



Review Article

## The Prevalence of *bla*<sub>N<sub>DM</sub>-1</sub> in Clinical Isolates of Carbapenem-resistant *Pseudomonas Aeruginosa*: A Systematic Review

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### Abstract

**Background:** *Pseudomonas aeruginosa* (*P. aeruginosa*) is a gram negative bacteria that is known to cause nosocomial infections. Carbapenem is used to treat the damage caused by *P. aeruginosa*, however it is becoming resistant to carbapenems because of the production of  $\beta$ -lactamases. The objectives of the study were to systematically review the prevalence of *bla*<sub>N<sub>DM</sub>-1</sub> in carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) and to review and analyze the clinical sources as well as the antibiotic resistance profile of CRPA carrying *bla*<sub>N<sub>DM</sub>-1</sub>. **Methods:** The researchers systematically searched PubMed, ScienceDirect, and Google Scholar. Studies that met the inclusion criteria were included in the review. In assessing the methodological quality of the included studies, the JBI Critical Appraisal Checklist for Studies Reporting Prevalence Data and the JBI Critical Appraisal Checklist for Case Reports were used. **Results:** A total of nine studies were included in which eight were cross-sectional studies and one was a case report. The highest prevalence rate reported was 54.55% in *bla*<sub>N<sub>DM</sub>-1</sub> positive CRPA isolates among the cross-sectional studies. The three most frequent sources of clinical isolates of CRPA carrying *bla*<sub>N<sub>DM</sub>-1</sub> include urine, wound discharge, and tissue, among the included studies. Lastly, this review showed that among the included studies, CRPA isolates carrying *bla*<sub>N<sub>DM</sub>-1</sub> were most resistant to ceftazidime and gentamicin. **Conclusions:** There is varying prevalence of *bla*<sub>N<sub>DM</sub>-1</sub> in CRPA in different countries. Urine, wound discharge, and tissue specimens being the most frequent sources of CRPA isolates carrying *bla*<sub>N<sub>DM</sub>-1</sub> poses a challenge that must be given attention by the infection control committee, thus the need for proper handling and processing of clinical specimens. Resistance to ceftazidime and gentamicin among the CRPA isolates carrying *bla*<sub>N<sub>DM</sub>-1</sub> highlights the growing challenge of successfully treating infections caused by this bacteria. This challenge reminds us of the importance and purpose of antibiotic stewardship that emphasizes the improvement of proper antibiotic prescription by the physicians and proper antibiotic use by the patients that can help in preventing harm and antibiotic resistance.

**Keywords:** Antibiotic Resistance; *bla*<sub>N<sub>DM</sub>-1</sub>; Carbapenem-resistant; Metallo-beta-lactamase; *Pseudomonas aeruginosa*.

## 1. Introduction

*Pseudomonas aeruginosa* is one of the major pathogens that causes nosocomial infections [1] and patients who have impaired immune functions are at a higher risk of acquiring *P. aeruginosa* infections [2]. In addition, this pathogen is able to cause hospital-acquired pneumonia, urinary tract infections, and bloodstream infections [3]. One of

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the therapeutic treatments of choice in serious infections that is related to *P. aeruginosa* is carbapenem, but infections caused by the said bacteria are becoming more difficult to treat due to increasing antibiotic resistance [4, 5].

Carbapenem, a  $\beta$ -lactam antibiotic, is utilized to resolve infections whenever the treatment of choice for a certain pathogen is already becoming ineffective [6]. This antibiotic is known to be very effective when it comes to treating both gram-negative and gram-positive bacterial infections, which includes the treatment for *P. aeruginosa* [7]. Carbapenem resistance may be due to irresponsible use of antibiotics in terms of dosage and treatment days, low quality medicines, and unnecessary prescriptions [8]. To support this claim, a study showed that human-related factors play a crucial role in the emergence and spread of carbapenem resistance, and these are mainly the (a.) inappropriate prescribing of antibiotics together with unregulated consumer access to antibiotics in many countries with poor sales regulations, (b.) lack of infection prevention controls in health care facilities after resistance to carbapenem has emerged, and (c.) usage of subtherapeutic antibiotic doses to promote animal growth in the agricultural sector [9].

Like most antibiotics,  $\beta$ -lactam resistance can occur through multiple molecular mechanisms including  $\beta$ -lactamases production, efflux systems overexpression, outer membrane permeability alteration, and/or penicillin-binding proteins alteration [2].  $\beta$ -lactamase enzymes production is the most common mechanism of bacterial resistance to  $\beta$ -lactam antibiotics such as carbapenems [10]. The New Delhi metallo- $\beta$ -lactamase (NDM-1) is a novel metallo- $\beta$ -lactamase that is encoded by the *bla*<sub>NDM-1</sub> gene [11]. This gene is found on large plasmids that are easily transferred in which it is said to have resistance to a majority of antibiotics, hence, spread to relevant bacteria will be fast and easy [12]. Most *bla*<sub>NDM-1</sub> strains are resistant to a wide range of antibiotics and transport several additional resistance genes to sulfonamides, aminoglycosides, fluoroquinolones and macrolides [13].

The resistance to carbapenem antibiotics of *P. aeruginosa* has posed a heavier burden among infected patients for it was said to be associated with their prolonged hospital stays which increased their financial burden [14]. Hence, this study aimed to review the prevalence of carbapenem-resistant *Pseudomonas aeruginosa* carrying *bla*<sub>NDM-1</sub>, its clinical sources, and its antibiotic resistance profile.

## 2. Methods

### 2.1. Search Strategy

Following the PRISMA guidelines [15], a literature search was performed in PubMed, ScienceDirect, and Google Scholar using the combination of keywords: *bla*<sub>NDM-1</sub>, *Pseudomonas aeruginosa*, carbapenem resistance, metallo-beta-lactamase, carbapenemases, and New Delhi metallo-beta-lactamase. Articles published from January 2015 to February 2021 were collected. The titles and abstracts of the studies collected were independently screened by two review authors of this systematic review (B.J.U.F and J.C.Y.G). Relevant studies were checked for eligibility after duplicates have been removed and full-text articles were then checked. Additional manual searches through reference lists of the included articles were performed and these articles were then also screened. Any disagreements between the two review authors regarding the inclusion and exclusion of articles were resolved through discussion with the help of a third reviewer (M.O.B.A).

### 2.2. Eligibility Criteria

Studies gathered from PubMed, ScienceDirect, and Google Scholar were included if they met the following criteria: (1.) Peer-reviewed, (2.) Published from January 2015 to February 2021, (3.) Written in the English language, (4.) Study samples are clinical isolates of carbapenem-resistant *P. aeruginosa*, (5.) Study design is cross-sectional study, cohort study, or case report, and (6.) Outcomes that focus on *bla*<sub>NDM-1</sub> gene isolated from carbapenem-resistant *P. aeruginosa*, its clinical sources as well as its antibiotic resistance profile. Studies were excluded if they met the following criteria: (1.) Not peer-reviewed, (2.) Published before January 2015, (3.) Written in language/s other than English, (4.) Study samples are non-clinical isolates of carbapenem-resistant *P. aeruginosa* or non-carbapenem-resistant *P. aeruginosa*, (5.) Study design is animal research study, editorial article, letter, systematic review or meta-analysis, and (6.) Outcomes did not focus on *bla*<sub>NDM-1</sub> gene isolated from carbapenem-resistant *P. aeruginosa*, its clinical sources as well as its antibiotic resistance profile.

### 2.3. Data Extraction

The data extraction of all included studies were independently performed by two review authors (B.J.U.F and J.C.Y.G). The following data were collected from the included studies: study information (title of study, first author, locus, publication year, study design), frequency of *bla*<sub>NDM-1</sub> gene isolated from carbapenem-resistant *P. aeruginosa*, clinical sources of the strains; for example, blood, wounds, and burns, and antibiotic resistance profile such as the list of antibiotics in which carbapenem-resistant *P. aeruginosa* carrying *bla*<sub>NDM-1</sub> exhibit resistance. Any disagreements among the two review authors regarding data extraction were resolved through discussion with the help of a third reviewer (M.O.B.A).

## 2.4. Quality Assessment

Selected studies were critically appraised by two independent reviewers (K.M.D.G and S.T.V). In assessing the methodological quality of cross-sectional studies, the JBI Critical Appraisal Checklist for Studies Reporting Prevalence Data [16] was used. This tool consists of 9 questions which will be rated as yes, no, unclear, or not applicable. An overall appraisal of a study may be rated as to include, exclude or seek further information. In assessing the quality for the case report, the JBI Critical Appraisal Checklist for Case Reports [17] was used. It consists of 8 questions which will be rated as yes, no, unclear, or not applicable. An overall appraisal of a study may be rated as to include, exclude, or seek further information. Any disagreements among the two review authors were resolved through discussion with the help of a third reviewer (M.O.B.A).

## 3. Results and Discussion

### 3.1. Search Results

The PRISMA flow diagram that displays the overview of the study selection process is shown in Figure 1. Records identified through PubMed, ScienceDirect, and Google Scholar yielded a total of 640 records. Additional manual searches through reference lists of the included articles yielded a total of thirteen records. After removal of duplicates (n = 119), 534 articles were screened based on their titles and abstracts in which 437 studies were excluded as they did not fulfill this review’s inclusion criteria. 97 full-text articles were then assessed for eligibility and from these, 88 articles were excluded because they did not focus on the clinical sources or the antibiotic resistance profile of the carbapenem-resistant *P. aeruginosa* isolates carrying *bla*<sub>NDM-1</sub>. Finally, a total of nine studies [46-54] were included for analysis. These include eight cross-sectional studies in which two were conducted in Iran [47,48], two in India [52,53], one in Saudi Arabia [46], one in Bulgaria [49], one in Malaysia [50], and one in Egypt [54]. The other study included in this review is a case report conducted in Canada [51].

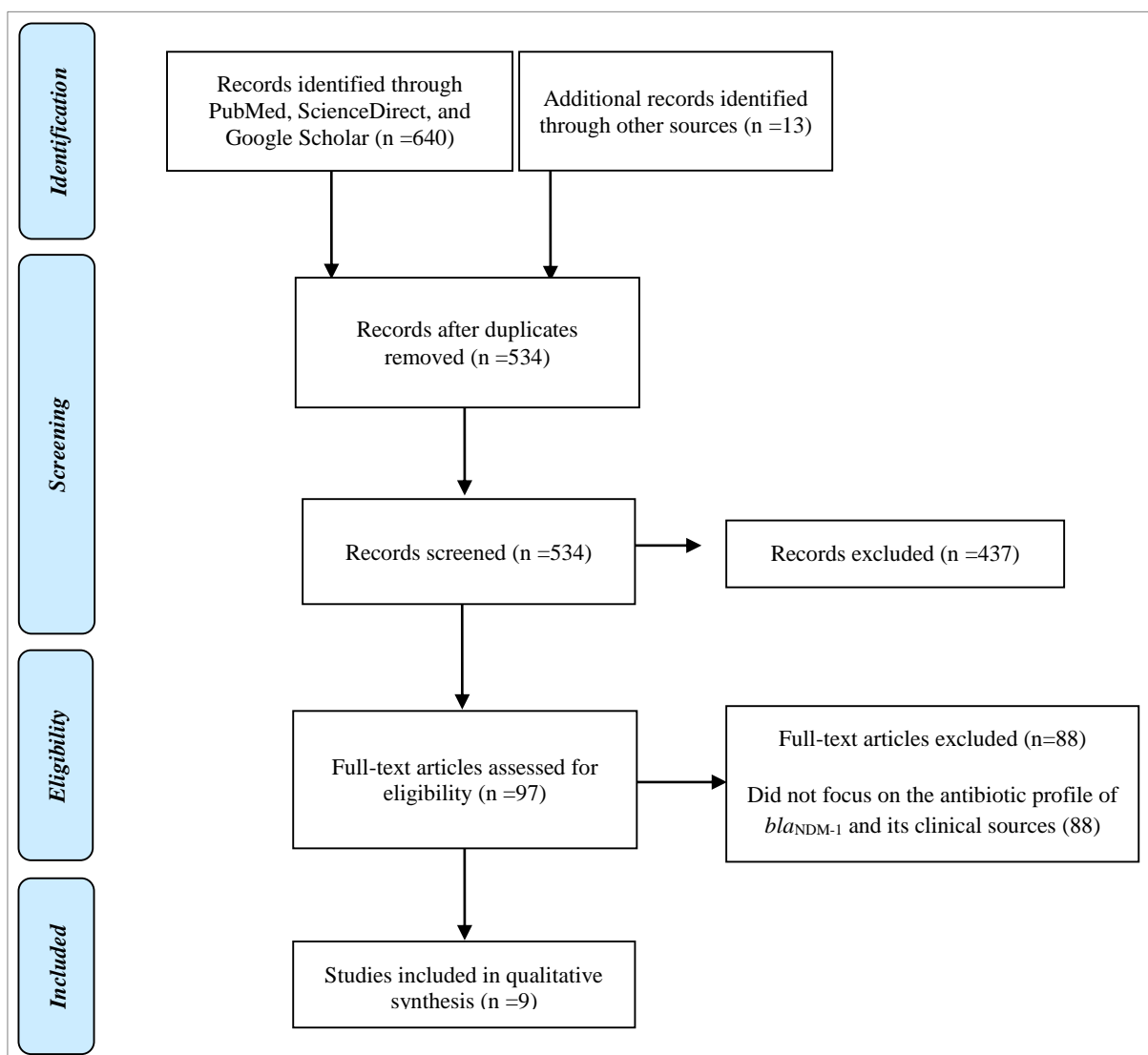


Figure 1. PRISMA flow diagram of study selection process

### 3.2. Prevalence of CRPA Isolates Carrying *bla*<sub>NDM-1</sub> among the Included Studies

New Delhi metallo- $\beta$ -lactamase-1 production due to *bla*<sub>NDM-1</sub> gene is one of the most common antibiotic resistance mechanisms found in Gram-negative bacteria such as *P. aeruginosa* against carbapenems [18]. As seen in Table 1, a prevalence rate of 54.55% in CRPA isolates carrying *bla*<sub>NDM-1</sub> is relatively the highest among the cross-sectional studies which was reported from India [53]. This is in line with both studies conducted in Iraq [19,20] in which a prevalence rate of 50% were reported. In India, a study [21] revealed a lower prevalence rate at 41%. Furthermore, findings of this review showed that the lowest prevalence rate among the cross-sectional studies is 2.86% which was reported from India [52]. Similar prevalence rate was reported by a study conducted in Bahrain at 2.5% [22]. A study [23] reported a higher prevalence rate wherein 9.4% of the CRPA isolates carried *bla*<sub>NDM-1</sub>. In contrast, a study conducted in Iraq showed a lower prevalence rate at 1.12% [24]. Among the included studies, the highest prevalence was reported in India in 2017 and this may be because *bla*<sub>NDM-1</sub> is endemic in the said country. However, the lowest prevalence was also reported in India in 2015. The increase of prevalence rate within 2015-2017 may be attributed to the rapid spread of the said gene. In addition, the difference in the prevalence rate of the two studies conducted in the same country may also be attributed to poor infection control in the healthcare settings.

The results of this review highlighted the global spread of *bla*<sub>NDM-1</sub> in CRPA isolates. Being hospitalized in endemic regions such as in India may cause further spread of *bla*<sub>NDM-1</sub> producing isolates [25] which leads to differences in the distribution of this gene in various countries. Despite the various prevalence rates shown in this study, *bla*<sub>NDM-1</sub> producers are of concern since these can spread rapidly [26] wherein it is possible that numerous cases will be found in the near future. Understanding and continuous monitoring of the prevalence and resistance mechanisms of carbapenem-resistant *P. aeruginosa* helps the healthcare professionals formulate appropriate treatment plans to fight against nosocomial infections [27].

### 3.3. Clinical Sources of the *bla*<sub>NDM-1</sub> Positive CRPA Isolates among the Included Studies

Of the nine included articles, findings of this review revealed that the most common clinical source of the strains carrying *bla*<sub>NDM-1</sub> is urine, four out of nine studies [49, 51, 53, 54]; followed by wound discharge, three out of nine studies [52-54]; and tissue, two out of nine studies [50, 52] as seen in Table 1. This is in line with the other studies conducted in India and Serbia, where they recovered the highest number of *bla*<sub>NDM-1</sub> isolates from urine and wound discharge specimens [28-31]. In another Indian study conducted at a tertiary care center, presence of *bla*<sub>NDM-1</sub> was most common in wound discharge specimens among the other clinical isolates [13]. Related study which recovered *bla*<sub>NDM-1</sub> from urine specimens in an Iraqi hospital reported the same results [32]. Our findings were also consistent with that of a study performed at a tertiary referral hospital in India, which reported *bla*<sub>NDM-1</sub> in tissue samples of patients with diabetic foot infections [33]. The predominance of urine, wound discharge, and tissue specimens may indicate that the urinary tract, wounds, and skin and soft tissue were the most frequent sites of infection [34, 35]. This highlights the importance of strict infection control programs in which specific policies and practices should be established to minimize the spread of infections.

### 3.4. Antibiotic Resistance Profile of CRPA Isolates Carrying *bla*<sub>NDM-1</sub> among the Included Studies

The full results of antibiotic resistance profile of the *bla*<sub>NDM-1</sub> positive *P. aeruginosa* isolates among the nine included articles is shown in Appendix I. Majority of the included studies used the disk diffusion method, six out of nine studies [47, 48, 50, 52-54]; and the Clinical and Laboratory Standards Institute (CLSI), eight out of nine studies [46-48, 50-54] (Appendix I). Of the nine included articles, this review found out that the most frequent resistance of the isolates were observed against ceftazidime, nine out of nine studies [46-54]; and gentamicin, nine out of nine studies [46-54] as seen in Table 1. These results are consistent with the study conducted in Singapore [36] who reported that ceftazidime and gentamicin showed 100% resistance among *bla*<sub>NDM-1</sub> positive CRPA isolates. Moreover, a study conducted in India [37] also showed similarity to the outcomes of this study regarding antibiotic resistance wherein all the *bla*<sub>NDM-1</sub> positive CRPA isolates were resistant to aminoglycosides such as gentamicin. Another study [38] also showed 100% resistance to ceftazidime and gentamicin. This resistance may be attributed to enzyme production that leads to antibiotic degradation and inactivation, which then results in a reduction of the permeability of the membrane and multidrug resistance efflux system [34].

The New Delhi metallo- $\beta$ -lactamase is capable of hydrolyzing all  $\beta$ -lactams except for aztreonam [2] which may explain why one of the antibiotics that the isolates most exhibit resistance to was ceftazidime. In addition, isolates that are metallo- $\beta$ -lactamase-producing are frequently aminoglycoside-resistant [39]. There is said to be an association between MBL genes and aminoglycoside resistant genes, wherein bacteria carrying MBL genes often exhibit co-resistance to aminoglycosides which is a challenge in giving proper therapeutic regimes [40]. This may explain why gentamicin was also one of the antibiotics that the isolates most exhibit resistance to. Other than these, resistance can also be attributed to mutational processes, resistance gene transfers, and poor infection control in the healthcare settings [34]. This review also showed that the CRPA isolates carrying *bla*<sub>NDM-1</sub> were least resistant to colistin as seen

in Appendix I. This is in line with the results of a study [36] wherein the isolates were susceptible to colistin. The said antibiotic is used to treat pathogens that are carbapenem-resistant [41]. Carbapenem resistance is of clinical concern and knowledge of the susceptibility of *P. aeruginosa* to antibiotics is urgently required since knowing antibiotic resistance pattern may help in treating infections caused by this bacteria [42].

The increased resistance rate of CRPA can be linked to the wide use of antibiotics that highlights the need for identifying improved courses of treatments to prolong its effectiveness [43]. This study gives contribution to the active surveillance of antibiotic resistance by including a more updated antibiotic resistance profile of the isolates included in this study. It can fill in the gaps in the study of antibiotic resistance since any available information is of great help so that treatment guidelines may be optimized and if no actions are taken to control this, the achievements gained on the early antibiotic use is in jeopardy [44]. Moreover, this can lead to the rise of new resistant strains of bacteria [45].

**Table 1. Summary of the extracted data from the included studies**

Authors (Publication Year)	Locus	Study Design	<i>bla</i> <sub>NDM-1</sub> positive n (%)	Clinical Sources of the Strains carrying <i>bla</i> <sub>NDM-1</sub> n (%)	CAZ n (%)	GEN n (%)
Abdalhamid et al. (2016) [46]	Saudi Arabia	Cross-sectional	4 (30.7%)	Rectal swab 4 (100%)	4 (100%)	4 (100%)
Dogonchi et al. (2018) [47]	Iran	Cross-sectional	1 (5%)	Respiratory tract sample 1 (100%)	1 (100%)	1 (100%)
Khosravi et al. (2019) [48]	Iran	Cross-sectional	14 (40%)	Burn wound 14 (100%)	14 (100%)	14 (100%)
Kostyanev et al. (2020) [49]	Bulgaria	Cross-sectional	2 (40%)	Urine 2 (100%)	2 (100%)	2 (100%)
Liew et al. (2018) [50]	Malaysia	Cross-sectional	1 (33.33%)	Tissue 1 (100%)	1 (100%)	1 (100%)
Mataseje et al. (2016) [51]	Canada	Case report	1(100%)	Urine 1 (100%)	1 (100%)	1 (100%)
Mishra et al. (2015) [52]	India	Cross-sectional	3 (2.86%)	Tissue 1 (33.33%) Central tip 1 (33.33%) Wound discharge 1 (33.33%)	3 (100%)	3 (100%)
Mohanam & Menon (2017) [53]	India	Cross-sectional	12 (54.55%)	Wound discharge 10 (83.33%) Urine 1 (8.33%) Tracheal wash 1 (8.33%)	12 (100%)	12 (100%)
Shaaban et al. (2017) [54]	Egypt	Cross-sectional	8 (50%)	Sputum 3 (37.5%) Urine 3 (37.5%) Wound discharge 2 (25%)	5 (62.5%)	5 (62.5%)

CRPA: Carbapenem-resistant *Pseudomonas aeruginosa*; NDM: New Delhi Metallo-β-lactamases; CAZ: Cefazidime; GEN: Gentamicin

### 3.5. Quality Assessment of the Included Studies

The results of the quality assessment of the eight cross-sectional studies are shown in Table 2.

**Table 2. JBI critical appraisal checklist for studies reporting prevalence data**

Authors	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Included
Abdalhamid et al. (2016) [46]	Y	Y	NA	Y	Y	Y	Y	Y	NA	✓
Dogonchi et al. (2018) [47]	Y	Y	NA	Y	Y	Y	Y	Y	NA	✓
Khosravi et al. (2019) [48]	Y	Y	NA	Y	Y	Y	Y	N	NA	✓
Kostyanev et al. (2020) [49]	Y	Y	NA	Y	Y	Y	Y	N	NA	✓
Liew et al. (2018) [50]	Y	Y	NA	Y	Y	Y	Y	N	NA	✓
Mishra et al (2015) [52]	Y	Y	NA	Y	Y	Y	Y	N	NA	✓
Mohanam & Menon (2017) [53]	Y	Y	NA	Y	Y	Y	Y	N	NA	✓
Shaaban et al. (2017) [54]	Y	Y	NA	Y	Y	Y	Y	Y	NA	✓

Y, yes; N, no; U, unclear; NA, Not applicable. Q1, Was the sample frame appropriate to address the target population? Q2, Were study participants sampled in an appropriate way? Q3, Was the sample size adequate? Q4, Were the study subjects and the setting described in detail? Q5, Was the data analysis conducted with sufficient coverage of the identified sample? Q6, Were valid methods used for the identification of the condition? Q7, Was the condition measured in a standard reliable way for all participants? Q8, Was there appropriate statistical analysis? Q9, Was the response rate adequate, and if not, was the low response rate managed appropriately? condition= presence of *bla*<sub>NDM-1</sub>; participants= clinical isolates

Based on the results using the JBI Critical Appraisal Checklist for Studies Reporting Prevalence Data, all eight cross-sectional studies met the majority of this tool’s criteria [46-50,52-53], meeting six to seven out of nine possible items. Two out of nine items were not applicable to all the studies wherein one item was relating to the adequacy of the sample size while the other one was relating to the adequacy of the response rates. These items were not applicable



to all the studies because sample size calculation is not performed since the study samples included only isolates available within the period of study. Also, there were no response rates since study samples include clinical isolates. Furthermore, some of the studies missed the item that was relating to statistical analysis because these studies used descriptive analysis. With these, the overall appraisal of these cross-sectional studies was to include all of them in this review.

The results of the quality assessment of the case report [51] is shown in Table 3. Based on the results using the JBI Critical Appraisal Checklist for Case Reports, it met five out of eight items. It missed the items relating to patient history, post-intervention, and adverse events. Patient history was stated in the said case report, but it was not presented in a timeline. Items regarding post-intervention as well as adverse events were missed because the said case report focused on the clinical isolates and not the patient himself. Therefore, the overall appraisal was to include this case report in this review.

**Table 3. JBI critical appraisal checklist for case reports**

Author	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Included
Mataseje et al. (2016) [51]	Y	N	Y	Y	Y	N	N	Y	✓

Y, yes; N, no; Q1, Were patient’s demographic characteristics clearly described? Q2, Was the patient’s history clearly described and presented as a timeline? Q3, Was the current clinical condition of the patient on presentation clearly described? Q4, Were diagnostic tests or assessment methods and the results clearly described? Q5, Was the intervention(s) or treatment procedure(s) clearly described? Q6, Was the post-intervention clinical condition clearly described? Q7, Were adverse events (harms) or unanticipated events identified and described? Q8, Does the case report provide takeaway lessons?

### 3.6. Limitations of the Study

The limitations of this systematic review include the exclusion of studies that were inaccessible, and written language/s other than English. Literature search was performed only in PubMed, ScienceDirect, and Google Scholar. These may have resulted in some relevant studies being missed. In addition, resistance data obtained with different method of susceptibility testing were combined in this systematic review. However, as the majority of the included studies used the disk diffusion method and the CLSI guidelines, the impact caused by the differences in their antimicrobial resistance methodology on the validity of the final results is minimal [44].

## 4. Conclusions and Recommendations

This review revealed that there is varying prevalence of *bla*<sub>NDM-1</sub> in CRPA in Saudi Arabia, Iran, Bulgaria, Malaysia, Canada, India, and Egypt. Therefore, immediate detection of CRPA that harbors *bla*<sub>NDM-1</sub> is essential in order to prevent the spread of this bacteria. This review showed that the three most frequent sources of clinical isolates of CRPA carrying *bla*<sub>NDM-1</sub> include urine, wound discharge, and tissue which poses a challenge that must be given attention by the infection control committee, thus the need for proper handling and processing of clinical specimens. Recognizing the critical need to improve antibiotic use in hospitals, the Centers for Disease Control and Prevention (CDC) has recommended the implementation of Antibiotic Stewardship Programs (ASPs) dedicated to optimizing infection treatment and reducing adverse events associated with antibiotic use [55]. In this review, CRPA isolates carrying *bla*<sub>NDM-1</sub> were most resistant to ceftazidime and gentamicin which highlights the growing challenge of successfully treating infections caused by this bacteria. This challenge reminds us of the importance and purpose of antibiotic stewardship that emphasizes the improvement of proper antibiotic prescription by the physicians and proper antibiotic use by the patients that can help in preventing harm and antibiotic resistance.

This review recommends implementing strict infection control policies and also strict surveillance on the alarming antibiotic resistance so that dissemination and rise of more resistant bacteria will be prevented. In order to minimize the risk of resistant *P. aeruginosa* strains spreading, we also recommend that antibiotics be used correctly in the care of patients as part of infection prevention measures in hospitals. Lastly, it is recommended that more researches regarding the antibiotic resistance profiles of CRPA isolates carrying *bla*<sub>NDM-1</sub> as well as their clinical sources be conducted to provide information about the local epidemiology of New Delhi metallo-β-lactamase in various healthcare settings. Research regarding prevalence, antibiotic resistance profile as well as the clinical sources of other carbapenem-resistant bacteria harboring metallo-β-lactamase is also recommended.

## 5. Declarations

### 5.1. Author Contributions

Conceptualization, B.J.U.F., M.O.B.A., K.M.A.D.G., J.C.Y.G., S.T.V., R.E.G.T., AND S.D.T.; methodology, B.J.U.F., M.O.B.A., K.M.A.D.G., J.C.Y.G., and S.T.V.; formal analysis, B.J.U.F., M.O.B.A., K.M.A.D.G., J.C.Y.G., and S.T.V.; investigation, B.J.U.F., M.O.B.A., K.M.A.D.G., J.C.Y.G., and S.T.V.; data curation, B.J.U.F., M.O.B.A., K.M.A.D.G., J.C.Y.G., and S.T.V.; writing—original draft preparation, B.J.U.F., M.O.B.A., K.M.A.D.G., J.C.Y.G., and S.T.V.; writing—review and editing, B.J.U.F., M.O.B.A., K.M.A.D.G., J.C.Y.G., S.T.V., R.E.G.T., AND S.D.T.;

project administration, B.J.U.F., AND S.D.T. All authors have read and agreed to the published version of the manuscript.

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## 5.4. Ethical Approval

The manuscript does not contain experiments on animals and humans; hence ethical permission not required.

## 5.5. Data Availability Statement

The data presented in this study are available in article.

## 5.6. Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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**Appendix I: Antibiotic Resistance Profile of CRPA Isolates Harboring *bla*<sub>NDM-1</sub>**

LVX n (%)	NET n (%)	CIP n (%)	TZP n (%)	TIM n (%)	PIP n (%)	PMB n (%)	TOB n (%)	FEP n (%)	CTX n (%)	CST n (%)	OFX n (%)	ATM n (%)	C/T n (%)	CZC n (%)	CZA n (%)	FOX n (%)	CRO n (%)	TGC n (%)	SXT n (%)
		4 (100%)						4 (100%)	4 (100%)	0									
1 (100%)		1 (100%)	0			0	1 (100%)			0									
	9 (64.29%)		5 (35.71%)		12 (85.71%)			12 (85.71%)		0		11 (78.57%)							
2 (100%)		2 (100%)	2 (100%)				2 (100%)	2 (100%)		0			2 (100%)		2 (100%)				
	1 (100%)	1 (100%)	1 (100%)	1 (100%)	1 (100%)														
	1 (100%)	1 (100%)	1 (100%)				1 (100%)	1 (100%)		1 (100%)		0				1 (100%)	1 (100%)	1 (100%)	1 (100%)
	3 (100%)	3 (100%)	3 (100%)			0	3 (100%)												
12 (100%)	12 (100%)	12 (100%)	12 (100%)		12 (100%)	0	12 (100%)	12 (100%)		0	12 (100%)	12 (100%)		12 (100%)					
6 (75%)																			

Authors (Publication Year)	Locus	<i>bla</i> <sub>NDM-1</sub> positive n (%)	Method of Susceptibility Testing	Susceptibility Testing Standard	CAZ n (%)	GEN n (%)	AMK n (%)
Abdallahmid et al.(2016)	Saudi Arabia	4 (30.7%)	Vitek 2 automatic system	CLSI	4 (100%)	4 (100%)	4 (100%)
Dogonchi et al (2018).	Iran	1 (5%)	Disk diffusion	CLSI	1 (100%)	1 (100%)	0
Khosravi et al.(2019)	Iran	14 (40%)	Disk diffusion	CLSI	14 (100%)	14 (100%)	14 (100%)
Kostyanov et al. (2020)	Bulgaria	2 (40%)	E-test	EUCAST	2(100%)	2 (100%)	2 (100%)
Liew et al (2018)	Malaysia	1 (33.33%)	Disk diffusion	CLSI	1(100%)	1(100%)	1(100%)
Mataseje et. al. (2016)	Canada	1 (100%)	MicroScan NEG 38 panel, E-test	CLSI, EUCAST, FDA breakpoint	1 (100%)	1 (100%)	1 (100%)
Mishra et al.(2015)	India	3 (2.86%)	Disk diffusion	CLSI	3 (100%)	3 (100%)	3 (100%)
Mohanam & Menon (2017)	India	12 (54.55%)	Disk diffusion	CLSI	12 (100%)	12 (100%)	12 (100%)
Shaaban et al. (2017)	Egypt	8 (50%)	Disk diffusion	CLSI	5(62.5%)	5(62.5%)	5(62.5%)

CRPA: Carbapenem-resistant *Pseudomonas aeruginosa*; NDM: New Delhi Metallo-β-lactamases; CLSI: Clinical and Laboratory Standards Institute; EUCAST: European Committee on Antimicrobial Susceptibility Testing; CAZ: Ceftazidime; GEN: Gentamicin; AMK: Amikacin; LVX: Levofloxacin; NET: Netilmicin; CIP: Ciprofloxacin; TZP: Piperacillin-tazobactam; TIM: Ticarcillin-clavulanic acid; PIP: Piperacillin; PMB: Polymyxin B; TOB: Tobramycin; FEP: Cefepime; CTX: Cefotaxime; CST: Colistin; OFX: Ofloxacin; ATM: Aztreonam; C/T: Ceftolozane-tazobactam; CZC: Ceftazidime-Clavulanic acid; CZA: Ceftazidime-avibactam; FOX: Cefoxitin; CRO: Ceftriaxone; TGC: Tigecycline; SXT: Trimethoprim-sulfamethoxazole