Epidemiology of Multidrug-Resistant *Pseudomonas aeruginosa* in the Middle East and North Africa Region

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ABSTRACT  Over the last decades, there has been a dramatic global increase in multidrug-resistant (MDR) pathogens particularly among Gram-negative bacteria (GNB). *Pseudomonas aeruginosa* is responsible for various health care-associated infections, while MDR *P. aeruginosa* causes significant morbidity and mortality. Middle East and North Africa (MENA) represent an unexplored geographical region for the study of drug resistance since many of these countries are at crossroads of high volume of travel, diverse expatriate populations, as well as high antibiotic consumption despite attempts to implement antimicrobial stewardship programs. This minireview analyzes epidemiology, microbiological, and genomic characteristics of MDR *P. aeruginosa* in the MENA region. Published data on MDR *P. aeruginosa* prevalence, antimicrobial resistance patterns, and genetic profiles from studies published during the past 10 years from 19 MENA countries have been included in this minireview. There is wide variation in the epidemiology of MDR *P. aeruginosa* in the MENA region in terms of prevalence, antimicrobial characteristics, as well as genetic profiles. Overall, there is high prevalence of MDR *P. aeruginosa* seen in the majority of the countries in the MENA region with similarities between neighboring countries, which might reflect comparable population and antibiotic-prescribing cultures. Isolates from critical care units are significantly resistant particularly from certain countries such as Saudi Arabia, Egypt, Libya, Syria, and Lebanon with high-level resistance to cephalosporins, carbapenems, and aminoglycosides. Colistin susceptibility patterns remains high apart from countries with high-level antibiotic resistance such as Saudi Arabia, Syria, and Egypt.

KEYWORDS  *Pseudomonas aeruginosa*, antibiotic resistance, multidrug resistance, Middle East and North Africa region, intensive care units, urinary tract infections, MDR, MENA

Over the past decades, there has been a remarkable global increase in antimicrobial resistance (AMR). A report published by the Centers for Disease Control and Prevention in 2019 stated that these pathogens are responsible for the annual infection of more than 2.8 million people and cause an estimated 35,000 deaths per year in the United States alone (1). In the European Union, infections with AMR pathogens cause approximately 33,000 deaths per year with an estimated annual economic loss of 1.5 billion dollars (2). Furthermore, it has been estimated that by 2050 if no action has been taken, mortality and morbidity from AMR will surpass any acute or chronic illnesses, including heart diseases and cancer with an estimated annual mortality of 10 million cases (2, 3). The escalated challenge caused by AMR pathogens extends beyond developing countries to include the Middle East and North Africa (MENA) region which has not been fully explored.
Of particular concern of the global propagation of AMR is the continuous emergence of multidrug-resistant (MDR) pathogens particularly in Gram-negative bacteria (GNB). Among GNB, members of the Enterobacteriaceae family, Pseudomonas aeruginosa, and Acinetobacter baumannii are considered major health care threats due to their vast rates of emergence, acquisition, and spread of different resistance mechanisms (4). This consequently led to challenges in initiating appropriate targeted therapy particularly in severe infections leading to increased morbidity and mortality as well as prolonged hospital stays and subsequently excessive health care costs (5). To counter these challenges, broad-spectrum antimicrobials such as advanced cephalosporins and carbapenems have been overprescribed repeatedly, leading to a vicious cycle with further accumulation of selective resistance profiles (6).

*P. aeruginosa* is an opportunistic GNB which was first identified in the early 1800s (7). It thrives best in moist settings particularly suitable aquatic environments, including health care settings (8). Despite widespread environmental spread, *P. aeruginosa* rarely colonizes healthy individuals (0% to 2% skin colonization rate) (8). However, it frequently colonizes hospitalized patients (>50% colonization rate) and is a major cause of health care-associated infections (HCAIs) leading to life-threatening acute or chronic infections, including recurrent exacerbations in patients with cystic fibrosis, hospital- and ventilator-associated pneumonia, bacteremia, urinary tract, as well as wounds and soft tissue infections (8, 9).

While studying the underlying resistance mechanism of AMR, *P. aeruginosa* is a cornerstone pathogen being highlighted among the important resistant ESKAPE bacteria (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *P. aeruginosa*, and *Enterobacter* species) which are the foremost challenging pathogens for community and hospital drug resistance (10). It is also considered a critical priority by the WHO’s ranking list of pathogens in need to develop and discover novel therapeutic modalities (11).

The Middle East and North Africa region represents a comprehensively uncharted geographical region for drug resistance studies, since many of these countries have high volume of travel, diverse expatriate populations, and wide availability of over-the-counter antibiotics despite recent attempts to control antimicrobial consumption through antimicrobial stewardship programs (ASPs) at community and hospital levels (12–16). Although there are published reports on the epidemiology of *P. aeruginosa* from individual countries, there has been no comprehensive review covering the entire region to the best of our knowledge. The aim of this minireview is to describe the prevalence of MDR *P. aeruginosa*, microbiological characteristics, and genomic mechanisms of antibiotic resistance focusing mainly on carbapenem resistance in the Middle East and North Africa region.

**MECHANISMS OF ANTIMICROBIAL RESISTANCE IN GNB INCLUDING *P. AERUGINOSA***

There are multiple antimicrobial mechanisms that evolved in Gram-negative bacteria (GNB) to become distinctively resistant. Integral to its resistance mechanisms is the production of β-lactamases which disrupt the β-lactam rings of antibiotics that target bacterial cell walls (4). All β-lactam antibiotics contain the 3-carbon and 1-nitrogen ring (beta-lactam ring), which includes commonly prescribed antibiotic classes such as penicillins, monobactams, cephalosporins, as well as carbapenems (17). According to molecular size and amino acid similarity in the active sites, β-lactamases are subdivided into molecular classes A through D (Ambler classification), and accumulation of diverse β-lactamase resistance genes manifest as highly resistant strains (18). Extended-spectrum β-lactamases (ESBLs) (which are mainly class A β-lactamases) are the most commonly encountered, leading to resistance to all β-lactams, except carbapenems and certain β-lactam β-lactamase inhibitor combinations (BLBLIs) (19). Conversely, metallo-β-lactamase (MBL) (zinc-based class B) cause resistance to all β-lactams, including BLBLIs except monobactams such as aztreonam. Because metallo-β-lactamases are encoded by mobile gene cassettes, they are often associated with other resistance genes such as
aminoglycosides and fluoroquinolones (4). Similarly, AmpC (class C) are broad-spectrum \(\beta\)-lactamases with cephalosporinase selection preference (9), while oxacillinases (class D) are clinically relevant \(\beta\)-lactamases capable of hydrolyzing the potent class of carbapenems, raising the height of resistance profiles (4). The most common \(\beta\)-lactamases in \(P.\ aeruginosa\) are class A (VEB, PME, BEL, GES, and PER), class B (VIM and IMP), and class D (OXA-2 and OXA-10) \(\beta\)-lactamases (20).

In addition to \(\beta\)-lactamases, GNB, particularly \(P.\ aeruginosa\), possess other corresponding resistance mechanisms which are either intrinsically present at the chromosomal level or horizontally acquired through plasmids demonstrated by downregulation of porin channels, upregulation of efflux pumps, antibiotic modification, as well as target site alteration (21). In \(P.\ aeruginosa\), the main chromosomally encoded intrinsic mechanisms are inducible AmpC cephalosporinase, MexAB-OprM efflux pumps, inducible MexXY efflux pump, as well as low outer membrane permeability and OXA-type oxacillinase (20). In addition to its naturally occurring intrinsic resistance mechanisms, \(P.\ aeruginosa\) is capable of accumulating resistance genes acquired via chromosomal mutations (21). Overproduction of chromosomal AmpC cephalosporinase is likely the most prevalent acquired \(\beta\)-lactam resistance mechanism, and it has been found in over 20% of clinical isolates (20, 22–24). Structural modification of AmpC is another potential cause of \(\beta\)-lactam resistance (25, 26). Inducible AmpC causes resistance to aminopenicillins (e.g., amoxicillin and ampicillin) and a number of cephalosporins (particularly cefotaxin) (20). Overexpression of efflux pumps can also be affected by chromosomal mutations. Overexpression of the MexAB-OprM efflux pump allows resistance to most of the \(\beta\)-lactams (except imipenem) and fluoroquinolones, and inducible MexXY efflux pump overexpression allows resistance to aminoglycosides, cefepime, and chloramphenicol (20). Although less common, MexCD-OprJ and MexEF-OprN overexpression can cause resistance to fluoroquinolones (20, 27, 28). In addition, inactivation or downregulation of the carbapenem-specific porin OprD can cause acquired resistance to imipenem and decreased susceptibility to meropenem (22, 29). Together, AmpC overproduction and OprD inactivation can potentially cause resistance to all antipseudomonal \(\beta\)-lactams (20, 30). Other mutation-driven resistance mechanisms that can be acquired are via mutations in DNA topoisomerases (ParC/ParE), both of which cause resistance to fluoroquinolones (8, 31). Additionally, mutations in FusA1 can cause resistance to aminoglycosides (28, 32). Last, among mutation-driven mechanisms, alteration, or modifications of the outer membrane liposaccharide (LPS) operon might generate resistance to colistin (20, 33).

Of note, horizontally transferred resistance is yet another method of acquiring resistance in \(P.\ aeruginosa\) (20). This is mostly seen in acquiring ESBLs and carbapenemases, specifically of class A serine carbapenemases (KPC), class B (metallo-\(\beta\)-lactamases), and class D (OXA-40) (9). The genes encoding these \(\beta\)-lactamases are found on class 1 integrons, which are inserted into mobile elements and mediate transfer between bacteria (34, 35). Horizontally transferred plasmid-mediated colistin resistance genes that disrupt outer LPS have been infrequently reported in \(P.\ aeruginosa\) (36). In addition, the class 1 integrons also carries determinants of aminoglycoside resistance, mainly acetyltransferases and nucleotidytransferases (9, 37). Transferrable fluoroquinolone resistance has also been reported in \(P.\ aeruginosa\) (38).

Despite extensive regional reporting of the epidemiology and microbiological and genomic characteristics of \(P.\ aeruginosa\), including resistant strains, limited similar information is available regarding the Middle East and North Africa (MENA) region. This minireview aims to explore available literature for the scale of the problem and report the microbiological and genetic characteristics of dominant strains in the MENA region, including highly resistant strains such as carbapenem-resistant \(P.\ aeruginosa\).

**METHODS AND DATA COLLECTION AND ANALYSIS**

Four clusters of the MENA region, encompassing 19 countries, were included in this study: the Levant region (Iraq, Syria, Lebanon, Palestine, Israel, and Jordan), Gulf...
Countries comprising the Gulf Cooperation Council (GCC) (Saudi Arabia, Kuwait, Qatar, United Arab Emirates [UAE], Bahrain, and Oman) in addition to Yemen, northeastern Africa (Egypt and Sudan), and northwestern Africa (Libya, Tunisia, Algeria, and Morocco) (Fig. 1). The PubMed database was searched for studies from the MENA region that report MDR rates in *P. aeruginosa*, antimicrobial susceptibility/resistance profiles, as well as reported resistance genes in carbapenem-resistant (CR) *P. aeruginosa*. Antibiotics and genes most reported and clinically relevant have been included in this minireview. Studied antibiotics are BLBLI (piperacillin-tazobactam [PTZ]), third-generation cephalosporin (ceftazidime [CTZ]), fourth-generation cephalosporin (cefe-pime [FEP]), carbapenems (imipenem [IMP] and meropenem [MER]), aminoglycosides (amikacin [AMK] and gentamicin [GEN]), fluoroquinolones (ciprofloxacin [CIP] and levofloxacin [LEV]), monobactam (aztreonam [AZT]), and colistin (COL).

The examined genes of interest are as follows: class A ESBL genes (*bla*<sub>SHV</sub>, *bla*<sub>GES</sub>, *bla*<sub>TEM</sub>, *bla*<sub>CTX-M</sub>, and *bla*<sub>VEB</sub>); class B metallo-β-lactamases (MBL) genes (Verona integron-encoded MBL [*bla*<sub>IMP</sub>], imipenemase MBL [*bla*<sub>NDM</sub>], New-Delhi MBL [*bla*<sub>NDM</sub>]); class C genes (*ampC*); class D oxacillinase genes (*bla*<sub>OXA</sub>), as well as the *oprD* gene and mex efflux pump genes (*mexAB-oprM*, *mexCD-oprJ*, *mexEF-oprN*, and *mexXY*). Overexpression of the efflux pumps MexAB, MexCD, MexEF, and MexXY was considered when transcription/protein of either components of the MexAB, MexCD, MexEF, or MexYZ are reported to be upregulated, respectively.

For the purpose of this minireview, for each country when data are available, *P. aeruginosa* isolates have been stratified based on their source: general clinical (GC) samples (mix of samples from various clinical units), intensive care unit (ICU) samples (reported studies primarily consisting of samples from intensive and critical care units), and urinary tract infection (UTI) samples. For each of the stratifications used in the minireview, the available most recent scientific papers from each country published within the past 10 years were included. Data from a total of 60 research papers are included in this minireview. The prevalence of MDR *P. aeruginosa* reflects reported rates of MDR *P. aeruginosa* out of the total *P. aeruginosa* infections. When reported, the standard definition of MDR *P. aeruginosa* has been generally adopted as resistance to at least one agent from three different classes as endorsed by agreed international consensus (39). Furthermore, this minireview describes regional variations in antibiotic susceptibility and resistance as well as genomic resistance profiles. When multiple publications are available, the most recent and up-to-date article has been selected and when
multiple publications from the same year are present, data with the most recent sample collection or bigger sample size have been analyzed.

MENA REGIONAL EPIDEMIOLOGY

Regarding the epidemiology of MDR *P. aeruginosa*, comparative regional data comprising sources of isolates, microbiological susceptibility profiles, as well as reported mechanisms of genetic resistance, including carbapenems resistance are outlined in Table 1.

COMPARATIVE REVIEW

**Prevalence of MDR *P. aeruginosa***. In the MENA region, there are wide regional and interregional variations in the reported prevalence of MDR *P. aeruginosa* from general clinical samples with the highest prevalence in Egypt (75.6%) and lowest prevalence in Morocco (0%), with modest prevalence in Saudi Arabia (7.3%) and Qatar (8.1%) (Fig. 2a). The Levant countries (Iraq, Lebanon, Palestine, Israel, and Jordan) were similarly variable with high-level resistance in Lebanon (64.5%), Jordan (52.5%), Palestine (47.6%), and Israel (30%) compared to Iraq (12.4%). This might reflect comparable regional culture of liberal antibiotic prescribing or nonuniform ASPs. It is worth mentioning that it is vital to interpret reported data cautiously to avoid selection biases since it might reflect different study methods or source locations. For example, the high rates of multidrug resistance (86%) reported from Bahrain stems from preexisting observed selection of high-level ciprofloxacin resistance (100%) from collected samples of ciprofloxacin-resistant *P. aeruginosa* (Table 1) (40). Of interest is the fact that reported ciprofloxacin high-level resistance is associated with concordant high-level resistance to broad-spectrum antipseudomonal agents such as piperacillin-tazobactam (90%) and carbapenems (88 to 90%), supporting observations that it is associated with other resistance mechanisms in MDR *P. aeruginosa* such as overproduction of efflux pumps (41). It is also interesting to note that in the Kingdom of Bahrain, carbapenem-resistant MDR *P. aeruginosa* isolates have been demonstrated to be mainly derived by *bla*<sub>VIM</sub> as in neighboring countries but uniquely differ in harboring *bla*<sub>NDM</sub> which is rare or absent in the region except for Saudi Arabia, Iraq, and Egypt (41–45). Comparative neighboring countries with similar population demographics such as Saudi Arabia and Qatar have similar prevalence of MDR *P. aeruginosa* (7.3% and 8.1%, respectively), which might reflect similar structured health care systems as well as antibiotic-prescribing culture compared to other GCC countries. It is needless to say that infection control and prevention together with effective antimicrobial stewardship programs (ASPs) are crucial concepts against the fight to control the spread of AMR, including *P. aeruginosa* (46).

While analyzing isolated samples of MDR *P. aeruginosa* in the region, it is important to pay attention to variations in the community or hospital settings as well as collected sample locations. The prevalence of MDR *P. aeruginosa* from ICU samples varied widely between the MENA region countries (Fig. 2b) with a discrepant opposite trend to that of general clinical samples. The highest rates were seen in Saudi Arabia (61%) and Syria (54%) compared to Egypt (22.5%), Libya (36.4%), Lebanon (33.3%), and Morocco (28.5%). Again, this probably reflects embedded culture of high antibiotic prescribing at critical care units or raises valid questions of efficiency of infection control and prevention measures as observed in multicenter studies from the region as well as potential possibilities of circulating or endemic high resistant clones (42, 47, 48). To emphasize the importance of sample diversity, out of the four countries for which urinary tract infection data are available, there was high-level resistance in Iraq (100%), Egypt (100%), and Saudi Arabia (88.9%), demonstrating difficulties in managing UTIs secondary to MDR *P. aeruginosa* (Fig. 2c) (49). In contrast, Lebanon had a much lower rate of MDR *P. aeruginosa* at 30% (Fig. 2c).

While highlighting the epidemiology of MDR *P. aeruginosa* in the region, it is worth signifying the role of ASPs in directing appropriate and judicious prescribing of antibiotics particularly in secondary care. The concept is relatively new in many MENA
TABLE 1 Epidemiology of MDR P. aeruginosa in the MENA region[1]

| Country          | Sample(s)       | Prevalence of MDR PA (%) | Antimicrobial resistance (%) | Resistance genes (%) | Reference(s) |
|------------------|-----------------|--------------------------|-----------------------------|----------------------|--------------|
|                  |                 |                          | PTZ | CTZ | FEP | A2T | GEN | AMK | CIP | LEV | MER | IMP | COL |                  |
| Iraq             | General(mixed)  | 12.4                     | 42.3 | 41.2 | -   | 40.2 | 28.9 | 18.6 | 22.7 | 19.6 | -   | 12.4 | 0   | MBL: blao_1 (33.3%), blao_2 (25%), blao_3 (8.3%) |
|                  | Urine           | 100% patients without kidney disease; 88.8% in outpatients with UTI infections | -   | 50  | -   | 38.7 | 27.7 | 38.7 | 38.7 | 0   | -   | 0   | -   | 65 |
| Syria            | ICU and urine   | 54                       | 45.5 | 71.4 | 83  | 73  | 57.2 | 70.8 | 65.3 | 40.9 | 43.9 | 10.9 | -   | 63 |
| Lebanon          | General(mixed)  | 64.5                     | 22  | 20  | 19  | 21  | 19  | 15  | 27  | -   | 30  | -   | -   | 67–70 |
|                  | ICU             | 33.3                     | 28.6 | 28.6 | 28.6 | 42.9 | 28.6 | 28.6 | 28.6 | -   | 42.9 | -   | -   | 71, 72 |
|                  | Urine           | 30                       | -   | 5   | -   | 50  | 15.4 | 0   | 96  | 12.5 | -   | 0   | -   | -   |
| Palestine        | General(mixed)  | 47.6                     | -   | -   | 100 | 0   | 0   | 0   | 0   | -   | 0   | -   | -   | 74 |
| Israel           | General(mixed)  | 30                       | 19.6 | 15.7 | -   | 17.6 | 11.8 | 7.8  | 17.6 | 0   | -   | -   | -   | 75, 76 |
| Jordan           | General(mixed)  | 52.5                     | 37.8 | 18  | 18  | 42.7 | 62.3 | 50.9 | 50.9 | 21.3 | 19.7 | 0   | -   | 77  |
|                  | Urine           | 30                       | 5   | 5   | 5   | 50  | 15.4 | 0   | 96  | 12.5 | -   | 0   | -   | -   |
| Saudi Arabia     | General(mixed)  | 7.3                      | 17.2 | 15.5 | 18.9 | -   | 16.6 | 5.53 | 18.1 | 26.3 | 30.7 | -   | -   | 79  |
| Kuwait           | ICU             | 61                       | 46.3 | 41.8 | 53.3 | 53.1 | 31.7 | 18.8 | 37.5 | 52.5 | 38.2 | 30 | -   | 85  |
|                  | Urine           | 88.9                     | 100 | 100 | 75  | -   | 25  | 25  | 50  | -   | 50  | -   | -   | -   |
| Bahrain          | General(mixed)  | 86% in ciprofloxacin- resistant P. aeruginosa | 90  | 86  | -   | -   | 86  | 72  | 100 | -   | 90  | 88 | 0   | 40, 86 |
| Qatar            | General(mixed)  | 8.1                      | 90.7 | 96.6 | -   | 73.2 | 58  | 91.2 | 90.2 | 3.4 | -   | -   | -   | 51, 55 |
|                  | ICU             | 7.7                      | 15.4 | 12.8 | -   | 7.7  | 7.7  | 7.7  | 7.7  | 0   | -   | -   | -   | 87  |
| UAE              | General(mixed)  | -                        | 7   | 10  | -   | -   | 16  | 20  | 15  | 42  | 0   | -   | -   | 58  |
| Oman             | General(mixed)  | -                        | 47.1 | 58.3 | -   | 31.3 | -   | 35.7 | 0   | -   | -   | -   | 88  |
| Yemen            | General(mixed)  | -                        | 37  | 66  | 70  | 37  | 91  | 79  | 91  | -   | 79  | 87 | 0   | 89  |
| Egypt            | General(mixed)  | 75.6 (MDR); 5.5 (pan drug resistant (resistant to all antimicrobial classes) | -   | 68  | 68  | 69  | 65  | 50  | 70  | -   | 62  | 62 | -   | 90–92 |
|                  | ICU             | 22.5                     | 44  | 56  | -   | 89  | 44  | 67  | 44  | 78  | 78  | 22 | -   | 45, 93, 94 |
|                  | Urine           | 100                      | 36  | 100 | 74  | -   | 6   | 2   | 8   | 6   | -   | 10 | -   | 95 |
| Libya            | General(mixed)  | -                        | 37  | 66  | 70  | 37  | 91  | 79  | 91  | -   | 79  | 87 | 0   | 96  |
|                  | ICU             | 36.4                     | 46  | 55  | 46  | 64  | 64  | 36  | 55  | 55  | 46  | 36  | 0   | 97  |
|                  | Urine           | 36.4                     | 0   | 11.1| 0   | 33.3| 0   | 0   | 11.1| 11.1| 22.2| 11.1| -   | 98  |

(Continued on next page)
TABLE 1 (Continued)

| Country     | Sample(s) | Prevalence of MDR PA\(^{a}\) (%) | Antimicrobial resistance\(^{c}\) (%) | Resistance genes\(^{d}\) | Reference(s) |
|-------------|-----------|----------------------------------|------------------------------------|-------------------------|--------------|
| Sudan       | General (mixed) | -                                | PTZ, CTZ, FEP, AZT, GEN, AMK, CIP, LEV, MER, IMP, COL | bla\(_{VIM}\) (38.8%), bla\(_{IMP}\), bla\(_{KPC}\), bla\(_{OXA}\), and bla\(_{GES}\) (0% each). | 99           |
| Tunisia     | General (mixed) | 54                               | PTZ, CTZ, FEP, AZT, GEN, AMK, CIP, LEV, MER, IMP, COL | bla\(_{VIM}\) (38.8%), bla\(_{IMP}\), bla\(_{KPC}\), bla\(_{OXA}\), and bla\(_{GES}\) (0% each). | 100          |
|             | ICU       | -                                | PTZ, CTZ, FEP, AZT, GEN, AMK, CIP, LEV, MER, IMP, COL | bla\(_{VIM}\) (38.8%), bla\(_{IMP}\), bla\(_{KPC}\), bla\(_{OXA}\), and bla\(_{GES}\) (0% each). | 101          |
| Algeria     | General (mixed) | -                                | PTZ, CTZ, FEP, AZT, GEN, AMK, CIP, LEV, MER, IMP, COL | bla\(_{VIM}\) (38.8%), bla\(_{IMP}\), bla\(_{KPC}\), bla\(_{OXA}\), and bla\(_{GES}\) (0% each). | 57, 102-104  |
|             | ICU       | -                                | PTZ, CTZ, FEP, AZT, GEN, AMK, CIP, LEV, MER, IMP, COL | bla\(_{VIM}\) (38.8%), bla\(_{IMP}\), bla\(_{KPC}\), bla\(_{OXA}\), and bla\(_{GES}\) (0% each). | 105, 106     |
| Morocco     | General (mixed) | 0                               | PTZ, CTZ, FEP, AZT, GEN, AMK, CIP, LEV, MER, IMP, COL | bla\(_{VIM}\) (6.06%), bla\(_{IMP}\), bla\(_{KPC}\), bla\(_{OXA}\), and bla\(_{GES}\) (0% each). | 107          |

\(^{a}\) Of note, percentages of resistance reported by different studies as such are not directly comparable, as the studies vary in selection criteria and period of time and often employ distinct antimicrobial susceptibility methodologies and interpretative criteria.

\(^{b}\) MDR PA rates represent the most recent reported MDR rates in *P. aeruginosa* in the respective country.

\(^{c}\) The antimicrobial resistance rates are the percentages of *P. aeruginosa* resistant to the respective antibiotic: PTZ, piperacillin-tazobactam; CTZ, ceftazidime; FEP, cefepime; AZT, aztreonam; GEN, gentamicin; AMK, amikacin; CIP, ciprofloxacin; LEV, levofloxacin; MER, meropenem; IMP, imipenem; COL, colistin. Values that were reported as resistance rate to antibiotic groups (carbapenem/aminoglycoside/fluoroquinolone) rather than to individual antibiotics are indicated with an asterisk (*). -, not reported/available.

\(^{d}\) In the Resistance genes column, the genes and the percentages of the carbapenem-resistant (CR) *P. aeruginosa* strains with the reported gene from these countries are shown. MBL, metallo-\(\beta\)-lactamase. Values that were results from different studies are indicated with a pound sign (#). -, not reported/available.

\(^{e}\) The disk diffusion method was used in this study to determine colistin resistance. This methodology is not recommended by the Clinical and Laboratory Standards Institute or the European Committee on Antimicrobial Susceptibility Testing.
countries with plans to roll it out both at primary and secondary care levels. A study from Qatar demonstrated that the introduction of an effective ASP in 2015 managed to steadily reduce the prevalence of MDR *P. aeruginosa* from 9% to 5.46% over a 3-year period (16).

**Antibiotic resistance patterns.** When comparing general clinical samples, the overall antipseudomonal drug resistance of the ciprofloxacin-resistant *Pseudomonas* strains from Bahrain is high, ranging between 72 and 100% for third-generation cephalosporins, carbapenems, aminoglycosides, fluoroquinolones, and piperacillin-tazobactam combinations (Fig. 3). Resistance to piperacillin-tazobactam is moderate in Iraq (42.3%), Jordan (37.8%), Libya (37%), and Lebanon (22%), while it was low in Israel.
As for antimicrobial susceptibility for third- and fourth-generation antipseudomonal cephalosporins, they are characteristically high, demonstrating low-level resistance, but exceptionally high resistance is seen in Qatar (96.6%), Bahrain (86%), Tunisia (70%), Egypt (68%), Libya (66%), Yemen (47.1%), and Iraq (41.2%) (Fig. 3a). In most countries, prevalent resistance rates for both ceftazidime and cefepime are similar. In Jordan, *P. aeruginosa* isolates showed low-level resistance to ceftazidime and cefepime (18% each) but mid-range resistance to aminoglycosides and fluoroquinolones (50.9% to 62.3% and 50.9%).
respectively) (Fig. 3b, d, and e). Similar to the high prevalence of cephalosporin resistance, high carbapenem resistance has been observed in Qatar (90.2%), Bahrain (88 to 90%), Egypt (62%), Sudan (61.1%), Libya (79 to 87%), and Tunisia (74%) (Fig. 3c, d, and e) along with high-level resistance to aminoglycosides and fluoroquinolones, except for Sudan for which these data were not available. Even though *P. aeruginosa* reported from Saudi Arabia and Oman has low-level resistance to cephalosporin, these isolates had higher carbapenem resistance rates of 26.3 to 30.7% and 42%, respectively (Fig. 3c). Resistance to aztreonam was high in all countries where data were available, with Palestine showing absolute resistance in all tested isolates. Algeria was an exception to this with none of the isolates showing resistance to monobactams (Fig. 3f), which raises potential possibilities of interregional variations of underlying resistance mechanisms such as class A ESBL which limits aztreonam activity as opposed to class B β-lactamases which aztreonam is capable to overcome (50).

Worryingly, the rising trends of rates of resistance to carbapenems in most countries in the region are alarming, since it has been the forefront class to combat AMR particularly in *Enterobacteriaceae* as well as *P. aeruginosa*, thus limiting available treatment options. In contrast, among general clinical samples, colistin remains highly active, approaching 100% in most regions, including GCC, although developing resistance is being seen in some countries like Qatar (3.4%) (51). Novel antibiotics such as ceftazidime-avibactam and ceftolozane-tazobactam demonstrated good antimicrobial susceptibilities in Gulf countries, but it is less compared to other regions probably because of high regional resistance such as in Qatar where 31.2% and 37.1% of the MDR strains showed resistance to ceftazidime-avibactam and ceftolozane-tazobactam, respectively, even before their introduction into clinical practice (52, 53). Such observation of lower susceptibility profiles for potent novel antibiotics not previously used in the region is worrisome, since it reflects significant embedded resistance (52). Despite its wide mechanism of action against multidrug-resistant organisms such as MDR *P. aeruginosa*, both ceftazidime-avibactam and ceftolozane-tazobactam remain vulnerable when encountering class B MBL-producing β-lactamases (54). That might explain some of the observed lower antimicrobial susceptibilities for the drugs in the region (52).

In general, antimicrobial susceptibility data for the ICU isolates were available for fewer countries (see Fig. S1 in the supplemental material). Out of the countries that reported antimicrobial susceptibility data from ICUs, Qatar is the only country that showed low-level resistance to all tested antibiotics with rates not exceeding 15.4% for any antibiotic and absolute sensitivity to colistin (Fig. 3g and Fig. S1). Saudi Arabia, Egypt, Syria, Libya, and Lebanon consistently showed high resistance levels for piperacillin-tazobactam, cephalosporins, carbapenems, monobactams, aminoglycosides, and fluoroquinolones except Egypt where data were not available for monobactams (Fig. 3g and Fig. S1). Additionally, from available reports for Saudi Arabia, Egypt, and Syria, the prevalent isolates from ICU in these regions are also showing increasing resistance to colistin (10.9 to 30%) (Fig. S1). Despite showing very high rates of resistance to all other tested antibiotics, isolates in Libya showed absolute susceptibility to colistin (Fig. S1e). Tunisia demonstrated a little different trend with high resistance to ceftazidime and carbapenems but no resistance to piperacillin-tazobactam, ciprofloxacin, and aminoglycosides (0%) (Fig. S1 and Fig. 3g). All countries with available data showed high resistance to aztreonam (Fig. S1).

Data were available for few select countries in the MENA region for UTI infections, and the available resistance patterns were very variable among UTI samples from different countries. Uropathogenic *P. aeruginosa* isolates from Saudi Arabia consistently showed high rates of resistance to all tested antibiotics: piperacillin-tazobactam, cephalosporins, carbapenems, fluoroquinolones, and aminoglycosides (Fig. S2). Out of three countries (Saudi Arabia, Egypt, and Libya) that reported data on piperacillin-tazobactam resistance, Saudi Arabia had the highest resistance rates (100%), followed by Egypt (36%), and Libya reported no resistance (Fig. S2a). For cephalosporins, Saudi Arabia (100%, 75%), Egypt (100%, 74%), and Iraq (50% and not available) showed highest rates
of resistance to ceftazidime and cefepime, respectively (Fig. S2b). Interestingly, from countries that reported carbapenem resistance data for UTI samples, only Saudi Arabia and Libya reported high rates of resistance to meropenem (50% and 22.2%, respectively) (Fig. S2c) compared to Egypt (10%), Libya (11.1%), Iraq and Jordan (0% each), all reporting low or no resistance to imipenem (Fig. S2c). Resistance to aminoglycosides (0 to 6%) and fluoroquinolones (8 to 11.1%) was also low in both Egypt and Libya (Fig. S2d and e). Saudi Arabia, Iraq, and Israel showed high resistance to aminoglycosides (25%, 27.7 to 38.7% and 33.3%, respectively) as well as fluoroquinolones (50%, 38.7%, and 44.4%, respectively) (Fig. S2d and e).

Genetic profiles. Although genomic studies are vital in understanding the epidemiology of AMR, including MDR P. aeruginosa, genetic data on MDR P. aeruginosa is not widely available in the MENA region with few studies exploring the concept. The more developed countries have more available data compared to the rest particularly among highly carbapenem-resistant P. aeruginosa (Fig. 3h and Fig. S3). For example, there was little data regarding ESBL production but there was an overall predominance of blaGES and blaVEB β-lactamase genes in MDR P. aeruginosa in the region (55, 56). In the general clinical samples, the main reported ESBL genes were blaGES-1,4,8 (8.8%) and blaVEB (47.1%) in Saudi Arabia, blaGES-5,9 (5.41%) in UAE, blaVEB (25.3%) in Qatar, as well as blaSHV (100%) in Algeria (Table 1) (55–58). Noteworthy, there are variations reported in blaGES when examined through molecular/genomic testing methods (59–61). While blaGES-1,7,19 are ESBLs, some others like blaGES-5,16,20, have carbapenemase activity and as the gene is not always sequenced in many studies, this limits the discrimination of the variant.

In general, for clinical samples from all countries where data were available, blaVIM is the most prevalent MBL, followed by blaIMP/blaNDM. For instance, in Iraq, blaIMP is the second most prevalent, whereas in Saudi Arabia, blaNDM is the second most prevalent (Fig. 3h). For P. aeruginosa isolates from ICU samples in the MENA region, extremely limited data on MBL genes were available. Among the four countries that reported MBL data and like general clinical samples from the region, blaVIM was mostly the most prevalent MBL gene (Fig. S3c) among the MDR P. aeruginosa ICU isolates. In contrast to other regions, blaNDM is rare in MDR P. aeruginosa ICU isolates in the MENA region, as it was identified in ICU isolates from only two countries: Saudi Arabia (30.8%) and Egypt (27.3%) (Fig. S3c) (44, 45, 47).

Mutations of the oprD gene were also prevalent in several countries, with the highest rates reported in Lebanon and Libya, where all carbapenem-resistant P. aeruginosa strains contained oprD mutations (Fig. S3a). None of the carbapenem-resistant strains in Egypt contained a mutation in the oprD gene (Fig. S3a). Among countries that reported MexAB efflux pump dysregulation, UAE showed the highest (75.6%) rate (Fig. S3b). MexXY efflux pump was highly prevalent in Lebanon (68.6%) and Egypt (62%) (Fig. S3b).

CONCLUSION

The MENA region is geographically close but with diverse economic, social, and cultural differences which are reflected in health care and resources, including liberal or limited antibiotic prescribing and consumption. There is an observed diversity in the epidemiology of MDR P. aeruginosa across the region in terms of antimicrobial resistance and genetic profiles. The overall paucity of published literature on AMR in the MENA region is concerning, in conjunction with unmatched studies in terms of sampling or methodology. Nevertheless, the observed variations could also be because of differences in the structure of health systems with variable settings between high- and low-income countries, variations in population demographics or differences in antibiotic prescribing across health care sectors, or inadequate implementation of infection control and prevention measures. Understanding these differences is crucial to allow for accurate identification, followed by appropriate interventions.

This minireview also highlights the alarming situation of AMR in the MENA region with significant resistance profile for MDR P. aeruginosa limiting treatment options
with all its deleterious consequences. It is imperative to obtain comprehensive collected data toward the control of AMR, which should be encouraged to limit its propagation in the MENA region. Although many countries in the region have implemented ASPs to support existing infection control practitioners, there is a clear need for regional cooperation to share challenges and experience. Last, such surveillance should be brought to the attention of policy and health care decision makers since it will have direct impact on health outcomes as well as on health care expenditure. It should also encourage creation of regional surveillance programs to monitor AMR as advocated by the WHO and leading infection bodies (62).

Despite this minireview covering an important aspect of AMR in a previously unexplored region, there are several study limitations. As highlighted, there is an absence of uniform comprehensive data and AMR reporting mechanisms from the MENA region. Also, there are no data from many countries in the region, which reflects a fundamental problem in published research from the region. Therefore, selecting individual non-national studies might certainly generate inaccurate reporting bias for prevalence rates, microbiological characteristics, or mechanisms of genetic resistance. Of note, when comparing antimicrobial susceptibility data from different studies regionally or globally, it is also important to keep in mind the differences between studies and the percentages of resistance reported by different studies because these studies are not directly comparable as they vary in selection criteria and period of time and often employ different antimicrobial susceptibility methodologies and interpretative criteria. For example, a previous study reporting colistin resistance (63) utilized disk diffusion methods which are less reliable compared to the current recommended practice of broth microdilution (64). Nevertheless, this minireview fills an important void in the literature and highlights that there are close similarities between neighboring countries, which supports that projected observations are interregionally reliable.

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.
FIG S1, DOCX file, 0.1 MB.
FIG S2, DOCX file, 1 MB.
FIG S3, DOCX file, 0.04 MB.

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