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.

Keywords: Africa, Antibiotic resistance, IHU Méditerranée Infection, Mediterranean, Multi-drug resistance

Article published online: 14 June 2018

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

New Microbe and New Infect 2018; 26: S52–S64
© 2018 The Author(s). Published by Elsevier Ltd
This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/)
https://doi.org/10.1016/j.nmni.2018.06.001
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

![Image](image_url)

**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.

© 2018 The Author(s). Published by Elsevier Ltd, NMNI, 26, S52–S64
This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).
| 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 pneumonia | 211           | 194                                           | ESBL                                                  |                                | [19]          |
| Algeria         | 2008–2012| Clinical isolates          | K. pneumoniae    | 221           | 190                                           | ESBL                                                  | bla<sub>TEM</sub> (146) |                                | [20]          |
| Algeria         | 2017     | Animal (45) and human (37) isolates | Salmonella spp. | 92            | 18                                            | ESBL                                                  | bla<sub>CTX-M-1</sub> (12) |                                | [21]          |
| Algeria         | 2011     | Clinical isolates          | Escherichia coli | 1             | 1                                             | Coli R                                                | moX- (8)                                      |                                | [22]          |
| Algeria         | 2014     | Clinical and environmental isolates | K. pneumoniae Enterobacter cloacae Acinetobacter baumannii Pseudomonas aeruginosa | 89 | 32                                           | ESBL Carbapenemases                                   | bla<sub>OXA-48</sub> (15) |                                | [24]          |
| Algeria         | 2013–2015| Environmental isolates     | A. baumannii     | 1             | 1                                             | Carbapenemases                                        | bla<sub>NDM-1</sub> (1) |                                | [25]          |
| Algeria         | 2010–2012| Clinical isolates          | Enterococcus spp. | 85            | 85                                           | Vanco R                                               | vanC                                      |                                | [26]          |
| Algeria         | 2010–2013| Clinical isolates          | A. baumannii     | 43            | 43                                           | Vanco R                                               | bla<sub>NDM-1</sub> (7) |                                | [27]          |
| Algeria         | 2013–2015| Clinical isolates          | Enterobactiaceae (161) P. aeruginosa (18) A. baumannii (7) | 186 | 36                                           | Carbapenemases                                        | bla<sub>OXA-48</sub> (2) |                                | [28]          |
| Algeria         | 2011–2013| Environmental isolates     | A. baumannii     | 67            | 61                                           | Carbapenemases                                        | bla<sub>NDM-1</sub> (7) |                                | [29]          |
| Algeria         | 2013–2014| Clinical isolates          | Streptococcus agalactiae | 93           | 74                                           | MLSB R                                                | ermB                                    |                                | [30]          |
| Algeria         | 2015     | Animal isolates            | E. coli         | 1             | 1                                             | Carbapenemase                                          | bla<sub>NDM-1</sub> (1) |                                | [31]          |
| Algeria         | 2014–2016| Animal isolates            | Enterobactiaceae | 380           | 3                                             | Carbapenemase                                          | bla<sub>OXA-48</sub> (3) |                                | [32]          |
| Algeria         | 2012–2014| Environmental isolates     | K. pneumoniae    | 44            | 44                                           | Carbapenemase                                          | bla<sub>TEM-M-1</sub> (41) |                                | [33]          |
| Algeria         | 2014–2015| Animal isolates            | Samples         | 503           | 389                                          | Carbapenemases                                        | bla<sub>PEN</sub> (128) |                                | [34]          |
| Algeria         | 2015     | Animal isolates            | Enterobactiaceae | 32            | 32                                           | Carbapenemases                                        | bla<sub>OXA-48</sub> (12) |                                | [35]          |
| Algeria         | 2013–2014| Animal (3) and human (1) isolates | E. coli | 4             | 4                                             | Coli R                                                | moX- (4)                                      |                                | [36]          |
| Algeria         | 2016     | Animal isolates            | E. coli (8)     | 8             | 8                                             | Coli R                                                | In progress                               | Unpublished results |
| Algeria         | 2017     | Animal (4) and environmental (5) isolates | E. cloacae (1) | 9            | 9                                             | Coli R                                                | In progress                               | Unpublished results |
| Year   | Strain type     | No. of samples | Tested phenotype | Type of antibiotic resistance genes detected (n) | Study          |
|--------|-----------------|---------------|-----------------|-----------------------------------------------|----------------|
| 2016   | Clinical isolates | 3             | Coli R          | In progress                                   | Unpublished results |
| 2015–2016 | Environmental isolates | 200           | Coli R          | In progress                                   | Unpublished results |
| 2011–2013 | Clinical isolates | 47            | Coli R          | In progress                                   | Unpublished results |
| 2013–2014 | Clinical isolates | 12            | Coli R          | In progress                                   | Unpublished results |
| 2016   | Clinical isolates | 200           | ESBL            | In progress                                   | Unpublished results |
| 2011–2012 | Clinical isolates | 42            | ESBL            | In progress                                   | Unpublished results |
| 2011   | Clinical isolates | 17            | ESBL            | In progress                                   | Unpublished results |
| 2012–2013 | Clinical isolates | 105           | ESBL            | In progress                                   | Unpublished results |
| 2010–2011 | Clinical isolates | 42            | ESBL            | In progress                                   | Unpublished results |
| 2010–2011 | Clinical isolates | 100           | ESBL            | In progress                                   | Unpublished results |
| 2013   | Animal isolates  | 33            | ESBL            | In progress                                   | Unpublished results |
| 2014–2015 | Clinical isolates | 7             | ESBL            | In progress                                   | Unpublished results |
| 2015   | Environmental isolates | 12            | ESBL            | In progress                                   | Unpublished results |
| 2015   | Animal isolates  | 1             | ESBL            | In progress                                   | Unpublished results |
| 2017   | Clinical isolates | 1             | ESBL            | In progress                                   | Unpublished results |
| 2010–2011 | Clinical isolates | 71            | ESBL            | In progress                                   | Unpublished results |
| 2010–2011 | Clinical isolates | 71            | ESBL            | In progress                                   | Unpublished results |
| Year       | Category          | Organism                                   | ESBL | Carbapenemases | Ampicillin/cephalosporinases | Aminoglycosides | Fluoroquinolones | Other resistance genes |
|------------|-------------------|--------------------------------------------|------|----------------|-------------------------------|-----------------|------------------|------------------------|
| 2013       | Clinical isolates | *K. pneumoniae*                            | 1    | 1              |                               |                 |                  |                         |
| 2015       | Environmental isolates | *E. coli* (12) | *K. pneumoniae* (3) | *R. armadillos* (3) | *C. freundii* (1) | 20 | 20 | *bla*TEM-1 (1) | *aadA* (36) | *aph(3′)III* (64) | *aadA* (45) | *ant* (2) | *ant* (20) | *aac(6′)Ib* (3) | *aadA* (6) | *parC* (67) |
| 2015       | Environmental isolates | *Shewanella xiamenensis* | 4    | 4              |                               |                 |                  |                         |
| 2014       | Animal isolates   | *E. coli*                                  | 20   | 20             |                               |                 |                  |                         |
| 2014       | Environmental isolates | *S. aureus* | *S. aureus* | *M. morgani* | *M. Providencia* | 250 | 64 | 106 | 72 |               |                                     |                     |
| 2014–2015  | Clinical (60) and environmental (39) isolates | *Enterobacteriaceae* | 99   | 10             |                               |                 |                  |                         |
| 2009–2012  | Clinical isolates | *P. aeruginosa*                            | 89   | 39             |                               |                 |                  |                         |
| 2008–2012  | Clinical isolates | *Acinetobacter spp.*                       | 113  | 113            |                               |                 |                  |                         |
| 2012       | Clinical isolates | *A. baumannii*                             | 123  | 77             |                               |                 |                  |                         |
| 2015       | Clinical isolates | *Staphylococcus saprophyticus* (31) | *S. aureus* (21) | *S. scavi* (17) | *S. cohnii* (5) | *S. hominis* (2) | *S. xylosus* (1) | *S. hominis* (1) | 78 | 21 | Methi R | *bla*OXA-23 (40) | *bla*OXA-24 (3) | *bla*OXA-23 (3) | *bla*OXA-24 (3) | *mcr-1* (19) |

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                     |
|-----------------|---------------|------------------|---------------------------------------------------------------------------------|----------------|-----------------------------------------------|------------------|-----------------------------------------------|---------------------------|
| Egypt           | 2015          | Clinical isolates| *Enterobacteaceae*                                                              | 157            | 103                                           | ESBL Carbenapenases | In progress                                   | Unpublished results       |
|                 |               |                  |                                                                                 |                |                                               | Carbenapenases Aminoglycosides             |                  |                                               |                           |
|                 | 2016          | Clinical isolates| *P. aeruginosa*                                                                 | 3              | 3                                             | ESBL Carbenapenases | In progress                                   | Unpublished results       |
|                 | 2012–2013     | Clinical isolates| *A. baumannii*                                                                  | 150            | 150                                           | ESBL Carbenapenases | In progress                                   | Unpublished results       |
|                 |               |                  |                                                                                 |                |                                               |                 |                                               |                           |
| Greece          | 2013–2017     | Clinical isolates| *P. mirabilis* *(4) P. putida* *(1) C. freundii* *(1) Enterobacteaceae* *(2) Providencia stuartii* *(8) P. aeruginosa* *(79) A. baumannii* *(158) E. cloacae* *(10) E. coli* *(33) K. pneumoniae* *(314)* | 610            | 610                                           | ESBL Carbenapenases | In progress                                   | Unpublished results       |
|                 |               |                  |                                                                                 |                |                                               |                 |                                               |                           |
| Israel          | 2011          | Clinical isolates| K. pneumoniae                                                                   | 1              | 1                                             | Carbenapemase    | bla*NDM-1* *(1)                                | [60]                      |
|                 | 2008–2011     | Clinical isolates| K. pneumoniae                                                                   | 15             | 15                                           | Carbenapenases Aminoglycosides             | In progress                                   | Unpublished results       |
|                 | 2010–2011     | Clinical isolates| K. pneumoniae                                                                   | 5              | 5                                             | Carbenapenases                              | bla*NDM-1* *(5)                                | [61]                      |
|                 |               |                  |                                                                                 |                |                                               |                 |                                               |                           |
| Ivory Coast     | 2014          | Clinical isolates| *M. morgani*                                                                    | 1              | 1                                             | Carbenapenases Aminoglycosides Fluoroquinolones | In progress                                   | Unpublished results       |
|                 | 2012–2015     | Clinical isolates| *Enterobacteaceae*                                                              | 153            | 153                                           | ESBL Carbenapenases Aminoglycosides Fluoroquinolones | In progress                                   | Unpublished results       |
|                 |               |                  |                                                                                 |                |                                               |                 |                                               |                           |
| Lebanon         | 2013          | Clinical isolates| *P. aeruginosa*                                                                 | 35             | 35                                           | Carbenapenases Cephalosporinases            | In progress                                   | Unpublished results       |
|                 | 2013          | Animal isolates  | *E. coli*                                                                       | 1              | 1                                             | ESBL Cephalosporinases                        | [14]                        |
|                 | 2013          | Animal isolates  | *P. aeruginosa* *(4) A. baumannii* *(4)                                         | 9              | 9                                             | ESBL Cephalosporinases                        | [63]                        |
|                 | 2015          | Clinical isolates| *R. ornitholytica*                                                              | 1              | 1                                             | Carbenapenases Cephalosporinase BLSE MLSB R Chloramphenicol Fluoroquinolones | In progress                                   | Unpublished results       |
|                 |               |                  |                                                                                 |                |                                               |                 |                                               |                           |
|                 | 2015          | Animal isolates  | *E. coli*                                                                       | 1              | 1                                             | ESBL Carbenapenases                           | [18]                        |
|                 | 2015          | Animal isolates  | *E. cloacae*                                                                    | 1              | 1                                             | Carbenapeninase                               | [64]                        |
|                 | 2015          | Animal isolates  | *K. pneumoniae* *(8) Escherichia fergusonii* *(1)*                               | 235            | 235                                           | ESBL Carbenapeninase                           | Unpublished results       |
## Antibiotic Resistance

| Year          | Category          | Organism(s)                                | Isolates(s) | ESBL     | Carbenemase(s) | Mutation(s) | Notes                          |
|---------------|-------------------|--------------------------------------------|-------------|----------|----------------|--------------|--------------------------------|
| 2017          | Animal isolates   | A. baumannii (1)                           | 1           |          |                |              |                                |
|               |                   | P. mirabilis (3)                           |             |          |                |              |                                |
|               |                   | E. cloacae (2)                              |             |          |                |              |                                |
|               |                   | E. coli (105)                               | 1           |          |                |              |                                |
|               |                   | E. fergusonii (2)                           |             |          |                |              |                                |
|               |                   | K. pneumoniae (4)                           | 1           |          |                |              |                                |
|               |                   | Enterobacter aerobacter (1)                 |             |          |                |              |                                |
|               |                   | Stenotrophomonas maltophilia (4)           |             |          |                |              |                                |
|               |                   | Serratia rubidae (1)                        |             |          |                |              |                                |
|               |                   | A. baumannii (4)                            |             |          |                |              |                                |
|               |                   | Acinetobacter genomospecies (4)            |             |          |                |              |                                |
|               |                   | Pseudomonas spp. (8)                       |             |          |                |              |                                |
|               |                   | Ochrobactrum spp. (1)                      |             |          |                |              |                                |
| 2017          | Environmental (53)Human (11) isolates     | E. coli (341)                               | 1           |          |                |              |                                |
|               |                   | K. pneumoniae (31)                         |             |          |                |              |                                |
|               |                   | Enterobacter aerobacter (1)                |             |          |                |              |                                |
|               |                   | Stenotrophomonas maltophilia (4)           |             |          |                |              |                                |
| 2016–2017     | Clinical isolates | Entrobacter lactum                        | 4           | 4        | Glycopeptides   | In progress | Unpublished results            |
| 2016          | Clinical isolates | A. baumannii                               | 31          | 31       | ESBL            | In progress | Unpublished results            |
|               |                   | Campylobacter jejuni                       | 1           | 1        | ESBL            | In progress | Unpublished results            |
| 2010–2016     | Clinical isolates | E. coli                                   | 43          | 43       | ESBL            | In progress | Unpublished results            |
| 2015          | Clinical isolates | K. pneumoniae                              | 3           | 3        | ESBL            | In progress | Unpublished results            |
| 2016–2017     | Clinical isolates | Enterobacter aerofacioc (8)                | 9           | 9        | ESBL            | In progress | Unpublished results            |
| 2012          | Clinical isolates | A. baumannii                               | 4           | 4        | Carbenemases    | In progress | [15]                           |
| 2013–2014     | Clinical isolates | Neisseria meningitidis                    | 58          | 1        | Carbenemases    | In progress | Unpublished results            |
| 2015          | Clinical isolates | A. baumannii                               | 36          | 36       | Carbenemases    | In progress | [67]                           |
| 2012          | Clinical isolates | A. baumannii                               | 3           | 3        | Carbenemases    | In progress | [68]                           |
| 2013          | Clinical isolates | Klebsiella spp.                            | 139         | 1        | Carbenemases    | In progress | [69]                           |
| 2014          | Clinical isolates | A. baumannii                               | 48          | 48       | Carbenemases    | In progress | [70]                           |
| 2013–2014     | Clinical isolates | E. coli                                   | 11          | 11       | Carbenemases    | In progress | [71]                           |
|               |                   | K. pneumoniae                              |             |          | ESBL            |              |                                |
| 2013–2014     | Clinical isolates | E. coli                                   | 28          | 28       | ESBL            | In progress | [72]                           |
|               |                   | K. pneumoniae                              |             |          | ESBL            |              |                                |
| 2013–2014     | Clinical isolates | Samples                                    | 218         | 73       | ESBL            | In progress | [73]                           |

[NMNI Peykl et al. IHU-MI in antibiotic resistance](http://creativecommons.org/licenses/by/4.0/)
| Country   | Year       | Bacterial genera | Type of antibiotic resistance genes detected (n) | Tested phenotype genes detected | Study |
|-----------|------------|------------------|-----------------------------------------------|--------------------------------|-------|
| Senegal   | 2011       | Acinetobacter baumannii | Carbapenemases | blaOXA-23 (3) [76] | Unpublished results |
|           | 2014       | M. morganii       | ESBL | CTX (112) | [77] |
|           | 2015       | Enterobacteriaceae | Carbapenemases | blaOXA-51 + OXA-23 (25) | [79] |
| Spain     | 2015       | K. pneumoniae     | ESBL | CTX (47) | [80] |
| Tunisia   | 2013       | E. coli           | Carbapenemases | blaOXA-23 (3) | [81] |
| Yemen     | 2013       | A. baumannii      | Carbapenemases | blaOXA-23 (3) | [81] |

*Samples indicate that no strains were isolated but samples were directly tested by PCR. 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 blaCTX-M, blaKPC, blaTEM [12], blaOXA-48 [13], blaNDM [82] and blaVIM [14] genes. Genes encoding for resistance to aminoglycosides were also reported, including, for example, armA or aac(6’)-Ib in Acinetobacter baumanii [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].
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 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

We are grateful to IHU-MI.

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.
Bakour S, Touati A, Bachiri T, Sahli F, Touati 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 2020;4:696–701.

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.

Bourafa N, Loucif L, Bouteftouhnet 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.

Touati M, Diene SM, Racherache A, Dhekhil M, Djahoui A, Rolain JM. Emergence of bla<sub>TEM-22</sub> and bla<sub>OXA-36</sub> carbapenemase-encoding genes in multidrug-resistant Acinetobacter baumannii isolates from University Hospital of Annaba, Algeria. Int J antimicrob Agents 2012;40:89–91.

Touati M, Diene SM, Dhekhil M, Djahoui A, Racherache A, Rolain JM. Dissemination of a class I integron carrying VIM-2 carbapenemase in <i>Pseudomonas aeruginosa</i> clinical isolates from a hospital intensive care unit in Annaba, Algeria. Antimicrob Agents Chemother 2013;57:2426–7.

Sassi A, Loucif L, Gupta SK, Dhekhil M, Chetbhi H, Rolain JM. NDM-1 carbapenemase-encoding gene in multidrug-resistant clinical isolates of <i>Escherichia coli</i> from Algeria. Antimicrob Agents Chemother 2014;58:5606–8.

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.

Belbel Z, Chetbhi H, Dhekhil M, Ladjama A, Nedjai S, Rolain JM. Outbreak of an <i>ama</i> methyltransferase-producing ST39 Klebsiella pneumoniae clone in a pediatric Algerian hospital. Microb Drug Resist 2014;20:310–5.

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

Loucif L, Kassah Lauar A, Saidi M, Essaala A, Chechigna W, Rolain JM. Outbreak of <i>OXA-48</i>-producing Klebsiella pneumoniae involving an ST 101 clone in Batna University Hospital, Algeria. Antimicrob Agents Chemother 2016;60:7494–7.

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

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

Loucif L, Chechigna W, Heils Y, Sebba F, Basoue RD, Zaoutt W, et al. First detection of <i>OXA-48</i>-producing Klebsiella pneumoniae in community-acquired urinary tract infections in Algeria. J Glob Antimicrob Resist 2018;12:115–6.

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

Bakour S, Touati A, Sahli F, Ameer 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.

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.

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

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

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

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.

Kempf M, Bakour S, Flaudrops C, Berrazeg M, Brunel MI, 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.

Koudokhon H, Dougnon TV, Setondji Islamathi K, Alidah A, Brice Armand FV, Frédéric L, et al. Meticillin-resistance of <i>Staphylococcus</i> species in southern Benin: resistance gene, virulence factor associated and staphylococcal chromosomal cassette distribution. Int J Microbiol Res 2017;9:976–80.

El-Sayed-Ahmed MAEG, Amin MA, Tawakol WM, Loucif L, Bakour S, Rolain JM. High prevalence of <i>bla</i><sub>NDM-1</sub>-carbapenemase-encoding gene and 16S rRNA amiB methyltransferase gene among <i>Acinetobacter baumannii</i> clinical isolates in Egypt. Antimicrob Agents Chemother 2015;59:3620–5.

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

Lachish T, Eleimeleh 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.

Olaitan AO, Diene SM, Gupta SK, Adler A, Assous MV, Rolain JM. Genome analysis of NDM-1 producing <i>Margarello margarini</i> clinical isolate. Expert Rev Ant Infect Ther 2014;12:1297–305.

Al Bayssari C, Olaitan AO, Dabboussi F, Hamze M, Rolain JM. Emergence of <i>OXA-48</i>-producing <i>Escherichia coli</i> clone ST38 in fowl. Int J Antimicrob Agents 2015;59:745–6.

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

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.

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

Mathlouthi N, El Salabi AA, Ben Jamaa-Jemili M, Bakour S, Al-Bayssari C, Zorgani AA, et al. Detection of metallo-β-lactamase NDM-1 and <i>OXA-23</i> carbapenemase-producing <i>Acinetobacter baumannii</i> in Libyan hospitals. Int J Antimicrob Agents 2016;48:46–50.

Olaitan AO, Berrazeg M, Fadade OE, Adelowo OW, Alti JA, Rolain JM. Emergence of multidrug-resistant <i>Acinetobacter baumannii</i> producing <i>OXA-23</i> carbapenemase, Nigeria. Int J Infect Dis 2013;17:e469–70.

Olaitan AO, Diene SM, Kempf M, Berrazeg M, Bakour S, Gupta SK, et al. Worldwide emergence of colistin resistance in <i>Klebsiella pneumoniae</i> from healthy humans and patients in Lao PDR, Thailand, Israel, Nigeria and France owing to inactivation of the PhoP/PhoQ regulator.
[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, Mmimz Z, Raoult D, Rolain J-M. 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 blaOXA-72 and Escherichia coli with blaoXA-58 carbapenemase genes. Antimicrob Agents Chemother 2016;60:5942–8.

[73] Leangapichart T, DIA NM, Olaitan AO, Gautret P, Brouqui P, Rolain J-M. 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 J-M, Memish ZA, Al-Tawfiq JA, Gautret P. Emergency 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, MemishZA, 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] Dieme 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] Dieme SM, Fenollar F, Fall B, Sow K, Niang B, Samba Ba P, et al. CTX-M-15-producing Margarella morgani from Hôpital Principal de Dakar, Senegal. New Microbe. New Microbiol. New Infect 2014;2:46–9.

[78] Villa-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, Boughalia-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 blaoXA-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;5:55–9.

[83] Olaitan AO, Thongmalayvong B, Akkhavong K, Somphavong S, Paboriboune P, Khouvy 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.