of a patient from Bahrain. *K. pneumoniae* strains resistant to cephalosporins and aminoglycosides were isolated from six patients in an ICU of a hospital in Oxford. A second outbreak involved three ICU patients in a London hospital and was caused by an ESBL-positive *K. pneumoniae* isolate that had an antibiotic resistance profile similar to that of the isolate of the first outbreak. The medical history of a female patient indicates that the patient was admitted multiple times over 3 years to a Bahraini hospital before being hospitalized in London and transferred to Oxford. Strain relatedness was confirmed using PFGE: all *K. pneumoniae* isolates from the Oxford, London, and Bahraini hospitals were found to be the same strain (Table 3). These outbreaks caused considerable financial cost to the two United Kingdom hospitals, since admission to the ICUs was stopped for 2 weeks and cardiothoracic surgical procedures were cancelled (113).

Since that time, the prevalence of ESBL production among *Enterobacteriaceae* in Bahrain has not been studied until recently. Bindayna et al. showed that 22.6% of 11,886 *Enterobacteriaceae* isolated from 2005 to 2006 were ESBL producers, mostly from inpatient specimens (87.7%). *E. coli* was the major ESBL producer (52.5%), followed by *K. pneumoniae* (24.3%) and *Proteus* spp. (17.6%). None of the *Enterobacteriaceae* were resistant to carbapenems (114). The rate of ESBL-positive *E. coli* isolated from an NICU (2002 to 2004) was 28.7% out of 160 and increased to 42% out of 116 from 2005 to 2007. ESBL-positive *Klebsiella* sp. isolates increased from 22% to 27% out of 180 isolates for both periods (115) (Table 1). Neither of the studies conducted PCR screening for ESBL genes.

To date, no plasmid-mediated AmpC from GNB in Bahrain has ever been reported.

Carbapenem Resistance in *P. aeruginosa* and *Acinetobacter*

Of *Acinetobacter* isolates from a hospital in Manama (2007 to 2009), 58% were found to be either resistant or intermediate in susceptibility to imipenem. Eight isolates were randomly selected, and two isolates were found to be clonally related and harbored $bla_{\text{OXA-23}}$ carried on transmissible plasmids. Only one *Acinetobacter* isolate carried $bla_{\text{OXA-58}}$, while the other five isolates produced OXA-72 (95) (Table 4).

ESBL AND CARBAPENEMASE CONCERNS IN THE ARABIAN PENINSULA

It is evident that the predominant ESBL type in most of the GCC states is the CTX-M family (Fig. 1). The predominant CTX-M type in Saudi Arabia is the CTX-M-1-like subgroup (16), which includes CTX-M-15. Similarly, CTX-M-15-positive *Enterobacteriaceae* are also prevalent in Kuwait (54), UAE (52, 54, 56), and Oman (102–104) (Table 2). This high prevalence may be due to immigrants arriving from countries with a high rate of CTX-M-15-positive *Enterobacteriaceae*, as typified in Kuwait, where the majority of CTX-M-15 producers were from patients from South Asia and non-Kuwaiti Arabs (76). About half of the population in Kuwait is from the Indian subcontinent and other Middle Eastern countries (116). The worldwide epidemic *E. coli* clone ST131 has been well described in Kuwait (79, 80). The ST131 clone frequently produces CTX-M-15 (78).

Other novel and rare β-lactamases have been identified in the

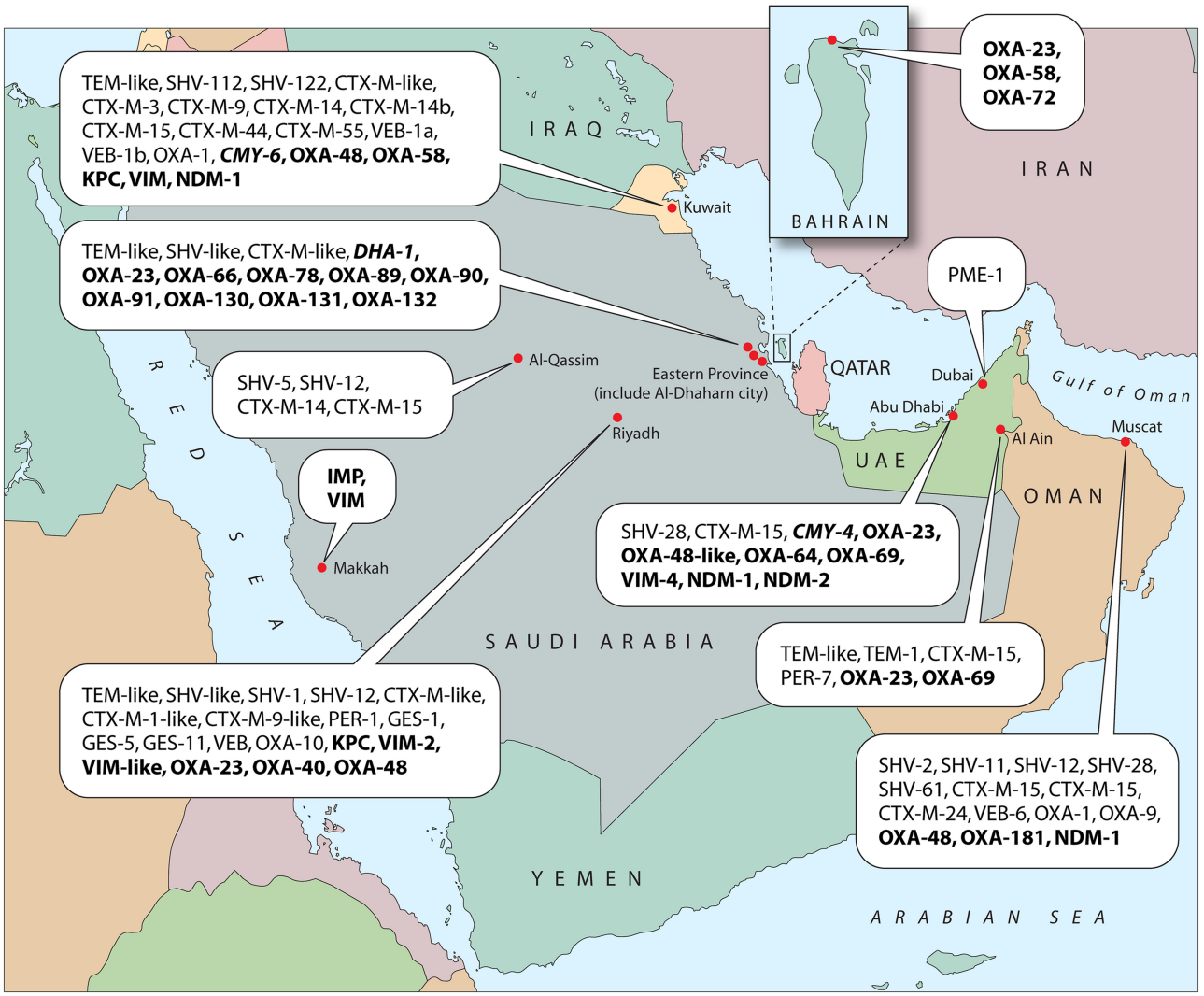

FIG 1 Geographical distribution of β-lactamases produced by GNB in the GCC states. The country and city correspond to those where the isolate has been recovered or originated. Extended-spectrum β-lactamases are shown in normal font, while the enzymes in bold font are carbapenemases. AmpC enzymes are shown in bold italic font.

region, including the VEB-type enzymes. *P. mirabilis* producing VEB-6 was isolated from two different patients in Oman (99), and in Kuwait, VEB-1a and VEB-1b were first identified from *P. aeruginosa* isolates from two different hospitals (86). Close to the Arabian Peninsula, $bla_{\text{VEB-1a}}$ was found in *Providencia stuartii* from Tunisia (117), while $bla_{\text{VEB-1b}}$ was also isolated from *P. stuartii* in neighboring Algeria (118). In Saudi Arabia, bla_{VEB}, was found alone in 7 and simultaneously with other β-lactamase genes in 10 of the 25-ESBL producing *P. aeruginosa* isolates from Riyadh (23). These findings imply that VEB-type ESBLs are common in the Middle East. The identification of SHV-112 as a novel ESBL variant has been reported only from Kuwait (83, 84). The novel PME-1 ESBL, a PER-7 variant, and the rare GES ESBL produced by *Acinetobacter* and *P. aeruginosa* from UAE and Saudi Arabia are other examples of the emerging and rare β-lactamases found in the Gulf states (23–25, 57, 58) (Fig. 1).

Since ESBL producers are frequently also resistant to quinolones and aminoglycosides, reliance on carbapenems becomes increasingly necessary (22). However, the increased prevalence of carbapenemases is beginning to eliminate this as a reliable treatment option. In *Acinetobacter*, this is most typically OXA-23, but rarer OXA types have been found in the Gulf states. *Acinetobacter* carrying $bla_{\text{OXA-72}}$ has been reported from Bahrain but prior to this was isolated from East Asian countries (119–121) and in limited cases from the Americas (122, 123). This resistance mechanism may be unintentionally imported from countries where it is endemic via regular expatriates and travelers. On the other hand, the detection of OXA-23 in *Acinetobacter* is common, and therefore such reports from UAE, Bahrain, and Saudi Arabia are expected (124).

The high transmissibility of NDM-1 is due to the high rates of transfer of plasmids carrying the $bla_{\text{NDM-1}}$ gene (125). This may assist acquisition of the newly emergent resistant gene via normal flora and other environmental microorganisms, resulting in worldwide spread (126). The NDM-1 cases described from Oman involve isolates of *K. pneumoniae* from local patients without re-

cent travel histories (102, 104), suggesting dissemination of the NDM-1 plasmids among Omani *K. pneumoniae* strains. Another type of MBL identified in various countries is VIM, particularly the ubiquitous VIM-2 (127). However, it has been described only in Saudi Arabia among *P. aeruginosa* (23, 42–44) and in Kuwait (80) and UAE (61) among *Enterobacteriaceae*.

Predictably, different β-lactamase resistance mechanisms in GCC states (Fig. 1) are associated with the presence of transmissible genetic elements. For example, bla_{VIM}-like MBL genes detected in *P. aeruginosa* isolates from Riyadh were found to be associated with class 1 integron (43). *Acinetobacter* isolates from Saudi Arabia and Bahrain carrying OXA-131 and OXA-23 also possess the adjacent insertion sequence IS*Aba1* (25, 45, 95). Similarly, in an *Acinetobacter* isolate from a hospital in UAE that carried bla_{OXA-23}, it was found to be a part of a Ts*2006* transposon (63).

Tigecycline and Colistin Resistance in Carbapenem-Resistant GNB

Tigecycline (74) and colistin (128) have become the mainstays of successful therapies for infections caused by MDR Gram-negative bacteria. Regardless of the debate concerning tigecycline effectiveness (129, 130) and colistin-related toxicity (131, 132), the identification of tigecycline-resistant KPC-producing *K. pneumoniae* in Riyadh (38) and NDM-1-positive *K. pneumoniae* and *Acinetobacter* resistant to tigecycline and colistin in Kuwait (87, 91) may herald an era of pan-resistant Gram-negative bacteria. However, a number of new antimicrobials are in advanced clinical development (for example, new cephalosporins and new β-lactamase inhibitors such as avibactam), and it is hoped that the specter of pan-resistance in the region may be avoided. Unfortunately, without these new treatment options, the emergence of antimicrobial resistance is likely to affect patient outcomes, contribute to treatment failure, prolong hospital stays, and increase the risk of further infections associated with a high morbidity, mortality, recurrent infection, and increased health care system costs.

Risk Factors for Acquisition of β-Lactamase-Producing Gram-Negative Bacilli in the Arabian Peninsula

Antibiotic use in health care settings. An example of the correlation between the emergence of MDR bacteria and antibiotic use comes from Bahrain. The occurrence of ESBL-producing *K. pneumoniae* in the 1980s in Bahrain was temporally associated with the introduction of extended-spectrum cephalosporins (112). A dramatic increase in ESBL producers was observed, such that by 1990, two-thirds of *K. pneumoniae* isolates were ESBL positive. This scenario has the potential to be repeated with the emergence of carbapenemase-producing bacteria in the region. Studies from the GCC states have reported that antibiotics are the most prescribed medicines and that many are used suboptimally (133, 134).

Only 25% of medical ICU patients in Qatar (2004) who received antibiotics had "microbiologically proven infections" (135). In Saudi Arabia, the overuse of antimicrobial agents was reported from 4 adult ICUs, where in 2010 the highest use was of meropenem (33.2 defined daily doses [DDD] per 100 bed-days), followed by piperacillin-tazobactam (16.0 DDD/100 bed-days) (136). In comparison, a review by the CDC in 2004 showed that the mean carbapenem use in 36 surveyed medical ICUs in the United States was much lower, at 3.75 DDD/100 bed-days, and that the mean antipseudomonal penicillin use was 7.08 DDD/100 bed-days (137). Results from other countries show that the utilization of meropenem and piperacillin-tazobactam in the ICU setting of a tertiary care hospital in Czech Republic in 2008 was only 3.57 and 3.17 DDD/100 bed-days, respectively (138), and in Brazil, the consumption of piperacillin-tazobactam in an adult ICU setting was between 1.9 and 2.3 DDD/100 bed-days (139). It is apparent that antibiotic stewardship in Gulf hospitals needs to be a priority.

Other issues exist in the community. Regrettably, the availability of over-the-counter antibiotics in GCC's community pharmacies allows patients to purchase antibiotics without prescriptions (140). Although nonprescription sales are illegal in Saudi Arabia, studies from the eastern province showed that only 1/88 pharmacists refused to sell antibiotics without a prescription to patients claiming to have a UTI (141). The same finding has been observed in Riyadh, as 77.6% of pharmacies dispensed antibiotics without a prescription mainly to treat scenarios consistent with viral infections (142). Although selling antibiotics without a prescription in UAE is also illegal, 68.4% of antibiotics from Abu Dhabi community pharmacies were sold over the counter, including injectable antibiotics (143).

Poor antibiotic susceptibility testing protocols also contribute to the problem of antibiotic resistance. A large Saudi study showed that the majority of the 24 participating hospitals in 2009 did not test for highly relevant antibiotics against *P. aeruginosa*, *Acinetobacter*, and *S. maltophilia.* For example, only 30.2% of the isolates combined were tested against ceftazidime, 12.2% against piperacillin-tazobactam, and 20.6% against polymyxin B; however, 83.4% and 39.3% of isolates were tested against ceftriaxone and erythromycin, respectively (41). Given that ceftazidime and piperacillin-tazobactam are widely used antipseudomonal antibiotics and that ceftriaxone and erythromycin are largely ineffective against nonfermentative bacteria, it seems that laboratory protocols in many hospitals may need revision.

Antibiotic use in animals. Antibiotic use in animals is also relevant to the issue of antibiotic resistance in the region and may be related to resistance in humans. The use of antimicrobial growth promoters in animal farming industries is evident in some poultry farms located in the Arabian Peninsula. Norfloxacin and tetracycline residues were found in tissue samples of chicken meat, raw egg materials, and livers from the majority of local farms (144, 145). The excessive and inappropriate use of antibiotics was demonstrated in *E. coli* isolates from fecal material of live chickens in Saudi Arabia, which were mostly resistant to ampicillin, tetracycline, and gentamicin (146). Another study documented the isolation of *E. coli* resistant to fluoroquinolones from poultry plants (147), and *Salmonella* sp. isolates from a poultry farm in Kuwait showed resistance to ampicillin and tetracycline (148). Altalhi et al. found that all multidrug-resistant *E. coli* isolates from raw chicken harbored bla_{TEM} along with other antibiotic resistance genes (149). These data may also suggest the existence of β-lactamase production among GNB in the animal farming industries. The contribution of the agricultural use of cephalosporins in the Gulf states to ESBL production occurring in humans is not yet known.

Hand hygiene. Studies of compliance with hand washing in 2003 at a Saudi hospital showed rates of just 6.7% before patient contact and 23.7% after patient contact (150). Saudi Arabia and Bahrain were among the first countries to sign the Hand Hygiene

Pledge in October 2005 and joined the First Global Patient Safety Challenge, which significantly increased hand hygiene compliance (HHC), especially after initiation of a successful nationwide program. UAE and Oman signed the pledge in 2006, followed by Kuwait and Qatar in 2007 (http://www.who.int/gpsc/en/). Despite these pledges, HHC results remain variable. More recent studies have shown hand hygiene compliance rates of 50.3% in a Saudi hospital and 33.4% in a Kuwaiti hospital (151, 152). Such suboptimal hand hygiene will invariably contribute to the spread of β-lactamase-positive bacteria in the GCC states. Conversely, increased HHC among ICU staff was an essential tool in successfully controlling the first documented outbreak caused by carbapenem-resistant *K. pneumoniae* in Riyadh (35). In Islam, alcohol is considered impure; however, alcohol-based hand rubs are considered culturally and religiously acceptable in the GCC states (153, 154).

Environmental contamination with antibiotic-resistant bacteria. Sewage effluent that contains human intestinal flora is discharged into the seawater of the Arabian Gulf, which may increase the proportion of antibiotic-resistant organisms in the environment. It was found that water samples and fish collected from two sites in Oman where sewage water is dumped 7 km apart were contaminated with antibiotic-resistant enteric bacteria, including *Klebsiella* spp. Rates of cephalosporin resistance were not reported in this study, but nearly 50% of isolates were nalidixic acid resistant (155). In Bahrain, it was found that sewage water discarded in Gulf seawater contained MDR coliforms, which survive in a high quantity for up to 30 h (156).

The spread of antibiotic-resistant organisms in water sources is a concern, because it indicates the wide spread of antibiotic-resistant organisms in the environment. Recently, Walsh et al. isolated several Gram-negative bacteria encoding NDM-1 from freshwater sources in India. This finding suggests that the acquisition of NDM-1 producers is not solely due to nosocomial infections (157). Similar studies have not been performed in the GCC states. Resistance to ceftriaxone was found in 15% of 120 randomly selected GNB from fresh vegetables collected from local markets and street vendors in Taif city, Saudi Arabia. It is possible that the use of contaminated fertilizers or irrigated water may be the source of transmitting antibiotic-resistant bacteria to vegetables (158).

Soil and desert sands of the GCC states could also harbor antibiotic-resistant bacteria. The Arabian Peninsula is well known for its sandstorms, which can be associated with respiratory illnesses (159). Interestingly, it was found that dust storms can transfer bacteria for more than 5,000 km (160). This could potentially mean that bacteria can transfer across continents without the need for patient transmission. Since antibiotic-resistant bacteria exist in the natural environments of different countries (155, 157, 161, 162), sandstorms may contribute to transferring the bacteria to/from desert soil in GCC states, although definitive data on this hypothesis are lacking.

Travel. Travel was reviewed elsewhere as a significant factor for acquiring infectious diseases (163), including those caused by antimicrobial-resistant microorganisms (164, 165). "Medical tourism" is a growing industry in Arab countries. Medical tourism involves not just cosmetic surgeries but also corrective surgery (166). For example, the Kuwaiti female patient who was found carrying OXA-48-producing *K. pneumoniae* in France traveled to receive a lower limb prosthesis (88). Other current and specific examples of the international spread of antimicrobial-resistant organisms due to hospitalization are the NDM-1-positive *K. pneumoniae* isolates from Omani patients who had traveled to India and Pakistan (102, 104) and ESBL-producing *K. pneumoniae* originating from Bahrain that caused outbreaks in United Kingdom hospitals (113).

The socioeconomic structure of the GCC states relies heavily on workforces originating from South Asia: about 37% of the total population of the GCC states are nonnational expatriates, mainly from the Indian subcontinent (116). It is well known that the ESBL type CTX-M-15 is ubiquitous in the Indian subcontinent (167–171). If inpatients are colonized with ESBL- or carbapenemases-positive bacteria, endogenous infections and/or patient-to-patient transmission can occur, which may account for the high prevalence of CTX-M-15 producers isolated from hospitals in Gulf countries (52, 54, 56, 76, 84).

More than 1.5 million foreign pilgrims from different nations travel to Saudi Arabia during the same period every year to perform Hajj (172). Hajj-related infections have been described elsewhere due to mass gathering and other factors (173). Usually pilgrim groups from different countries travel to Makkah and Madinah with their own health care professionals. However, critical cases are treated in satellite medical centers (174) and in local hospitals based in the holy cities (175). Clinical isolates from two major hospitals in Makkah showed 24.6%, 34.4%, and 52.7% resistance to ceftazidime in *E. coli*, *K. pneumoniae*, and *P. aeruginosa*, respectively. Carbapenem resistance was observed in 8.1% of *E. coli* isolates and 9.1% of *K. pneumoniae* isolates, while 38.5% and 19.8% of *P. aeruginosa* isolates were resistant to imipenem and meropenem, respectively. Similarly, 45.9% of *Acinetobacter* isolates were resistant to imipenem and 28% to meropenem (176). In a different study it was found that septicemia episodes at hospitals in Makkah are increased by 16.5% during Hajj time due to the influx of international patients (177).

THE NEED FOR REGIONAL SURVEILLANCE STUDIES

Developing local surveillance of antimicrobial-resistant organisms in hospitals helps to track emerging resistances to antibiotics and to identify outbreaks (178). As an example of antibiogram tracking programs that are used in a GCC state, ABSOFT is in-house software that is used in a hospital in Qatar. It can show the antibiogram based on the bacterial species, wards, and sites of acquisition (e.g., from the community). It also compares the antibiotic data based on the National Nosocomial Infections Surveillance (NNIS) system benchmark (now National Health Surveillance Network [NHSN]) (179). Local surveillance may aid empirical antibiotic choice in seriously ill patients. For example, Mokaddas et al. found that 73% of 184 septicemic patients infected with ESBL-producing *Enterobacteriaceae* needed a change in antimicrobial therapy (73). Knowledge of a high prevalence of ESBL-producing organisms may have allowed more appropriate empirical antibiotic selections.

One of the main pillars in WHO policies to combat antimicrobial resistance is to initiate "strength surveillance and laboratory capacity" (http://www.who.int/world-health-day/2011). Due to the geographical location of the GCC states and the ethnic relationships of residents, major medical collaborations have been developed since the establishment of the GCC. For example, the GCC Center for Infection Control was established to exchange reports, develop statewide surveillance, implement prevention strategies to combat disease spread, and provide expert consulta-

tion in the field. The center's aspirations are articulated in the current unified manuals for infection control practices and surveillance based on the guidelines of the National Health Surveillance Network (NHSN). Examples of the latter are surveillance for meningococcal serogroups in the region (180) and surveillance of organisms associated with community-acquired pneumonia (CAP) and their antibiotic susceptibility profiles (181). However, it is clear that effort is still needed to survey antibiotic-resistant organisms, including Gram-negative bacteria, particularly those resistant to β-lactam antibiotics (182).

The use of molecular-based techniques to study antibiotic resistance among clinical and environmental microorganisms is a necessity in modern health care practices; these techniques are essential for investigating antibiotic resistance mechanisms or understanding clonal dissemination (178). Studies of most of the outbreaks listed in Table 3 utilized molecular typing tools to describe similarities/discriminations.

Active guidelines should be implemented to restrict the irrational use of antibiotics in the GCC states (183). Antimicrobial stewardship programs would reduce overprescription, shorten hospital stays, and reduce costs (184). Antibiotic stewardship should invariably include community pharmacies, and the abolition of over-the-counter sales of antimicrobials should be mandatory. Similarly, regulations and strategies should be used to enforce the ban on antibiotics as growth-promoters in poultry plants in GCC states, in a manner similar to the action taken by the European Union (185, 186).

Last but not least, microbiology laboratories should be aware that diagnosis for some carbapenemase-producing GNB can be problematic. Hence, microbiologists should be regularly updated with regional surveillance data to ensure that state-of-the art screening and confirmatory testing are in place (187, 188). Molecular and protein-based identification tools should also be considered to improve diagnosis and to reduce turnaround time (189).

CONCLUSION

In conclusion, the global spread of antibiotic resistance among clinically important Gram-negative bacilli is also a growing problem in the GCC states. However, the extent of the problem is not fully reported because of the lack of studies identifying resistance mechanisms. Travel to countries where certain classes of ESBLs or MBLs are endemic is an obvious risk factor that is likely to continue, if not escalate. Different management strategies to combat antimicrobial resistance in GNB the GCC States include (i) implementing antimicrobial stewardship programs in health care facilities, (ii) prohibiting the availability of antibiotics without a prescription, (iii) initiating mass educational campaigns about antibiotic use, (iv) improving basic infection control precautions (e.g., hand hygiene), (v) ensuring that microbiology laboratories are equipped to detect emerging resistance problems, and (vi) developing regional surveillance on antibiotic resistance.

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