The Prevalence of Metallo-β-Lactamase-Producing *Pseudomonas aeruginosa* in Egypt: A Systematic Review and Meta-Analysis

Ahmed Azzam¹*, Heba Khaled², Marwan Hesham¹

¹Department of Microbiology and Immunology, Faculty of Pharmacy, Helwan University, Ain Helwan 11795, Cairo, Egypt.
²Department of Biochemistry, Faculty of Pharmacy, Cairo University, Cairo, 11562, Egypt.

*Corresponding author: Ahmed Azzam, Department of Microbiology and Immunology, Faculty of Pharmacy, Helwan University, Ain-Helwan, Cairo 11795, Egypt. Tel. (+2)0237222210 Email address: ahmed.abdelkareem@pharm.helwan.edu.eg

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ABSTRACT

**Background:** Metallo-beta-lactamase (MBL)-producing *Pseudomonas aeruginosa* represents a serious hazard to humanity because of its high mortality rate, ability to hydrolyze all beta-lactam antibiotics, including carbapenem, and absence of a clinically approved inhibitor. There are several studies conducted in Egypt that report a heterogeneous incidence of MBL among *Pseudomonas aeruginosa* clinical isolates.

**Methods:** We performed a systematic search in MEDLINE [PubMed], Scopus, Google scholar, and Web of Science. Out of 1882 records, 20 studies agreed with the inclusion and exclusion criteria and are included in our review.

**Results:** Our investigation revealed a high incidence of MBL-producing *Pseudomonas aeruginosa* of about 33.7% (95% CI: 19.3-48) and MBL-mediated Imipenem resistance among *P. aeruginosa* of about 74.1% (95% CI: 63.5-84.6). Furthermore, based on the included studies and other molecular studies conducted in Egypt, among MBL-encoding genes, *blaVIM* appeared to be the most prevalent MBL gene in clinically isolated *Pseudomonas aeruginosa* in Egypt.

**Conclusion:** This high disseminating rate raises the alarm to support both antimicrobial stewardship activities and infection control programs to prevent further increases.

**Keywords:** *Pseudomonas aeruginosa*; Imipenem-resistant *P. aeruginosa* MBL; *blaVIM*, Egypt; Systematic review.

INTRODUCTION

*Pseudomonas aeruginosa* (*P. aeruginosa*) is an opportunistic Gram-negative rod that is responsible for 11% of all nosocomial infections and it is recognized as one of the leading causes of nosocomial infections, especially in immunocompromised patients. It is listed as Priority 1 (Critical) in the 2017 WHO list of bacteria for which new antibiotics are urgently needed. The CDC has also classified MDR *P. aeruginosa* as a serious threat and therefore listed it in the 2019 Antibiotic Resistance Threat Report.

*P. aeruginosa* can resist the insult effect of antibiotics not only due to its antibiotic-inactivating enzymes (acquired resistance) but also due to its high capability of intrinsic resistance and biofilm formation (adaptive resistance). Beta-lactamases are enzymes produced by bacteria that confer resistance through hydrolysis of the beta lactam ring, and it is considered the most important mechanism of resistance to beta-lactam antibiotics.

The most frequently used method for classification of beta lactamases is Ambler classification (a structural classification based on primary amino acids...
sequence homology) that categorized beta lactamases into four classes: class A, B, C and D. Classes: A, C, and D are serine-β-lactamases (SBLs), while class B is metallo-β-lactamases (MBLs) that requires zinc at their active sites. 7-9

MBL-producing Pseudomonas aeruginosa represents a real concern due to their robust resistance to all β-lactam antibiotics and no clinically approved inhibitor has been developed. Among the metallo-beta-lactamase enzymes are VIM, IMP, NDM, SPM, and GIM. BlavIM-2 is the most widely distributed MBL-encoding gene in P. aeruginosa and was detected in over 30 countries. 11-12

There’s a great variability in studies reporting the prevalence of MBL-producing P. aeruginosa in Egypt. Therefore, we conducted a systematic review and meta-analysis that combined all of the different incidences of MBL-producing P. aeruginosa from different regions of Egypt into a single numerical estimate and also determined the percentage of MBL-mediated Imipenem resistance among P. aeruginosa to guide infection control programs in taking preventive measures and thus reduce its growing spread. In addition, we reviewed molecular studies that were not included in the systematic review to identify the most prevalent MBL-encoding gene in Egypt.

METHODS

Search strategy

Four databases, including MEDLINE [PubMed], Scopus, Google Scholar, and Web of Science, were searched for by the following key words: Pseudomonas aeruginosa or P. aeruginosa or MBL-producing P. aeruginosa or metallo-beta-lactamases producing P. aeruginosa or multi-drug resistance P. aeruginosa and MBL or metallo-beta-lactamases, MBL-encoding gene, and Egypt. The search was restricted to studies published in English only and the filtration of studies was in accordance with the Preferred Reporting Items for Systematic Reviews and Meta Analyses guidelines (PRISMA). 15

Inclusion criteria were as follows:

1- P. aeruginosa clinical samples that were isolated from Egyptian patients.

2- Phenotypic detection of MBL includes Imipenem/EDTA combined disc test (CDT), 16 or Imipenem-EDTA double disc synergy test (DDST), 17 or MBL E-test 18 with or without PCR for detection of MBL-encoding genes.

Exclusion criteria

1- Selection of antibiotic-resistant strains of P. aeruginosa (for example, MDR or XDR) for screening of MBL.

2- Unclear materials and methods.

3- Studies that do not report results of MBL screening.

4- Studies that included a small P. aeruginosa sample size.

5- Repetitive samples.

Data extraction

From each included study, the following data were extracted by two independent reviewers (HK and MH), publication time, government, methods of screening of MBL, total P. aeruginosa isolates, MBL producers, and number of P. aeruginosa isolates harboring MBL-encoding genes. The authors' disagreements were settled through discussion. If more than one technique is used the result of MBL E-test is taken because it is the most sensitive.22-23-24

Statistical analysis

Heterogeneity between studies was assessed by I-squared, and the prevalence of MBL-producing P. aeruginosa was pooled in a forest plot using OpenMeta [Analyst] by the DerSimonian and Laird random-effects model. Using JASP (version 0.16.1.), the risk of bias within studies was evaluated by visual inspection of the funnel plot and also tested with a non-parametric rank test, Begg's test, and the parametric regression test (also known as "Egger’s test")20. In both cases, low p-values (P <0.05) are indicative of asymmetry and were taken as evidence of publication bias.

RESULTS

Study selection

The study selection process is depicted in Figure 1 flow chart. Upon initial searching, a total of 1882 studies were identified. All the identified records were first filtered based on title and abstract. Non-relevant, duplicate, and review articles (1822) were excluded. After removal of non-clinical samples, studies were then identified by screening the full text according to the aforementioned criteria of inclusion and exclusion. The extracted data from the selected studies was summarized in Table 1.

The prevalence of MBL among Pseudomonas aeruginosa

Heterogeneities between the 20 selected studies were as follows:

(I2 = 98.83 %, P < 0.001) as shown in Table 2, which indicates high heterogeneity. So, the DerSimonian and Laird random effects model was used. Publication bias was first assessed visually by the funnel plot (Figure 2) and slight asymmetry was found, but there was no evidence of publication bias by Egger’s regression test (P value = 0.477) and Begg’s rank test (P value = 0.351). The pooled prevalence of MBL among

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1802 *Pseudomonas aeruginosa* isolates was 33.7% (95% CI: 19.3-48) as depicted in Figure 3.

**Prevalence of MBL among Imipenem resistant *Pseudomonas aeruginosa***

Out of the 20 selected studies, 13 studies only report MBL prevalence among Imipenem resistant *P. aeruginosa*. Diab et al.\(^25\) reported a higher number of MBL producers relative to Imipenem resistant isolates. This is due to screening of MBL was not restricted to Imipenem resistant isolates. So, out of 36 Imipenem resistant isolates, there are 32 and 31 MBL producers by the MBL E-test and CDT respectively.

Out of 1200 *P. aeruginosa* isolates, 347 were Imipenem resistant and of those, 254 were MBL producers. The pooled prevalence, heterogeneity, and publication bias tests are summarized in Table 2. (The funnel plot and forest plot are depicted in Figures 2 and 3 respectively).

**DISCUSSION**

*P. aeruginosa* is one of the leading causes of many nosocomial infections. Unfortunately, these bacteria have a high ability of resistance to many antibiotics due to their intrinsic and extrinsic resistance. Several studies have found that MBL producing *P. aeruginosa* has a high mortality rate.\(^57\)-\(^61\). Carbapenems are the drugs of choice for treating severe infections caused by AmpC or ESBL-producing *P. aeruginosa*.\(^62\) But, they have poor stability to metallo-beta lactamase enzymes.\(^63\) This highlights the significance of epidemiological studies that reveal the prevalence of MBL producers among *P. aeruginosa*.

To our knowledge, this is the first systematic review and meta-analysis conducted in Egypt that summarized the heterogeneous incidence rate of MBL among pseudomonas in one numerical estimate. Our study revealed that the overall pooled prevalence is 33.7% (95% CI: 19.3-48) which is relatively similar to
found that MBL prevalence among P. aeruginosa, respectively, reports from Spain and Italy revealed a 0.1% MBL prevalence among P. aeruginosa. In Egypt, the MBL prevalence is substantially higher than in Europe. For instance, reports from Spain and Italy revealed a 0.1% MBL prevalence among P. aeruginosa (11.8%). The overall MBL prevalence in P. aeruginosa in Egypt is substantially higher than in Europe. For instance, reports from Spain and Italy revealed a 0.1% and 1.3% MBL prevalence among P. aeruginosa, respectively. In Mexico, the MBL prevalence in P. aeruginosa was estimated at 0.7%, which is very low compared to our study.

Table 1. Characteristics of studies included in the meta-analysis

<table>
<thead>
<tr>
<th>Authors</th>
<th>Published time</th>
<th>Government or city</th>
<th>Total sample size</th>
<th>Imipenem resistant isolates</th>
<th>MBL producers</th>
<th>Method of detection of MBL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abaza et al.</td>
<td>2017</td>
<td>Alexandria</td>
<td>30</td>
<td>NA</td>
<td>30</td>
<td>MBL E-test-PCR</td>
</tr>
<tr>
<td>Salah Eldin et al.</td>
<td>2012</td>
<td>Cairo</td>
<td>180</td>
<td>36</td>
<td>35</td>
<td>MBL E-test-Imipenem/EDTA CDT-DDST</td>
</tr>
<tr>
<td>Amer et al.</td>
<td>2016</td>
<td>Tanta</td>
<td>46</td>
<td>NA</td>
<td>30</td>
<td>Imipenem/EDTA CDT</td>
</tr>
<tr>
<td>Ali and Abdel-Razik</td>
<td>2009</td>
<td>Cairo</td>
<td>56</td>
<td>16</td>
<td>15</td>
<td>MBL E-test-PCR-Imipenem/EDTA CDT-DDST</td>
</tr>
<tr>
<td>El-Mahdy et al.</td>
<td>2019</td>
<td>Mansoura</td>
<td>80</td>
<td>34</td>
<td>18</td>
<td>Imipenem/EDTA CDT-PCR</td>
</tr>
<tr>
<td>Mousa et al.</td>
<td>2021</td>
<td>Assuit</td>
<td>74</td>
<td>NA</td>
<td>26</td>
<td>Imipenem/EDTA CDT-DDST</td>
</tr>
<tr>
<td>Hashem et al.</td>
<td>2017</td>
<td>Ismailia</td>
<td>147</td>
<td>NA</td>
<td>25</td>
<td>Imipenem/EDTA CDT-DDST-PCR</td>
</tr>
<tr>
<td>Zafer et al.</td>
<td>2014</td>
<td>Cairo</td>
<td>122</td>
<td>48</td>
<td>33</td>
<td>Imipenem/EDTA CDT-PCR</td>
</tr>
<tr>
<td>Raouf et al.</td>
<td>2018</td>
<td>Minia</td>
<td>70</td>
<td>20</td>
<td>17</td>
<td>MBL E-test-PCR</td>
</tr>
<tr>
<td>Diab et al.</td>
<td>2013</td>
<td>Giza</td>
<td>50</td>
<td>36</td>
<td>41*</td>
<td>MBL E-test-Imipenem/EDTA CDT-PCR</td>
</tr>
<tr>
<td>Abbas et al.</td>
<td>2018</td>
<td>Zagazig</td>
<td>50</td>
<td>5</td>
<td>2</td>
<td>Imipenem/EDTA CDT-PCR</td>
</tr>
<tr>
<td>El-Mosallamy et al.</td>
<td>2015</td>
<td>Benha</td>
<td>100</td>
<td>25</td>
<td>15</td>
<td>Imipenem/EDTA CDT-PCR</td>
</tr>
<tr>
<td>Makharita et al.</td>
<td>2020</td>
<td>Cairo</td>
<td>36</td>
<td>10</td>
<td>6</td>
<td>Imipenem/EDTA CDT</td>
</tr>
<tr>
<td>Abd El-Baky et al.</td>
<td>2013</td>
<td>Minia</td>
<td>58</td>
<td>NA</td>
<td>31</td>
<td>Imipenem/EDTA CDT</td>
</tr>
<tr>
<td>El-Maraghy et al.</td>
<td>2015</td>
<td>Ismailia</td>
<td>65</td>
<td>25</td>
<td>24</td>
<td>Imipenem/EDTA CDT</td>
</tr>
<tr>
<td>El-Naggar et al.</td>
<td>2011</td>
<td>Mansoura</td>
<td>200</td>
<td>NA</td>
<td>41</td>
<td>Imipenem/EDTA CDT-DDST*</td>
</tr>
<tr>
<td>Bahey et al.</td>
<td>2019</td>
<td>Tanta</td>
<td>40</td>
<td>NA</td>
<td>17</td>
<td>Imipenem/EDTA CDT</td>
</tr>
<tr>
<td>Shabany et al.</td>
<td>2010</td>
<td>Zagazig</td>
<td>45</td>
<td>21</td>
<td>15</td>
<td>Imipenem/EDTA CDT-PCR</td>
</tr>
<tr>
<td>Gerges and Amian</td>
<td>2014</td>
<td>Zagazig</td>
<td>85</td>
<td>40</td>
<td>32</td>
<td>Imipenem/EDTA CDT-PCR</td>
</tr>
<tr>
<td>Amer et al.</td>
<td>2007</td>
<td>Zagazig</td>
<td>261</td>
<td>31</td>
<td>10</td>
<td>MBL E-test-PCR</td>
</tr>
</tbody>
</table>

Abbreviation: NA: Not available, Imipenem/EDTA CDT: imipenem-EDTA combined disk method, DDST: double disk synergy test, PCR: Polymerase chain reaction*. The number of MBL producers is higher than the number of Imipenem resistant isolates as the screening is not restricted to carbapenem resistant isolates.

Table 2. Statistics of the Meta-analysis

<table>
<thead>
<tr>
<th>Study subgroup</th>
<th>Included studies number</th>
<th>Pooled Prevalence</th>
<th>Heterogeneity</th>
<th>Egsger’s test</th>
<th>Begg’s test</th>
</tr>
</thead>
<tbody>
<tr>
<td>MBL among P. aeruginosa</td>
<td>20</td>
<td>33.7%</td>
<td>98.83 %</td>
<td>&lt;0.001</td>
<td>0.477</td>
</tr>
<tr>
<td>MBL among Imipenem resistant P. aeruginosa</td>
<td>13</td>
<td>74.1%</td>
<td>88.59 %</td>
<td>&lt;0.001</td>
<td>0.612</td>
</tr>
</tbody>
</table>

a meta-analysis study of MBL prevalence among P. aeruginosa in Iran that reported that the prevalence of MBL among P. aeruginosa was 32.4% and lower than a study conducted in China that reported 149 MBL producers among 329 P. aeruginosa (45.28%) but higher than a study conducted in India that reported 15 MBL producers among 127 isolates of P. aeruginosa. The overall MBL prevalence in P. aeruginosa in Egypt is substantially higher than in Europe. For instance, reports from Spain and Italy revealed a 0.1% and 1.3% MBL prevalence among P. aeruginosa, respectively. In Mexico, the MBL prevalence in P. aeruginosa was estimated at 0.7%, which is very low compared to our study.

The loss or alteration of the outer membrane porin protein OprD is the most widespread mechanism of resistance to imipenem in P. aeruginosa, but our study revealed that MBL-mediated imipenem resistance to P. aeruginosa is one of the major mechanisms. Out of 347 Imipenem resistant isolates, 254 are MBL producers with a pooled prevalence of 74.1% (95% CI: 63.5–84.6). This slightly similar to studies conducted in Pakistan and Brazil. In Pakistan Ameen et al. found that MBL production was confirmed in 74 of 114 Imipenem-
Figure 2. Funnel plot for publication bias. The effect sizes calculated from each study (Logit event rate) against their respective standard errors are displayed in a funnel plot with a pseudo 95% confidence interval (SEs). (A) The prevalence of MBL among *Pseudomonas aeruginosa*. (B) Prevalence of MBL among Imipenem resistant *Pseudomonas aeruginosa*.

Figure 3: Forest plot of the studies included in this meta-analysis. (A) The prevalence of MBL among *P. aeruginosa*. (B) The Prevalence of MBL among Imipenem resistant *P. aeruginosa*.

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Table 3. Distribution of MBL-genes in the included studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Tested isolates</th>
<th>MBL-encoding genes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>blαGIM</td>
</tr>
<tr>
<td>Abuz et al. (2015)</td>
<td>total (30) Imipenem resistant P. aeruginosa (n=16)</td>
<td>NA</td>
</tr>
<tr>
<td>Ali and Abdel-Razik</td>
<td>Imipenem resistant P. aeruginosa (n=34)</td>
<td>NA</td>
</tr>
<tr>
<td>El-Mahdy et al. (2019)</td>
<td>MBL producer isolates (n=25)</td>
<td>GIM-1=12</td>
</tr>
<tr>
<td>Hashem et al. (2020)</td>
<td>Imipenem resistant isolates (n=20)</td>
<td>0</td>
</tr>
<tr>
<td>Raouf et al. (2020)</td>
<td>Imipenem resistant isolates (n=20)</td>
<td>NA</td>
</tr>
<tr>
<td>Diab et al. (2020)</td>
<td>total isolates (n=50) Not clear Imipenem resistant isolates(n=32)</td>
<td>NA</td>
</tr>
<tr>
<td>Abbas et al. (2020)</td>
<td>Imipenem resistant isolates(n=25)</td>
<td>0</td>
</tr>
<tr>
<td>EL-Mosallamy et al. (2020)</td>
<td>MBL producer isolates (n=40)</td>
<td>NA</td>
</tr>
<tr>
<td>Shaheen et al. (2020)</td>
<td>total isolates (n=45) Imipenem resistant isolates=10</td>
<td>NA</td>
</tr>
<tr>
<td>Amer et al. (2020)</td>
<td>Imipenem resistant isolates=10</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA: not available

Table 4 Characteristics of molecular studies that are not involved in meta-analysis

<table>
<thead>
<tr>
<th>Author (publication year)</th>
<th>Tested isolates</th>
<th>MBL-encoding gene</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>blαGIM</td>
</tr>
<tr>
<td>Zafer et al. (2015)</td>
<td>MBL producer isolates (n=33)</td>
<td>0</td>
</tr>
<tr>
<td>Farhan et al. (2019)</td>
<td>carbenem-resistant isolates (n=21)</td>
<td>11</td>
</tr>
<tr>
<td>Gaballah et al. (2020)</td>
<td>carbenem-resistant isolates (n=32)</td>
<td>0</td>
</tr>
<tr>
<td>Essa and Affifi (2007)</td>
<td>Imipenem resistant isolates (n=40)</td>
<td>NA</td>
</tr>
<tr>
<td>Hassuna et al. (2020)</td>
<td>carbenem-resistant isolates (n=32)</td>
<td>NA</td>
</tr>
<tr>
<td>El-Domany et al. (2017)</td>
<td>total isolates (n=114)</td>
<td>NA</td>
</tr>
<tr>
<td>Ramadan et al. (2018)</td>
<td>carbenem-resistant isolates (n=22)</td>
<td>NA</td>
</tr>
<tr>
<td>Soliman et al. (2020)</td>
<td>carbenem-resistant isolates (n=7)</td>
<td>NA</td>
</tr>
<tr>
<td>Basha et al. (2020)</td>
<td>11 selected XDR P. aeruginosa</td>
<td>NA</td>
</tr>
<tr>
<td>El-Domany et al. (2016)</td>
<td>Imipenem resistant isolates (n=14)</td>
<td>11</td>
</tr>
<tr>
<td>Emara et al. (2020)</td>
<td>total isolates (n=114)</td>
<td>NA</td>
</tr>
<tr>
<td>Kishk et al. (2016)</td>
<td>total isolates (n=26)</td>
<td>NA</td>
</tr>
<tr>
<td>Elhabibi et al. (2016)</td>
<td>total isolates (n=200)</td>
<td>NA</td>
</tr>
<tr>
<td>Abo-Alella et al. (2021)</td>
<td>carbenem-resistant isolates (n=6)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviation: NA: not available

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resistant isolates (64.9%)\textsuperscript{72} and in Brazil, Franco et al. reported that 53 out of 69 (76.8%) Imipenem-resistant *Pseudomonas aeruginosa* isolates produced MBL\textsuperscript{73}.

The high incidence of MBL producer and MBL-mediated Imipenem resistance could be attributed to the misuse of carbapenem and lack of antimicrobial stewardship in Egypt \textsuperscript{74,75}.

In the studies included in our review, bla*\text{VIM}* seemed to be the most prevalent among MBL-encoding genes, and this is consistent with other molecular studies conducted in Egypt as shown in table 3. For instance Zafer et al. demonstrated a 85% of *P. aeruginosa* MBL producers harbored bla*\text{VIM}*\textsuperscript{4}. Furthermore, Farhan et al. and Gaballah et al. revealed that out of 21 and 32 carbapenem resistant *P. aeruginosa* isolates, bla*\text{VIM}* was identified in 11 (52.3%)\textsuperscript{44} and 27 (84.4%)\textsuperscript{45} respectively. Similar findings were recorded in neighboring nations. In Sudan, for example, the, bla*\text{VIM}* was found in 28 (38.9%) of the 72 positive MBL genes\textsuperscript{76}. Moreover, in Saudi Arabia the bla*\text{VIM}* was identified in all MBL producers\textsuperscript{77,78}. In Libya, all *P. aeruginosa* MBL-positive strains produced bla*\text{VIM}*\textsuperscript{29} and in Iran a systematic review and meta-analysis showed that, the bla*\text{VIM}* is the prevalent in Iranian burn centers (21.4%)\textsuperscript{80}.

There are some limitations to our study. For example, our results do not fully reflect the prevalence of MBL-producing *P. aeruginosa* in Egypt, as not all regions in Egypt report the prevalence of MBL producers among *P. aeruginosa* clinical isolates. Also, there are some variations among the aforementioned phenotypic methods for screening of MBL.

Giving the fact that selective pressure of antibiotics is the driving force of evolution and diversity of beta lactamases and MBL could be evolved from carbapenem use\textsuperscript{81,82} antimicrobial stewardship should be implemented strictly, especially for carbapenem overuse as empirical therapy in Egypt and infection control programs must be strengthened considering this high disseminating rate.

**CONCLUSION**

In conclusion, our results revealed a high incidence of MBL producers among *P. aeruginosa* clinical isolates and that MBL is a major mechanism of resistance in imipenem-resistant *P. aeruginosa*. Further investigations are needed to identify other possible mechanisms of imipenem resistance in *P. aeruginosa*.

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**Conflict of interest**

The authors declare that there is no conflict of interest regarding the publication of this paper.

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