Role of Institut Hospitalo-Universitaire Méditerranée Infection in the surveillance of resistance to antibiotics and training of students in the Mediterranean basin and in African countries

L. Peyclit, A. Chanteloup, L. Hadjadj and J.-M. Rolain

Aix-Marseille Université, IRD, APHM, MEPHI, IHU-Méditerranée Infection, Marseille, France

Abstract

Surveillance of antibiotic resistance has become a public global concern after the rapid worldwide dissemination of several antibiotic resistance genes. Here we report the role of the Institut Hospitalo-Universitaire Méditerranée Infection created in 2011 in the identification and description of multidrug-resistant bacteria thanks to collaborations and training of students from the Mediterranean basin and from African countries. Since the creation of the institute, 95 students and researchers have come from 19 different countries from these areas to characterize 6359 bacterial isolates from 7280 samples from humans (64%), animals (28%) and the environment (8%). Most bacterial isolates studied were Gram-negative bacteria (n = 5588; 87.9%), mostly from Algeria (n = 4190), Lebanon (n = 946), Greece (n = 610), Saudi Arabia (n = 299) and Senegal (n = 278). Antibiotic resistance was diversified with the detection and characterization of extended-spectrum β-lactamases, carbapenemases and resistance to colistin, vancomycin and methicillin. All those studies led to 97 indexed international scientific papers. Over the last 6 years, our institute has created a huge network of collaborations by training students that plays a major role in the surveillance of resistance to antibiotics in these countries.
© 2018 The Author(s). Published by Elsevier Ltd.

Corresponding author: J.-M. Rolain, Aix-Marseille Université, IRD, APHM, MEPHI, Institut Hospitalo-Universitaire Méditerranée Infection, Marseille, France.
E-mail: jean-marc.rolain@univ-amu.fr

Introduction

During the last decade, antibiotic resistance has become one of the major public health priorities in the world [1] because of the emergence of new mechanisms of resistance. Moreover, the massive media coverage has tended to predict of thousands of human deaths every year [2]. However, recent epidemiologic data from our institution demonstrate that the level of antibiotic resistance for the most common bacterial species of clinical interest did not significantly change over the last 15 years in Marseille, France [3,4]. Similarly, we found a huge disparity between mortality attributable to antibiotic resistance using simple model estimations and empirical data of true deaths in our institution [5]. Data on the level of antibiotic resistance in Europe show disparities between countries and bacterial species for certain antibiotics; for example, resistance to carbapenems is much more frequent in Romania, Italy and Greece [3]. It appears from those studies that a better understanding and surveillance of antibiotic resistance at the local and national levels is critical to manage antibiotic-resistant bacterial infections in the future [5]. However, data on antibiotic resistance and surveillance of the emergence and spread of new mechanisms of resistance in the Mediterranean basin and in African countries were lacking in most of those countries until now.

Here we report the specific and unique role of the Institut Hospitalo-Universitaire Méditerranée Infection (IHU-MI), created in November 2011, in the identification, description and surveillance of multidrug-resistant bacteria thanks to collaborations among and training of students coming from the Mediterranean basin and from African countries in our institute. The majority of students who come to our institute for

surveillance and analysis of antibiotic resistance came with their own bacterial isolates from their countries.

Methods

This study analyses data collected from 2011 (the date of creation of the IHU-MI) through the completion of this article in February 2018. The number of students by level of graduation and by country of origin per year was sorted from our administrative database of students and scientific visitors during the study period from the team dedicated to antibiotic resistance research (JMR team). Students from the Mediterranean basin and Africa were counted from this primary list and were sorted by level of graduation (master's degree, PhD, postdoc and scientific visitors) and by country. Because some students stayed at our institute both for master's and PhD courses, we deduplicated the total count. The number of students present per year in the team was also calculated from this list to show the student kinetics of reception per year.

All students facing antibiotic resistance in their country came with their own isolates to analyse them as a course training. Most of them continued to collaborate with our institute, resulting in real-time surveillance of antibiotic resistance according to their field of research (humans, animals or the environment). Initially there was no rationale for the recruitment and analysis of the samples because no data existed at the beginning of this network. Now, however, the follow-up of antibiotic resistance is mainly focused on the current antibiotic resistance situation. For each epidemiologic study, the number and type of samples and/or bacterial isolates and the country of origin were counted, and data were presented in a single table, with all data provided by country.

Antibiotic resistance for each sample or bacterial isolates was studied using the same procedure. Antibiotic resistance was assessed either directly from samples by PCR or from bacterial isolates by culture and molecular assays. The first step consisted of sample culture and isolation of strains on specific agar media: Columbia agar with 5% sheep's blood, trypticase soy agar or MacConkey (bioMérieux, Marcy l'Etoile, France) with or without addition of antibiotics. All collected strains were subjected to matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) for identification [6]. Antibiotic susceptibility testing (AST) was performed using the disc diffusion method on Mueller-Hinton medium agar for phenotypic characterization of the mechanism of resistance. Specific panels of antibiotics were tested according to the bacteria species (e.g. *Enterobacteriaceae,* nonfermentative Gram-negative bacteria, Gram-positive bacteria). Then AST results were interpreted according to

European Committee on Antimicrobial Susceptibility Testing guidelines [7]. Genotypic identification of resistance genes were screened by real-time quantitative PCR and confirmed by standard PCR and sequencing when necessary, and sequences were analysed using ARG-ANNOT software [8] to identify the specific antibiotic resistance gene. Multilocus sequence typing was performed to evaluate genetic relatedness of strains. If necessary, a whole genome sequence study was performed to obtain the complete resistome of a strain [9] or to describe the genetic environment of an antibiotic resistance gene [10,11].

Each student hosted by our institution received specific training for the study of antibiotic resistance (MALDI-TOF MS, AST, molecular training, genomics, bioinformatics) and presented the progress of their work and their results every week so that we could prepare tables and figures to be used for publication. Finally, each student was trained by the senior member of the team (JMR) to write their scientific papers and to create their own bibliography on the topic. Most of them also wrote a review on their topic while writing their PhD thesis. Weekly seminars or bibliographic sessions were also provided each Friday to improve students' knowledge in the field. The number of indexed international scientific papers per type of sample and per country was also calculated on the basis of published and submitted papers on antibiotic resistance during the study period.

Results

Since the creation of this institute, the JMR team has welcomed a total of 126 students or visiting scientists, including 95 deduplicated students (75.4%) from academic exchanges with 19 countries from the Mediterranean basin, Africa and Middle East. The number of students present in a given year has significantly increased during the study period (ten students in 2011, 15 in 2012, 21 in 2013, 28 in 2014, 27 in 2015, 40 in 2016 and 44 in 2017) to a total of 95 students. Most of the students are from Algeria (52, 55.3%), followed by Lebanon (12, 12.8%), Senegal (7, 7.4%) and Tunisia (5, 5.3%). All these 95 students were from Europe (Spain, 3 students, 3.2%; Italy, 2, 2.1%; Greece, 1, 1.1%), West Africa (Senegal, 7, 7.3%; Benin, Central Africa Republic, Guinea, Ivory Coast, Mali, Nigeria, Togo, 8, 8.4%), North Africa (Algeria, 52, 55.3%; Tunisia, 5, 5.3%; Egypt, 1, 1.1%; Morocco, 1, 1.1%), Middle East (Lebanon, 12, 12.8%; Qatar, Syria, 2, 2.1%) and Madagascar (1, 1.1%).

Each student had a different level of education, including master's degree (n = 15), PhD students (n = 65), scientific visitors and postdocs (n = 22). Overall, the number of PhD

students from these countries significantly increased during the study period, from eight in 2011 to 30 in 2017 (2011: 8; 2012: 11; 2013: 16; 2014: 20; 2015: 23; 2016: 28; 2017: 30). The number of postdocs varied from two to four between these different years (2011, 2013, 2015, 2017: 2 students; 2012: 3; 2014, 2016: 4), as did the number of students seeking master's degrees, from one to four (2011, 2012: 1; 2013: 2; 2014, 2015: 3; 2016, 2017: 5). Students trained at the IHU-MI will return to their country of origin and continue to work in this field with

our institute, which is now identified as the core laboratory for surveillance of antibiotic resistance and further analysis of new bacterial isolates from those countries.

A total of 7280 samples from human ($n = 4657$; 64%), animal ($n = 2058$; 28%) or environment ($n = 565$; 8%) from 15 different countries were analysed during the study period (Fig. 1(A)). More than half of those samples came from Algeria ($n = 4190$; 57.6%), followed by Lebanon ($n = 946$; 12.9%), Greece ($n = 610$; 8.4%), Saudi Arabia ($n = 299$; 4.1%) and
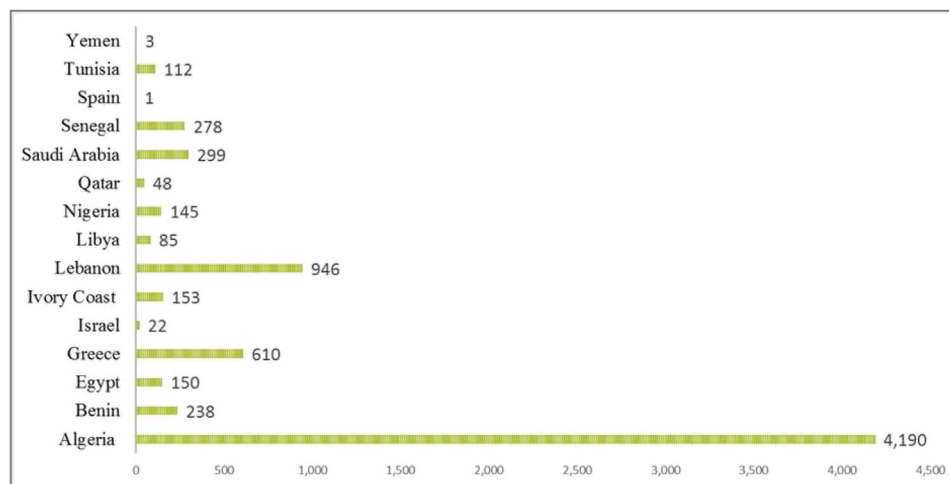
A
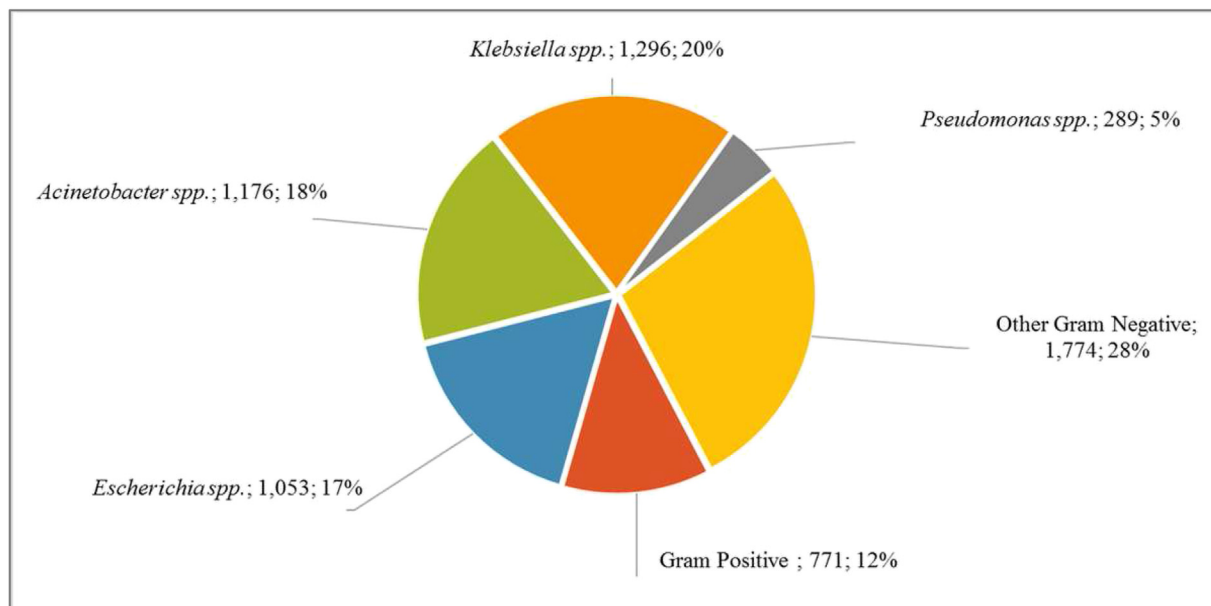
B

FIG. 1. (A) Geographic distribution of samples studied in publications of IHU-MI from 2011 to 2017 ($n = 7280$). (B) Repartition of bacterial species studied from Mediterranean basin or African countries in IHU-MI from 2011 to 2017 ($n = 6359$). IHU-MI, Institut Hospitalo-Universitaire Méditerranée Infection.

TABLE 1. Samples and publications studied according to countries in Institut Hospitalo-Universitaire Méditerranée Infection from 2011 to 2017

Country	Year	Strain type	Studied strains	No. of samples	No. of positive samples with an AR gene detected	Tested phenotype	Type of antibiotic resistance genes detected (n)	Study
Algeria	2008–2011	Clinical isolates	Klebsiella pneumoniae	211	194	ESBL Cephalosporinases Penicillinase HLP		[19]
	2008–2012	Clinical isolates	K. pneumoniae	221	190	ESBL Cephalosporinases Penicillinase HLP	bla_{TEM} (146) bla_{SHV} (154) bla_{CTX-M} (130)	[20]
	2017	Animal (45) and human (37) isolates	Salmonella spp.	92	18	ESBL	$bla_{CTX-M-1}$ (12) $bla_{CTX-M-15}$ (5) bla_{TEM} (8)	[21]
	2011	Clinical isolates	Escherichia coli	1	1	Coli R	mcr-1	[22]
	2015	Animal isolates	E. coli (30) K. pneumoniae (17)	47	47	Coli R ESBL	$bla_{CTX-M-15}$ (47) bla_{TEM-1} (25)	[23]
	2014	Clinical and environmental isolates	K. pneumoniae Enterobacter cloacae Acinetobacter baumannii Pseudomonas aeruginosa	89	32	ESBL Carbapenemases	bla_{OXA-48} (5) bla_{NDM-1} (7) bla_{OXA-43} (2) bla_{TEM} (6) bla_{SHV} + bla_{CTX-M} (7)	[24]
	2013–2015	Environmental isolates	A. baumannii	1	1	Carbapenemases ESBL Fluoroquinolones	bla_{NDM-1} (1)	[25]
	2010–2013	Clinical isolates	Enterococcus spp.	85	85	Vanco R	vanC	[26]
	2010–2013	Clinical isolates	A. baumannii	43	43	Carbapenemases	bla_{NDM-1} (7) bla_{OXA-23} (28) bla_{OXA-24} (1) bla_{OXA-58} (6) bla_{OXA-51} (43) bla_{OXA-23} + bla_{NDM-1} (2) bla_{OXA-58} + bla_{NDM-1} (1)	[27]
	2013–2015	Clinical isolates	Enterobacteriaceae (161) P. aeruginosa (18) A. baumannii (7)	186	36	Carbapenemases ESBL	bla_{OXA-48} (2) bla_{VIM-4} (2) bla_{NDM-1} (2) bla_{OXA-23} (5)	[28]
	2011–2013	Environmental isolates	A. baumannii	67	61	Carbapenemases	bla_{OXA-23} (29) bla_{NDM-1} (32)	[29]
	2013–2014	Clinical isolates	Streptococcus agalactiae	93	74	MLSB R	ermB (18) ermA mef(A) mef(E)	[30]
	2015	Animal isolates	E. coli	1	1	Carbapenemase	bla_{NDM-5} (1)	[31]
	2014–2016	Animal isolates	Enterobacteriaceae	380	3	Carbapenemases ESBL Cephalosporinases	bla_{OXA-48} (3)	[32]
	2012–2014	Environmental isolates	K. pneumoniae	44	44	ESBL Cephalosporinases Fluoroquinolones Aminoglycosides	$bla_{CTX-M-15}$ (41) $bla_{CTX-M-3}$ (3)	[33]
	2014–2015	Animal isolates	Samples	503	389	Carbapenemases ESBL	bla_{TEM} (128) bla_{SHV} (83) bla_{CTX-M} (46) bla_{OXA-58} (132)	[34]
	2015	Animal isolates	Enterobacteriaceae	32	32	Carbapenemases ESBL	bla_{OXA-48} (32) $bla_{CTX-M-15}$ (1) bla_{TEM} (2)	[35]
	2013–2014	Animal (3) and human (1) isolates	E. coli	4	4	Coli R	mcr-1 (4)	[36]
	2016	Animal isolates	E. coli	8	8	Coli R	In progress	Unpublished results
	2017	Animal (4) and environmental (5) isolates	E. coli (8) E. cloacae (1)	9	9	Coli R	In progress	Unpublished results

Continued

TABLE 1. Continued

Country	Year	Strain type	Studied strains	No. of samples	No. of positive samples with an AR gene detected	Tested phenotype	Type of antibiotic resistance genes detected (n)	Study
	2016	Clinical isolates	K. pneumoniae	3	3	Coli R	In progress	Unpublished results
	2015–2016	Environmental isolates	Staphylococcus aureus	200	153	Methi R	In progress	Unpublished results
	2011–2013	Clinical isolates	A. baumannii	47	47	Carbapenemases Aminoglycosides Fluoroquinolones	bla_{OXA-23} (33) bla_{OXA-24} (10) bla_{NDM} (11) $armA$ (4) $aph(3')VI$ (24) $aadA$ (6) $ant(2')I$ (10) $aac(3)Ia$ (33) Mutation in $gyrA$, $parC$ (45)	[37]
	2013–2014	Clinical isolates	A. baumannii	12	12	Coli R Carbapenemases	bla_{OXA-24} (4) bla_{OXA-23} (6) bla_{OXA-51} (12) bla_{NDM-1} (2)	[38]
	2016–2017	Animal isolates	Samples	200	4	ESBL	In progress	Unpublished results
	2013	Clinical isolates	Enterococcus hirae	1	1			[39]
	2016	Clinical isolates	K. pneumoniae (20) A. baumannii (12) P. aeruginosa (9) E. coli (27)	68	68	Carbapenemases ESBL	In progress	Unpublished results
	2011–2012	Clinical isolates	A. baumannii	30	24	Carbapenemases	bla_{OXA-23} (22) bla_{OXA-58} (1) bla_{OXA-23} + bla_{OXA-58} (1)	[40]
	2011	Clinical isolates	P. aeruginosa	17	17	Carbapenemases	bla_{VIM-2} (14) Mutation in $oprD$ (3)	[41]
	2012–2013	Clinical isolates	E. coli	105	3	Carbapenemases ESBL Aminoglycosides Fluoroquinolones	bla_{NDM-5} (3) bla_{TEM} (3) bla_{CTX-M} (3) $aadA$ (3)	[42]
	2010–2011	Clinical isolates	E. coli (3) K. pneumoniae (24) E. cloacae (11) Serratia marcescens (4)	42	39	ESBL	bla_{CTX-M} (10) bla_{TEM} (14) bla_{SHV} (15)	[43]
	2010–2011	Clinical isolates	K. pneumoniae	100	100	ESBL Aminoglycosides Fluoroquinolones	bla_{CTX-M} (76) bla_{TEM} (74) bla_{SHV} (73) $armA$ (23) $aadA$ (35) $aac(6')Ib$ (50) $qnrB$ (22)	[44]
	2013	Animal isolates	Acinetobacter spp.	33	4	Carbapenemases	bla_{OXA-23} + bla_{OXA-58} + bla_{OXA-51} (1) bla_{OXA-58} + bla_{OXA-51} (1) bla_{OXA-58} (2)	[45]
	2014–2015	Clinical isolates	K. pneumoniae	7	7	ESBL Carbapenemases	bla_{OXA-48} + $bla_{CTX-M-15}$ + bla_{SHV-1} + bla_{TEM-1D} (7)	[46]
	2015	Environmental isolates	Enterobacteriaceae	12	9	Carbapenemases ESBL	$bla_{CTX-M-15}$ (9) bla_{OXA-48} (1) bla_{TEM} (1)	[47]
	2015	Animal isolates	Pseudomonas putida	1	1	Carbapenemases ESBL	bla_{VIM-2}	[48]
	2017	Clinical isolates	K. pneumoniae	1	1	Carbapenemases ESBL	bla_{OXA-48} (1) bla_{SHV-27} (1)	[49]
	2010–2011	Clinical isolates	A. baumannii	71	71	Carbapenemases	bla_{OXA-23} (31) bla_{OXA-24} (5) bla_{OXA-51} (71)	[50]
	2010–2011	Clinical isolates	A. baumannii	71	71	Carbapenemases ESBL	bla_{TEM} (53) $ampC$ (69)	[51]

Country	Year	Isolate type	Species	n	R	Resistance	Genes	Ref
						Aminoglycosides	$aph(3')VI$ (36)	
						Fluoroquinolones	$aadA$ (45)	
							$ant(2')I$ (10)	
							$aac(3)Ia$ (64)	
							$aac(6')Ib$ (3)	
							Mutation $gyrA$, $parC$ (67)	
	2013	Clinical isolates	*K. pneumoniae*	1	1	Carbapenemases	bla_{KPC-3}	[52]
						ESBL	bla_{TEM}	
						Aminoglycosides	bla_{SHV}	
						Fluoroquinolones	$aac(6')Ib$	
							$aadA$	
	2015	Environmental isolates	*E. coli* (12)	20	20	ESBL	bla_{OXA-48} (17)	[13]
			K. pneumoniae (3)			Carbapenemases	$bla_{OXA-24}4$ (3)	
			Raoultella ornithinolytica (3)				bla_{TEM-1} (9)	
			Citrobacter freundii (1)				$bla_{CTX-M-15} + bla_{TEM-1}$ (3)	
			Citrobacter braakii (1)					
	2016	Environmental isolates	*K. pneumoniae*	87	3	ESBL	bla_{OXA-48} (3)	[16]
						Carbapenemases	bla_{TEM-1} (1)	
	2014	Animal isolates	*E. coli*	20	20	Carbapenemases	bla_{TEM-1} (20)	[12]
						ESBL	$bla_{CTX-M-1}$ (2)	
						Aminoglycosides	$bla_{SHV}-12$ (14)	
							CMY-2 (4)	
							$aadA$ (20)	
	2015	Environmental isolates	*Shewanella xiamenensis*	4	4	Carbapenemases	bla_{OXA-48} (1)	[11]
							$bla_{OXA-19}9$ (1)	
							$bla_{OXA-18}I$ (2)	
	2016	Animal isolates	*Enterobacteriaceae*	86	1	Coli R	$mcr-1$	[17]
							$bla_{CTX-M-15}$	
							bla_{TEM-1}	
							$qnrB19$	
	2014	Clinical isolates	*S. aureus*	250	171	Methi R	In progress	Unpublished results
	2005–2007	Clinical isolates	*S. aureus*	64	64	Methi R	$mecA$ (64)	[53]
	2011	Clinical isolates	*Proteus mirablis*	106	72	ESBL	In progress	Unpublished results
			Morganella spp.			Carbapenemases		
			Providencia spp.			Aminoglycosides		
						Fluoroquinolones		
	2014–2015	Clinical (60) and environmental (39) isolates	*Enterobacteriaceae*	99	10	Carbapenemases	bla_{NDM-1} (5)	[54]
			Acinetobacter spp.			ESBL	bla_{OXA-23} (3)	
						Cephalosporinases	bla_{OXA-48} (2)	
						Aminoglycosides	$bla_{SHV-148} + bla_{TEM-163}$ (2)	
							$aph(3')VI-ant(2'')I$ (2)	
							$aac(3)Ia$ $aadA$ (3)	
							AME-encoding genes (5)	
	2009–2012	Clinical isolates	*P. aeruginosa*	89	39	Carbapenemases	bla_{VIM-2} (2)	[55]
						Aminoglycosides	$aadA$ (10)	
							$aac(3)Ia$ (3)	
	2008–2012	Clinical isolates	*Acinetobacter* spp.	113	113	Carbapenemases	bla_{OXA-23} (40)	[56]
						ESBL	bla_{OXA-24} (17)	
						Aminoglycosides	bla_{NDM} (5)	
						Fluoroquinolones	$aph(3')VI$ (70)	
							$aadA$ (57)	
							$ant(2')I$ (60)	
							$aac(3)Ia$ (77)	
							$aac(6')Ib$ (1)	
	2012	Clinical isolates	*A. baumannii*	123	77	Carbapenemases	bla_{OXA-23} (40)	[57]
						ESBL	bla_{OXA-24} (3)	
							$bla_{OXA-23} + bla_{OXA-24}$ (3)	
Benin	2015	Clinical isolates	*Staphylococcus saprophyticus* (31)	78	21	Methi R	$mecA$ (19)	[58]
			S. aureus (21)					
			Staphylococcus sciuri (17)					
			Staphylococcus conhii (5)					
			Staphylococcus haemolyticus (2)					
			Staphylococcus xylosus (1)					
			Staphylococcus hominis (1)					

Continued

TABLE 1. Continued

Country	Year	Strain type	Studied strains	No. of samples	No. of positive samples with an AR gene detected	Tested phenotype	Type of antibiotic resistance genes detected (n)	Study
	2015	Clinical isolates	Enterobacteriaceae	157	103	ESBL Carbapenemases	In progress	Unpublished results
	2016	Clinical isolates	P. aeruginosa	3	3	Carbapenemases	In progress	Unpublished results
Egypt	2012–2013	Clinical isolates	A. baumannii	150	150	Carbapenemases Aminoglycosides	bla_{NDM-1} (59) bla_{OXA-23} (115) armA (141) bla_{OXA-51} (150) bla_{NDM-1} + bla_{OXA-23} (53) armA + bla_{NDM-1} + bla_{OXA-23} (52)	[59]
Greece	2013–2017	Clinical isolates	P. mirablis (4) P. putida (1) C. freundii (1) Enterobacter aerogenes (2) Providencia stuartii (8) P. aeruginosa (79) A. baumannii (158) E. cloacae (10) E. coli (33) K. pneumoniae (314)	610	610	Carbapenemases ESBL Coli R Fluoroquinolones	In progress	Unpublished results
Israel	2011	Clinical isolates	Providencia rettgeri	1	1	Carbapenemase	bla_{NDM-1} (1)	[60]
	2008–2011	Clinical isolates	K. pneumoniae	15	15	Carbapenemases Coli R Aminoglycosides	In progress	Unpublished results
	2010–2011	Clinical isolates	K. pneumoniae (1) E. coli (1) P. mirabilis (1) P. rettgeri (1) Morganella morganii (1)	5	5	Carbapenemases	bla_{NDM-1} (5)	[61]
	2014	Clinical isolates	M. morganii	1	1	Carbapenemases	bla_{NDM-1} (1)	[62]
Ivory Coast	2012–2015	Clinical isolates	Enterobacteriaceae	153	153	ESBL Aminoglycosides Fluoroquinolones	In progress	Unpublished results
Lebanon	2013	Clinical isolates	P. aeruginosa	35	35	Carbapenemases Cephalosporinases	bla_{VIM-2} (16) bla_{IMP-15} (2) ampC (8)	[14]
	2013	Animal isolates	E. coli	1	1	ESBL Carbapenemases	bla_{OXA-48} (1) $bla_{CTX-M-1}$4 (1) bla_{TEM-1} (1)	[63]
	2013	Animal isolates	P. aeruginosa (4) A. baumannii (5)	9	9	Carbapenemases	bla_{OXA-23} (4) bla_{OXA-58} (1) bla_{VIM-2} (4)	[64]
	2015	Clinical isolates	R. ornithinolytica	1	1	Carbapenemases Cephalosporinase BLSE MLSB R Chloramphenicol Fluoroquinolones	bla_{OXA-48} ampC ampH $bla_{TEM-166}$ macA macB cmr cat gyrA mutated	[10]
	2015	Animal isolates	E. coli	1	1	ESBL Coli R	$bla_{TEM-135}$-like (1) mcr-1 (1)	[18]
	2015	Animal isolates	E. cloacae	1	1	Cephalosporinase Coli R	In progress	Unpublished results
	2015	Animal isolates	E. coli (217) K. pneumoniae (8) Escherichia fergusonii (1)	235	235	ESBL Cephalosporinases	In progress	Unpublished results

Country	Year	Isolate type	Species (count)	n	n	Resistance	Genes/mechanism	Reference
			A. baumannii (1)					
			P. mirabilis (3)					
			E. cloacae (2)					
	2017	Animal isolates	*E. coli* (105)	111	111	ESBL	In progress	Unpublished results
			E. fergusonii (2)			Cephalosporinase		
			K. pneumoniae (4)			Coli R		
	2017	Animal (346)	*E. coli* (341)	399	399	ESBL	In progress	Unpublished results
		Environmental (53)	*K. pneumoniae* (31)			Cephalosporinase		
		Human (11) isolates	*Enterobacter asburiae* (1)			Coli R		
			Stenotrophomonas maltophilia (4)					
			Serratia rubidae (1)					
			A. baumannii (4)					
			Acinetobacter genomospecies (4)					
			Pseudomonas spp. (8)					
			Ochrobactrum spp. (1)					
			E. cloacae (4)					
	2016–2017	Clinical isolates	*Enterobacter faecium*	4	4	Glycopeptides	In progress	Unpublished results
	2016	Clinical isolates	*A. baumannii*	31	31	ESBL	In progress	Unpublished results
						Carbapenemases		
	2016	Clinical isolates	*Campylobacter jejuni*	1	1	ESBL	In progress	Unpublished results
						Carbapenemases		
	2010–2016	Clinical isolates	*E. coli*	43	43	ESBL	In progress	Unpublished results
	2015	Clinical isolates	*K. pneumoniae*	3	3	ESBL	$bla_{CTX-M-15}$ + bla_{TEM-12} + bla_{SHV-5} (2)	[65]
						Coli R	bla_{SHV-5} (1)	
							Mutation *mgrB* (2)	
							phoQ (1)	
							pmrA (1)	
	2016–2017	Clinical isolates	*Enterobacteriaceae* (8)	9	9	ESBL	In progress	Unpublished results
			P. aeruginosa (1)			Carbapenemases		
						Coli R		
	2012	Clinical isolates	*A. baumannii*	4	4	Carbapenemases	bla_{NDM-1} (4)	[15]
							bla_{OXA-94} (4)	
	2016	Clinical isolates	*Neisseria meningitidis*	58	1		In progress	Unpublished results
Libya	2013–2014	Clinical isolates	*P. aeruginosa* (24)	49	43	Carbapenemases	bla_{OXA-24} (3)	[66]
			A. baumannii (25)				bla_{OXA-23} (19)	
							bla_{VIM-2} (19)	
	2015	Clinical isolates	*A. baumannii*	36	36	Carbapenemases	bla_{OXA-23} (29)	[67]
							bla_{NDM-1} (8)	
							bla_{NDM} (36)	
Nigeria	2012	Clinical isolates	*A. baumannii*	3	3	Carbapenemases	bla_{OXA-23} (3)	[68]
	2012–2013	Clinical isolates	*Klebsiella* spp.	139	1	Coli R	*mgrB* (1)	[69]
	2012	Animal (2) and human (1) isolates	*E. coli*	3	1	Coli R	*mcr-1* (1)	[70]
Qatar	2011–2012	Clinical isolates	*A. baumannii*	48	48	Carbapenemases	bla_{OXA-23} (48)	[68]
Saudi Arabia	2013–2014	Clinical isolates	*E. coli* (10)	11	11	Coli R	*mcr-1* (11)	[71]
			K. pneumoniae (1)			ESBL	bla_{TEM-1} (10)	
							bla_{SHV-1} (1)	
							$bla_{CTX-M-15}$ (1)	
	2014	Clinical isolates	*A. baumannii*	42	28	Carbapenemases	oxa-72 (1)	[72]
						ESBL	bla_{NDM-5} (1)	
						Aminoglycosides	bla_{NDM-1} (1)	
							bla_{OXA-48} (1)	
							bla_{OXA-58} (22)	
							bla_{OXA-51} + bla_{OXA-72} (1)	
							bla_{NDM-5} + $bla_{CTX-M-15}$ + bla_{TEM-1} + aadA2 (1)	
							bla_{NDM-5} + bla_{TEM-1} + aadA2 (1)	
	2013–2014	Clinical isolates	*E. coli* (23)	28	28	ESBL	bla_{CTX-M} (27)	[73]
			K. pneumoniae (5)				bla_{TEM} (19)	
							bla_{SHV} (4)	
	2013–2014	Clinical isolates						[74]
	2013–2014	Clinical isolates	Samples	218	73	ESBL	bla_{CTX-M} (73)	[75]

Continued

TABLE 1. Continued

Country	Year	Strain type	Studied strains	No. of samples	No. of positive samples with an AR gene detected	Tested phenotype	Type of antibiotic resistance genes detected (n)	Study
Senegal	2011	Clinical isolates	*A. baumannii*	5	3	Carbapenemases	bla_{OXA-23} (3)	[76]
	2014	Clinical isolates	*M. morganii*	112	112	ESBL	bla_{CTX} (112) bla_{TEM} (86) bla_{SHV} (63)	[77]
	2015–2017	Clinical isolates	*Enterobacteriaceae*	161	120	Carbapenemases ESBL Aminoglycosides Fluoroquinolones Coli R	In progress	Unpublished results
Spain	2015	Clinical isolates	*Acinetobacter nosocomialis*	1	1	Coli R		[78]
Tunisia	2013–2016	Clinical isolates	*A. baumannii*	25	25	Carbapenemases	bla_{OXA-51} + bla_{OXA-23} (25) bla_{OXA-58} (1)	[79]
	2015	Clinical isolates	*E. coli* (51) *K. pneumoniae* (36)	87	68	Carbapenemases ESBL	bla_{CTX} (47) bla_{TEM-1} (31) bla_{SHV} (18) bla_{OXA} (10)	[80]
Yemen	2013	Clinical isolates	*A. baumannii*	3	3	Carbapenemases Aminoglycosides Fluoroquinolones	bla_{OXA-23} (3) $armA$ (3) $aac(6')Ib$ (1) Mutated $gyrA$ (3)	[81]
			Total studied samples	7280				
			Total studied strains	6359			Total no. of publications	97

'Samples' indicates that no strains were isolated but samples were directly tested by PCR. Coli R, colistin resistance; ESBL, extended-spectrum β-lactamase; HLP, high-level penicillinase; Methi R, methicillin resistance; MLSB, macrolide–lincosamide–streptogramin B phenotype; Vanco R, vancomycin resistance.

Senegal (*n* = 278; 3.8%) (Fig. 1(A)). From those 7280 samples, 6359 bacterial isolates were cultured and analysed phenotypically (bacterial identification by MALDI-TOF MS and AST) and genetically (molecular detection of antibiotic resistance genes).

Bacterial genera studied included *Enterobacteriaceae* (1296 *Klebsiella* and 1053 *Escherichia*), followed by *Acinetobacter* (*n* = 1176) or other Gram-negative organisms (*n* = 1774 including bacteria of the genera *Serratia, Salmonella, Enterobacter, Salmonella, Raoultella* and *Shewanella*) and *Pseudomonas* (*n* = 289) (Fig. 1(B)). Gram-positive strains were represented with 771 strains (12%), including bacteria of the genera *Enterococcus, Staphylococcus* or *Streptococcus* (Fig. 1(B)).

All these studies allowed the detection and characterization of specific antibiotic resistance genes in multidrug-resistant bacteria from these genera and led to 97 scientific international indexed publications. Table 1 lists the publications and findings of specific antibiotic resistance determinants by country and bacterial species.

The main antibiotic resistance determinants detected and characterized were extended-spectrum β-lactamases (ESBLs) and carbapenemases including bla_{CTX-M}, bla_{SHV}, bla_{TEM} [12], bla_{OXA-48} [13], bla_{NDM} [82] and bla_{VIM} [14] genes. Genes encoding for resistance to aminoglycosides were also reported, including, for example, $armA$ or $aac(6')$-*Ib* in *Acinetobacter baumannii* [81]. Resistance to colistin mediated by the newly plasmid-mediated *mcr-1* gene in human and animal isolates has been tested to date in 21 studies from eight countries (Algeria, Greece, Israel, Lebanon, Nigeria, Saudi Arabia, Senegal and Spain), leading to ten scientific publications (Table 1). An overview of the global distribution of the main findings of antibiotic resistance determinants in the 7280 samples studied per country and type of samples is provided in the map in Fig. 2.

Discussion

Here we show the unique role of IHU-MI in training about 100 students working in the field of antibiotic resistance from the Mediterranean basin and Africa over the last 6 years. This has led to the description and surveillance of new mechanisms of resistance to antibiotics in 15 various countries reported in 97 scientific publications, including 24 different peer-reviewed journals. The majority of the publications have reported the first detection of antibiotic resistance genes, mainly ESBLs [47], carbapenemases [15,16,31] and the *mcr-1* plasmid-mediated colistin resistance gene [17,18,22] in these countries in both humans and animals. One of the main contributions in the field is the description of a strong link between antibiotic consumption in animals and emergence and spread of antibiotic resistance genes in animals as well as the transfer to humans [83].
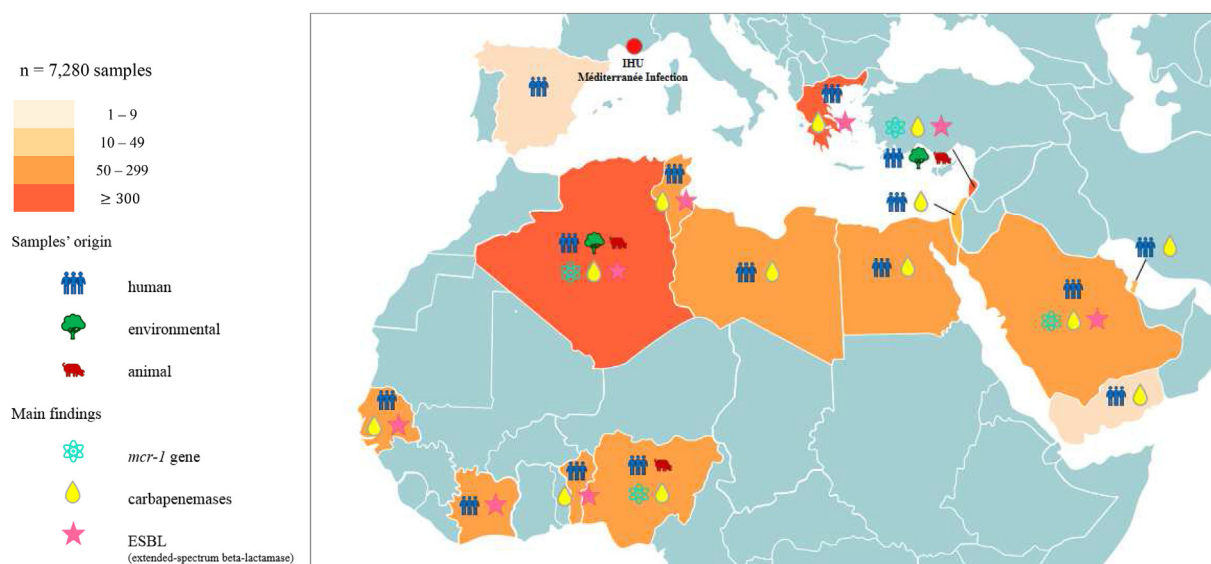
FIG. 2. Global distribution of samples in Mediterranean basin and African countries.

Antibiotics are widely used in agricultural settings in these countries, without clear control policies; this situation has affected human health and is implicated in the evolution of new mechanisms of resistance [84]. Epidemiologic descriptions are essential, and our results confirmed that surveillance should continue in Africa and in the Mediterranean basin to monitor and control the emergence and spread of antibiotic resistance genes. Thanks to these students and their training at the IHU-MI, the institute has created a unique collaborative network for surveillance and study of antibiotic resistance in Africa and in the Mediterranean basin because most of these students returned to their country of origin and created microbiology laboratories to study and survey antibiotic resistance in collaboration with the IHU-MI institute. Further engagements with key individuals are ongoing to create new partnerships to study antibiotic resistance in humans and animals in Italy, Morocco, Turkey and in the Balkans, and should be reinforced in Egypt and Libya as well as the Middle East, although the political situation is currently complex. The current migrant crisis in Europe should prompt us to survey antibiotic resistance in humans and animals from these countries, including Syria and Iraq, to avoid the possible spreading of specific clones, as previously reported in Greece [85,86] and Israel [87] for *Klebsiella pneumoniae* carbapenemase producers.

Because of its special location as a seaport in the Mediterranean basin, Marseille has historically always been a critical place for the entrance of infectious diseases such as plague or cholera [88]. Because antibiotic-resistant bacteria and antibiotic resistance genes that could spread in the Mediterranean basin do not have borders, the IHU-MI in Marseille plays a critical role in the surveillance of resistance in these areas as well as in African countries that historically have links to France. Thus, over the last 6 years, the institute has become a reference centre for the surveillance of antibiotic resistance and the training of students from countries in the Mediterranean basin and Africa. Such a collaborative network will expand in the future, permitting real-time surveillance of antibiotic resistance determinants that may emerge and spread in these areas [89].

Acknowledgement

Conflict of interest

None declared.

References

[1] World Health Organization; Organisation mondiale de la Santé. Résistance aux antibiotiques. Updated 5 February 2018. Available at: http://www.who.int/fr/news-room/fact-sheets/detail/résistance-aux-antibiotiques.

[2] Neill JO. Antimicrobial resistance: tackling a crisis for the health and wealth of nations. Review on antimicrobial resistance. December 2014. Available at: https://amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations_1.pdf.

[3] Rolain JM, Abat C, Jimeno MT, Fournier PE, Raoult D. Do we need new antibiotics? Clin Microbiol Infect 2016;22:408–15.

[4] Abat C, Raoult D, Rolain JM. Antibiotic resistance: are we living a nightmare? Clin Microbiol Infect 2018.

[5] Abat C, Rolain JM, Dubourg G, Fournier PE, Chaudet H, Raoult D. Evaluating the clinical burden and mortality attributable to antibiotic resistance: the disparity of empirical data and simple model estimations. Clin Infect Dis 2017;65:S58−63.

[6] Seng P, Drancourt M, Gouriet F, La Scola B, Fournier P, Rolain JM, et al. Ongoing revolution in bacteriology: routine identification of bacteria by matrix-assisted laser desorption ionization time-of-flight mass spectrometry. Clin Infect Dis 2009;49:543−51.

[7] European Committee on Antimicrobial Susceptibility Testing (EUCAST). Breakpoint tables for interpretation of MICs and zone diameters, version 8. Available at: http://www.eucast.org/clinical_breakpoints/.

[8] Gupta SK, Padmanabhan BR, Diene SM, Lopez-Rojas R, Kempf M, Landraud L, et al. ARG-ANNOT, a new bioinformatic tool to discover antibiotic resistance genes in bacterial genomes. Antimicrob Agents Chemother 2014;58:212−20.

[9] Rolain JM, Diene SM, Kempf M, Gimenez G, Robert C, Raoult D. Real-time sequencing to decipher the molecular mechanism of resistance of a clinical pan−drug-resistant *Acinetobacter baumannii* isolate from Marseille, France. Antimicrob Agents Chemother 2013;57:592−6.

[10] Al-Bayssari C, Olaitan AO, Leangapichart T, Okdah L, Dabboussi F, Hamze M, et al. Whole-genome sequence of a bla_{OXA-48}−harboring *Raoultella ornithinolytica* clinical isolate from Lebanon. Antimicrob Agents Chemother 2016;60:2548−50.

[11] Tafoukt R, Leangapichart T, Hadjadj L, Bakour S, Diene SM, Rolain JM, et al. Characterization of $bla_{OXA-538}$, a new variant of bla_{OXA-48} in *Shewanella xiamenensis* isolated from river water in Algeria. J Glob Antimicrob Resist 2017;13:70−3.

[12] Belmahdi M, Bakour S, Al Bayssari C, Touati A, Rolain JM. Molecular characterisation of extended-spectrum β-lactamase− and plasmid AmpC−producing *Escherichia coli* strains isolated from broilers in Béjaïa, Algeria. J Glob Antimicrob Resist 2016;6:108−12.

[13] Tafoukt R, Touati A, Leangapichart T, Bakour S, Rolain JM. Characterization of OXA-48−like−producing *Enterobacteriaceae* isolated from river water in Algeria. Water Res 2017;120:185−9.

[14] Al Bayssari C, Diene SM, Loucif L, Gupta SK, Dabboussi F, Mallat H, et al. Emergence of VIM-2 and IMP-15 carbapenemases and inactivation of *oprD* gene in carbapenem-resistant *Pseudomonas aeruginosa* clinical isolates from Lebanon. Antimicrob Agents Chemother 2014;58: 4966−70.

[15] Rafei R, Dabboussi F, Hamze M, Eveillard M, Lemarié C, Mallat H, et al. First report of bla_{NDM-1}−producing *Acinetobacter baumannii* isolated in Lebanon from civilians wounded during the Syrian war. Int J Infect Dis 2014;21:21−3.

[16] Touati A, Mairi A, Baloul Y, Lalaoui R, Bakour S, Thighilt L, et al. First detection of *Klebsiella pneumoniae* producing OXA-48 in fresh vegetables from Béjaïa city, Algeria. J Glob Antimicrob Resist 2017;9:17−8.

[17] Bachiri T, Lalaoui R, Bakour S, Allouache M, Belkebla N, Rolain JM, et al. First report of the plasmid-mediated colistin resistance gene *mcr-1* in *Escherichia coli* ST405 isolated from wildlife in Bejaia, Algeria. Microb Drug Resist 2017:mdr.2017.0026. https://doi.org/10.1089/mdr.2017.0026.

[18] Dandachi I, Leangapichart T, Daoud Z, Rolain JM. First detection of *mcr-1* plasmid-mediated colistin-resistant *Escherichia coli* in Lebanese poultry. J Glob Antimicrob Resist 2018;12:137−8.

[19] Berrazeg M, Diene SM, Drissi M, Kempf M, Richet H, Landraud L, et al. Biotyping of multidrug-resistant *Klebsiella pneumoniae* clinical isolates from France and Algeria using MALDI-TOF MS. PLoS One 2013;8: e61428.

[20] Berrazeg M, Drissi M, Medjahed L, Rolain JM. Hierarchical clustering as a rapid tool for surveillance of emerging antibiotic-resistance phenotypes in *Klebsiella pneumoniae* strains. J Med Microbiol 2013;62: 864−74.

[21] Djeffal S, Bakour S, Mamache B, Elgroud R, Agabou A, Chabou S, et al. Prevalence and clonal relationship of ESBL-producing *Salmonella* strains from humans and poultry in northeastern Algeria. BMC Vet Res 2017;13:132.

[22] Berrazeg M, Hadjadj L, Ayad A, Drissi M, Rolain JM. First detected human case in Algeria of *mcr-1* plasmid-mediated colistin resistance in a 2011 *Escherichia coli* isolate. Antimicrob Agents Chemother 2016;60: 6996−7.

[23] Bachiri T, Bakour S, Ladjouzi R, Thongpan L, Rolain JM, Touati A. High rates of CTX-M-15−producing *Escherichia coli* and *Klebsiella pneumoniae* in wild boars and Barbary macaques in Algeria. J Glob Antimicrob Resist 2017;8:35−40.

[24] Bouguenoun W, Bakour S, Bentorki AA, Al Bayssari C, Merad T, Rolain JM. Molecular epidemiology of environmental and clinical carbapenemase-producing Gram-negative bacilli from hospitals in Guelma, Algeria: multiple genetic lineages and first report of OXA-48 in *Enterobacter cloacae*. J Glob Antimicrob Resist 2016;7:135−40.

[25] Chaalal W, Chaalal N, Bakour S, Kihal M, Rolain JM. First occurrence of NDM-1 in *Acinetobacter baumannii* ST85 isolated from Algerian dairy farms. J Glob Antimicrob Resist 2016;7:150−1.

[26] Bourafa N, Abat C, Loucif L, Olaitan AO, Bentorki AA, Boutefnouchet N, et al. Identification of vancomycin-susceptible major clones of clinical *Enterococcus* from Algeria. J Glob Antimicrob Resist 2016;6:78−83.

[27] Ramoul A, Loucif L, Bakour S, Amiri S, Dekhil M, Rolain JM. Co-occurrence of bla_{NDM-1} with bla_{OXA-23} or bla_{OXA-58} in clinical multidrug-resistant *Acinetobacter baumannii* isolates in Algeria. J Glob Antimicrob Resist 2016;6:136−41.

[28] Mellouk FZ, Bakour S, Meradji S, Al-Bayssari C, Bentakouk MC, Zouyed F, et al. First detection of VIM-4−producing *Pseudomonas aeruginosa* and OXA-48−producing *Klebsiella pneumoniae* in north-eastern (Annaba, Skikda) Algeria. Microb Drug Resist 2017;23: 335−44.

[29] Zenati K, Touati A, Bakour S, Sahli F, Rolain JM. Characterization of NDM-1− and OXA-23−producing *Acinetobacter baumannii* isolates from inanimate surfaces in a hospital environment in Algeria. J Hosp Infect 2016;92:19−26.

[30] Bergal A, Loucif L, Benouareth DE, Bentorki AA, Abat C, Rolain JM. Molecular epidemiology and distribution of serotypes, genotypes, and antibiotic resistance genes of *Streptococcus agalactiae* clinical isolates from Guelma, Algeria and Marseille, France. Eur J Clin Microbiol Infect Dis 2015;34:2339−48.

[31] Yousfi M, Mairi A, Bakour S, Touati A, Hassissen L, Hadjadj L, et al. First report of NDM-5−producing *Escherichia coli* ST1284 isolated from dog in Bejaia, Algeria. New Microbe. New Infect 2015;8:17−8.

[32] Bachiri T, Bakour S, Lalaoui R, Belkebla N, Allouache M, Rolain JM, et al. Occurrence of carbapenemase-producing *Enterobacteriaceae* isolates in the wildlife: first report of OXA-48 in wild boars in Algeria. Microb Drug Resist 2018;24:337−45.

[33] Zenati K, Sahli F, Garcia V, Bakour S, Belhadi D, Rolain JM, et al. Occurrence and clonal diversity of multidrug-resistant *Klebsiella pneumoniae* recovered from inanimate surfaces in Algerian hospital environment: first report of armA, qnrB and aac(6′)-Ib-cr genes. J Glob Antimicrob Resist 2017;10:148−53.

[34] Selma C, Hamza L, Bernard D, Atef A, Rolain JM. Prevalence of extended-spectrum beta lactamase and carbapenemase-encoding genes in poultry feces from Algeria and Marseille, France. J Glob Antimicrob Resist 2017;13:28−32.

[35] Bouaziz A, Loucif L, Ayachi A, Guehaz K, Bendjama E, Rolain JM. Migratory white stork (*Ciconia ciconia*): a potential vector of the OXA-48−producing *Escherichia coli* ST38 clone in Algeria. Microb Drug Resist 2018;24:461−8.

[36] Hadjadj L, Riziki T, Zhu Y, Li J, Diene S, Rolain JM. Study of *mcr-1* gene−mediated colistin resistance in *Enterobacteriaceae* isolated from humans and animals in different countries. Genes (Basel) 2017;8:394.

[37] Bakour S, Touati A, Bachiri T, Sahli F, Tiouit D, Naim M, et al. First report of 16S rRNA methylase *ArmA*-producing *Acinetobacter baumannii* and rapid spread of metallo-β-lactamase NDM-1 in Algerian hospitals. J Infect Chemother 2014;20:696–701.

[38] Bakour S, Olaitan AO, Ammari H, Touati A, Saoudi S, Saoudi K, et al. Emergence of colistin- and carbapenem-resistant *Acinetobacter baumannii* ST2 clinical isolate in Algeria: first case report. Microb Drug Resist 2015;21:279–85.

[39] Bourafa N, Loucif L, Boutefnouchet N, Rolain JM. Enterococcus hirae, an unusual pathogen in humans causing urinary tract infection in a patient with benign prostatic hyperplasia: first case report in Algeria. New Microbe. New Infect 2015;8:7–9.

[40] Touati M, Diene SM, Racherache A, Dekhil M, Djahoudi A, Rolain JM. Emergence of bla_{OXA-23} and bla_{OXA-58} carbapenemase-encoding genes in multidrug-resistant *Acinetobacter baumannii* isolates from University Hospital of Annaba, Algeria. Int J Antimicrob Agents 2012;40:89–91.

[41] Touati M, Diene SM, Dekhil M, Djahoudi A, Racherache A, Rolain JM. Dissemination of a class 1 integron carrying VIM-2 carbapenemase in *Pseudomonas aeruginosa* clinical isolates from a hospital intensive care unit in Annaba, Algeria. Antimicrob Agents Chemother 2013;57: 2426–7.

[42] Sassi A, Loucif L, Gupta SK, Dekhil M, Chettibi H, Rolain JM. NDM-5 carbapenemase-encoding gene in multidrug-resistant clinical isolates of *Escherichia coli* from Algeria. Antimicrob Agents Chemother 2014;58: 5606–8.

[43] Labid A, Gacemi-Kirane D, Timinouni M, Amoura K, Rolain JM. High prevalence of extended spectrum beta-lactamase (ESBL) producers in fatal cases of pediatric septicemia among the *Enterobacteriaceae* in the pediatric hospital of Annaba, Algeria. Afr J Microbiol Res 2014;8: 947–54.

[44] Belbel Z, Chettibi H, Dekhil M, Ladjama A, Nedjai S, Rolain JM. Outbreak of an *armA* methyltransferase-producing ST39 *Klebsiella pneumoniae* clone in a pediatric Algerian hospital. Microb Drug Resist 2014;20:310–5.

[45] Morakchi H, Loucif L, Gacemi-Kirane D, Rolain JM. Molecular characterisation of carbapenemases in urban pigeon droppings in France and Algeria. J Glob Antimicrob Resist 2017;9:103–10.

[46] Loucif L, Kassah Laouar A, Saidi M, Messala A, Chelaghma W, Rolain JM. Outbreak of OXA-48–producing *Klebsiella pneumoniae* involving an ST 101 clone in Batna University Hospital, Algeria. Antimicrob Agents Chemother 2016;60:7494–7.

[47] Loucif L, Gacemi-Kirane D, Cherak Z, Chamlal N, Grainat N, Rolain JM. First report of German cockroaches (*Blattella germanica*) as reservoirs of CTX-M-15 extended-spectrum-β-lactamase- and OXA-48 carbapenemase-producing *Enterobacteriaceae* in Batna University Hospital, Algeria. Antimicrob Agents Chemother 2016;60:6377–80.

[48] Loucif L, Cherak Z, Chamlal N, Bendjama E, Gacemi-Kirane D, Grainat N, et al. First detection of VIM-2 metallo-β-lactamase–producing *Pseudomonas putida* in *Blattella germanica* cockroaches in an Algerian hospital. Antimicrob Agents Chemother 2017;61: e00357–17.

[49] Loucif L, Chelaghma W, Helis Y, Sebaa F, Baoune RD, Zaatout W, et al. First detection of OXA-48–producing *Klebsiella pneumoniae* in community-acquired urinary tract infections in Algeria. J Glob Antimicrob Resist 2018;12:115–6.

[50] Bakour S, Kempf M, Touati A, Ameur AA, Haouchine D, Sahli F, et al. Carbapenemase-producing *Acinetobacter baumannii* in two university hospitals in Algeria. J Med Microbiol 2012;61:1341–3.

[51] Bakour S, Touati A, Sahli F, Ameur AA, Haouchine D, Rolain JM. Antibiotic resistance determinants of multidrug-resistant *Acinetobacter baumannii* clinical isolates in Algeria. Diagn Microbiol Infect Dis 2013;76:529–31.

[52] Bakour S, Sahli F, Touati A, Rolain JM. Emergence of KPC-producing *Klebsiella pneumoniae* ST512 isolated from cerebrospinal fluid of a child in Algeria. New Microbe. New Infect 2015;3:34–6.

[53] Ouchenane Z, Agabou A, Smati F, Rolain JM, Raoult D. Staphylococcal cassette chromosome mec characterization of methicillin-resistant *Staphylococcus aureus* strains isolated at the military hospital of Constantine/Algeria. Pathol Biol 2013;61:280–1.

[54] Yagoubat M, Ould El-Hadj-Khelil A, Malki A, Bakour S, Touati A, Rolain JM. Genetic characterisation of carbapenem-resistant Gram-negative bacteria isolated from the University Hospital Mohamed Boudiaf in Ouargla, southern Algeria. J Glob Antimicrob Resist 2017;8: 55–9.

[55] Sefraoui I, Berrazeg M, Drissi M, Rolain JM. Molecular epidemiology of carbapenem-resistant *Pseudomonas aeruginosa* clinical strains isolated from western Algeria between 2009 and 2012. Microb Drug Resist 2014;20:156–61.

[56] Mesli E, Berrazeg M, Drissi M, Bekkhoucha SN, Rolain JM. Prevalence of carbapenemase-encoding genes including New Delhi metallo-β-lactamase in *Acinetobacter* species, Algeria. Int J Infect Dis 2013;17: 739–43.

[57] Kempf M, Bakour S, Flaudrops C, Berrazeg M, Brunel JM, Drissi M, et al. Rapid detection of carbapenem resistance in *Acinetobacter baumannii* using matrix-assisted laser desorption ionization–time of flight mass spectrometry. PLoS One 2012;7:e31676.

[58] Koudokpon H, Dougnon TV, Setondji Islamiath K, Alidah A, Brice Armand FV, Frédéric L, et al. Methicillin-resistance of *Staphylococcus species* in southern Benin : resistance gene, virulence factor associated and staphylococcal chromosomal cassette distribution. Int J Microbiol Res 2017;9:976–80.

[59] El-Sayed-Ahmed MAEG, Amin MA, Tawakol WM, Loucif L, Bakour S, Rolain JM. High prevalence of bla_{NDM-1} carbapenemase-encoding gene and 16S rRNA *armA* methyltransferase gene among *Acinetobacter baumannii* clinical isolates in Egypt. Antimicrob Agents Chemother 2015;59:3602–5.

[60] Olaitan AO, Diene SM, Assous MV, Rolain JM. Genomic plasticity of multidrug-resistant NDM-1 positive clinical isolate of *Providencia rettgeri*. Genome Biol Evol 2016;8:723–8.

[61] Lachish T, Elimelech M, Arieli N, Adler A, Rolain JM, Assous MV. Emergence of New Delhi metallo-β-lactamase in Jerusalem, Israel. Int J Antimicrob Agents 2012;40:566–7.

[62] Olaitan AO, Diene SM, Gupta SK, Adler A, Assous MV, Rolain JM. Genome analysis of NDM-1 producing *Morganella morganii* clinical isolate. Expert Rev Anti Infect Ther 2014;12:1297–305.

[63] Al Bayssari C, Olaitan AO, Dabboussi F, Hamze M, Rolain JM. Emergence of OXA-48–producing *Escherichia coli* clone ST38 in fowl. Antimicrob Agents Chemother 2015;59:745–6.

[64] Al Bayssari C, Dabboussi F, Hamze M, Rolain JM. Emergence of carbapenemase-producing *Pseudomonas aeruginosa* and *Acinetobacter baumannii* in livestock animals in Lebanon. J Antimicrob Chemother 2015;70:950–1.

[65] Okdah L, Leangapichart T, Hadjadj L, Olaitan AO, Al-Bayssari C, Rizk R, et al. First report of colistin-resistant *Klebsiella pneumoniae* clinical isolates in Lebanon. J Glob Antimicrob Resist 2017;9:15–6.

[66] Mathlouthi N, Areig Z, Al Bayssari C, Bakour S, Ali El Salabi A, Ben Gwierif S, et al. Emergence of carbapenem-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii* clinical isolates collected from some Libyan hospitals. Microb Drug Resist 2015;21:335–41.

[67] Mathlouthi N, El Salabi AA, Ben Jomàa-Jemili M, Bakour S, Al-Bayssari C, Zorgani AA, et al. Early detection of metallo-β-lactamase NDM-1– and OXA-23 carbapenemase–producing *Acinetobacter baumannii* in Libyan hospitals. Int J Antimicrob Agents 2016;48:46–50.

[68] Olaitan AO, Berrazeg M, Fagade OE, Adelowo OO, Alli JA, Rolain JM. Emergence of multidrug-resistant *Acinetobacter baumannii* producing OXA-23 carbapenemase, Nigeria. Int J Infect Dis 2013;17:e469–70.

[69] Olaitan AO, Diene SM, Kempf M, Berrazeg M, Bakour S, Gupta SK, et al. Worldwide emergence of colistin resistance in *Klebsiella pneumoniae* from healthy humans and patients in Lao PDR, Thailand, Israel, Nigeria and France owing to inactivation of the PhoP/PhoQ regulator

mgrB: an epidemiological and molecular study. Int J Antimicrob Agents 2014;44:500−7.

[70] Olaitan AO, Chabou S, Okdah L, Morand S, Rolain JM. Dissemination of the *mcr-1* colistin resistance gene. Lancet Infect Dis 2016;16:147.

[71] Leangapichart T, Gautret P, Brouqui P, Mimish Z, Raoult D, Rolain JM. Acquisition of *mcr-1* plasmid-mediated colistin resistance in *Escherichia coli* and *Klebsiella pneumoniae* during Hajj 2013 and 2014. Antimicrob Agents Chemother 2016;60:6998−9.

[72] Leangapichart T, Gautret P, Griffiths K, Belhouchat K, Memish Z, Raoult D, et al. Acquisition of a high diversity of bacteria during the Hajj pilgrimage, including *Acinetobacter baumannii* with *bla*OXA-72 and *Escherichia coli* with *bla*NDM-5 carbapenemase genes. Antimicrob Agents Chemother 2016;60:5942−8.

[73] Leangapichart T, Dia NM, Olaitan AO, Gautret P, Brouqui P, Rolain JM. Acquisition of extended-spectrum β-lactamases by *Escherichia coli* and *Klebsiella pneumoniae* in gut microbiota of pilgrims during the Hajj pilgrimage of 2013. Antimicrob Agents Chemother 2016;60:3222−6.

[74] Leangapichart T, Rolain JM, Memish ZA, Al-Tawfiq JA, Gautret P. Emergence of drug resistant bacteria at the Hajj: a systematic review. Travel Med Infect Dis 2017;18:3−17.

[75] Leangapichart T, Tissot-Dupont H, Raoult D, Memish ZA, Rolain JM, Gautret P. Risk factors for acquisition of CTX-M genes in pilgrims during Hajj 2013 and 2014. J Antimicrob Chemother 2017;72:2627−35.

[76] Diene SM, Fall B, Kempf M, Fenollar F, Sow K, Niang B, et al. Emergence of the OXA-23 carbapenemase-encoding gene in multidrug-resistant *Acinetobacter baumannii* clinical isolates from the principal hospital of Dakar, Senegal. Int J Infect Dis 2013;17:e209−10.

[77] Diene SM, Fenollar F, Fall B, Sow K, Niang B, Samba Ba P, et al. CTX-M-15−producing *Morganella morganii* from Hôpital Principal de Dakar, Senegal. New Microbe. New Infect 2014;2:46−9.

[78] Vila-Farrés X, Ferrer-Navarro M, Callarisa AE, Martí S, Espinal P, Gupta S, et al. Loss of LPS is involved in the virulence and resistance to colistin of colistin-resistant *Acinetobacter nosocomialis* mutants selected *in vitro*. J Antimicrob Chemother 2015; 2015;70:2981−6.

[79] Mathlouthi N, Ben Lamine Y, Somai R, Bouhalila-Besbes S, Bakour S, Rolain J-M, et al. Incidence of OXA-23 and OXA-58 carbapenemases coexpressed in clinical isolates of Acinetobacter baumannii in Tunisia. Microb Drug Resist 2018;24:136−41. https://doi.org/10.1089/mdr.2016.0306.

[80] Mathlouthi N, Al-Bayssari C, El Salabi A, Bakour S, Ben Gwierif S, Zorgani AA, et al. Carbapenemases and extended-spectrum β-lactamases producing *Enterobacteriaceae* isolated from Tunisian and Libyan hospitals. J Infect Dev Ctries 2016;10:718−27.

[81] Bakour S, Alsharapy SA, Touati A, Rolain JM. Characterization of *Acinetobacter baumannii* clinical isolates carrying *bla*OXA-23 carbapenemase and 16S rRNA methylase *armA* genes in Yemen. Microb Drug Resist 2014;20:604−9.

[82] Yagoubat M, Ould El-Hadj-Khelil A, Malki A, Bakour S, Touati A, Rolain JM. Genetic characterisation of carbapenem-resistant Gram-negative bacteria isolated from the University Hospital Mohamed Boudiaf in Ouargla, southern Algeria. J Glob Antimicrob Resist 2017;8:55−9.

[83] Olaitan AO, Thongmalayvong B, Akkhavong K, Somphavong S, Paboriboune P, Khounsy S, et al. Clonal transmission of a colistin-resistant *Escherichia coli* from a domesticated pig to a human in Laos. J Antimicrob Chemother 2015;70:3402−4.

[84] Zhu YG, Johnson TA, Su JQ, Qiao M, Guo GX, Stedtfeld RD, et al. Diverse and abundant antibiotic resistance genes in Chinese swine farms. Proc Natl Acad Sci USA 2013;110:3435−40.

[85] Papagiannitsis CC, Di Pilato V, Giani T, Giakkoupi P, Riccobono E, Landini G, et al. Characterization of KPC-encoding plasmids from two endemic settings, Greece and Italy. J Antimicrob Chemother 2016;71:2824−30.

[86] Karampatakis T, Antachopoulos C, Iosifidis E, Tsakris A, Roilides E. Molecular epidemiology of carbapenem-resistant *Klebsiella pneumoniae* in Greece. Future Microbiol 2016;11:809−23.

[87] Geffen Y, Adler A, Paikin S, Khabra E, Gorenshtein S, Aronov R, et al. Detection of the plasmid-mediated KPC-2 carbapenem-hydrolysing enzyme in three unusual species of the *Enterobacteriaceae* family in Israel. J Antimicrob Chemother 2013;68:719−20.

[88] Bataille J, Brouqui P. Building an intelligent hospital to fight contagion. Clin Infect Dis 2017;65:S4−11.

[89] Raoult D. Alice's living croquet theory. Int J Antimicrob Agents 2016;47:249.