

## RESEARCH ARTICLE

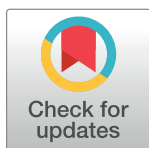
# Prevalence of carbapenem resistance in *Acinetobacter baumannii* and *Pseudomonas aeruginosa* in sub-Saharan Africa: A systematic review and meta-analysis

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## Abstract

Carbapenems are effective drugs against bacterial pathogens and resistance to them is considered a great public health threat, especially in notorious nosocomial pathogens like *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. In this study, we aimed to determine the prevalence of carbapenem resistance in *A. baumannii* and *P. aeruginosa* infections in Sub-Saharan Africa. Databases (PubMed, Scopus, Web of Science, and African Journal Online) were systematically searched following the Preferred Reporting Items for Systematic review and meta-analysis protocols (PRISMA-P) 2020 statements for articles reporting carbapenem-resistant *Acinetobacter baumannii* (CRAB) and carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) prevalence between 2012 and 2022. Pooled prevalence was determined with the random effect model and funnel plots were used to determine heterogeneity in R. A total of 47 articles were scanned for eligibility, among which 25 (14 for carbapenem-resistant *A. baumannii* and 11 for carbapenem-resistant *P. aeruginosa*) were included in the study after fulfilling the eligibility criteria. The pooled prevalence of CRPA in the present study was estimated at 8% (95% CI; 0.02–0.17;  $I^2 = 98\%$ ;  $P < 0.01$ ). There was high heterogeneity ( $Q = 591.71$ ,  $I^2 = 98.9\%$ ;  $P < 0.0001$ ). In addition, this study's pooled prevalence of CRAB was estimated at 20% (95% CI; 0.04–0.43;  $I^2 = 99\%$ ;  $P < 0.01$ ). There was high heterogeneity ( $Q = 1452.57$ ,  $I^2 = 99\%$ ;  $P < 0.0001$ ). Also, a funnel plot analysis of the studies showed high degree of heterogeneity. The carbapenemase genes commonly isolated from *A. baumannii* in this study include *bla*<sub>OXA23</sub>, *bla*<sub>OXA48</sub>, *bla*<sub>GES</sub>, *bla*<sub>NDM</sub>, *bla*<sub>VIM</sub>, *bla*<sub>OXA24</sub>, *bla*<sub>OXA58</sub>, *bla*<sub>OXA51</sub>, *bla*<sub>SIM-1</sub>, *bla*<sub>OXA40</sub>, *bla*<sub>OXA66</sub>, *bla*<sub>OXA69</sub>, *bla*<sub>OXA91</sub>, with

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*bla*<sub>OXA23</sub> and *bla*<sub>VIM</sub> being the most common. On the other hand, *bla*<sub>NDM</sub>, *bla*<sub>VIM</sub>, *bla*<sub>IMP</sub>, *bla*<sub>OXA48</sub>, *bla*<sub>OXA51</sub>, *bla*<sub>SIM-1</sub>, *bla*<sub>OXA181</sub>, *bla*<sub>KPC</sub>, *bla*<sub>OXA23</sub>, *bla*<sub>OXA50</sub> were the commonly isolated carbapenemase genes in *P. aeruginosa*, among which *bla*<sub>VIM</sub> and *bla*<sub>NDM</sub> genes were the most frequently isolated. Surveillance of drug-resistant pathogens in Sub-Saharan Africa is essential in reducing the region's disease burden. This study has shown that the region has significantly high multidrug-resistant pathogen prevalence. This is a wake-up call for policymakers to put in place measures to reduce the spread of these critical priority pathogens.

## Introduction

Antimicrobial resistance (AMR) is a leading public health threat globally, considerably escalating morbidity, mortality and treatment failure of microbial infections, as well as economic losses to individuals and nations [1]. According to the 2016 Review on Antimicrobial Resistance, AMR would be responsible for 10 million deaths yearly by 2050 with a large amount of these deaths occurring in Sub-Saharan Africa [2]. However, a recent report of almost 5 million deaths linked with AMR in 2019 alone has shown that we will be reaching the 10 million AMR-associated deaths sooner than earlier predicted [3].

Carbapenems are beta-lactam antibiotics with broad-spectrum bactericidal activities against both Gram-positive and negative pathogens [4]. They are often used as last-line drugs against bacterial infections [5]. Unfortunately, bacterial pathogens have developed resistance to this last-resort group of antibiotics through various genetic modifications and production of carbapenem-hydrolysing enzymes [6]. Treatment of infections have become more difficult and expensive, especially against the notorious Gram-negative bacteria, due to resistance to last-line antibiotics.

*Acinetobacter baumannii* and *Pseudomonas aeruginosa* are Gram-negative pathogens that belong to the ESKAPE group (an acronym for the group of bacteria, encompassing both Gram-positive and Gram-negative species, made up of *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter species* [7]). These are bacterial pathogens that are notorious for their resistance to clinically relevant antimicrobials. Furthermore, carbapenem-resistant *A. baumannii* (CRAB) and *P. aeruginosa* (CRPA) have both been grouped as critical priority pathogens for which there is a need to develop new and effective antimicrobials. These have made the surveillance of these two pathogens a necessity, especially in low-middle-income countries where surveillance is poor. A recent report shows that CRAB and CRPA have mortality rates of 30.5% and 24.5% within 90 days of a positive culture [8]. Moreover, CRAB and CRPA were reported to be responsible for 57,700 and 38,100 deaths globally in 2019 respectively [3].

Sub-Saharan Africa (SSA) is known for having a high burden of infectious diseases which might be linked to the poverty level and poor water, sanitation, and hygiene (WASH) practices in the region [9,10]. The [3] report also showed that Sub-Saharan Africa suffers the highest prevalence of AMR-associated death globally. The scarcity of AMR data from SSA has made it difficult to determine the true risk and burden of AMR infections in the region. Also, a recent study predicting the global prevalence of carbapenemase-producing *P. aeruginosa* could not include majority of Sub-Saharan African countries in the analysis due to scarcity of data. This further emphasizes the need to surveillance of AMR pathogens in Africa, especially in Sub-Saharan Africa. To the best of our knowledge, there is currently no up-to-date systematic

review and meta-analysis that reports the pooled prevalence of carbapenem-resistant *P. aeruginosa* and *A. baumannii* in Sub-Saharan Africa. This systematic review is an extensive analysis of the prevalence of carbapenem-resistant *A. baumannii* with the aim to describe the epidemiology within Sub-Saharan Africa. This study also investigated the prevalence of carbapenemase genes in the region. This would provide insight on the public health risks posed by these priority pathogens and the development of sustainable prevention and control interventions in this region.

## Method

### Search strategy

This study was performed according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines [11]. Electronic databases (PubMed, Scopus, Web of Science, and African Journal Online) were searched for articles published on carbapenem-resistant *A. baumannii* and/or *P. aeruginosa* in sub-Saharan Africa. The last search was on the 31st of July 2022.

### Eligibility criteria

This study only included studies published in Sub-Saharan Africa between January 2012 and July 2022. Only studies that reported *A. baumannii* and/or *P. aeruginosa* prevalence in humans were considered for the analysis. Studies that reported *A. baumannii* and/or *P. aeruginosa* prevalence from countries outside Sub-Saharan Africa were excluded from the analysis. Also, only studies that reported at least one case of carbapenem resistance in *A. baumannii* and/or *P. aeruginosa* were included. Only studies published in English or with English translations available were included in the final analysis. Lastly, cross-sectional studies, retrospective, and longitudinal analyses were considered in this analysis. Literature and systematic reviews were excluded from this analysis.

### Screening strategy

Articles were first screened based on their titles and abstracts by two independent researchers. Two other researchers then screened eligible articles by reading through their full text, ineligible articles were excluded and the reasons for their exclusion were stated (Fig 1). All disagreements were resolved through discussions. A third researcher confirmed the eligibility of the included studies before including them in the analysis. During extraction, for studies that reported different percentages for imipenem or meropenem, preference was given to meropenem since it has better activity against Gram-negative bacteria [12].

### Data extraction and quality appraisal

A data extraction table was created by one reviewer and two other reviewers extracted the following data from the eligible articles; first author, study design, study country, study aim, sample size, sample source, organism prevalence, carbapenem-resistance prevalence, Antimicrobial Susceptibility Testing (AST) method, carbapenem used. All disagreements were resolved through discussions and a fourth reviewer confirmed the extracted data. This step was performed for each of the organisms.

### Data analysis

The data extracted was cleaned for any eligibility criterion error, and the meta-analysis was performed using RStudio version 4.2.0. The Carbapenem-resistant *A. baumannii* (CRAB) and

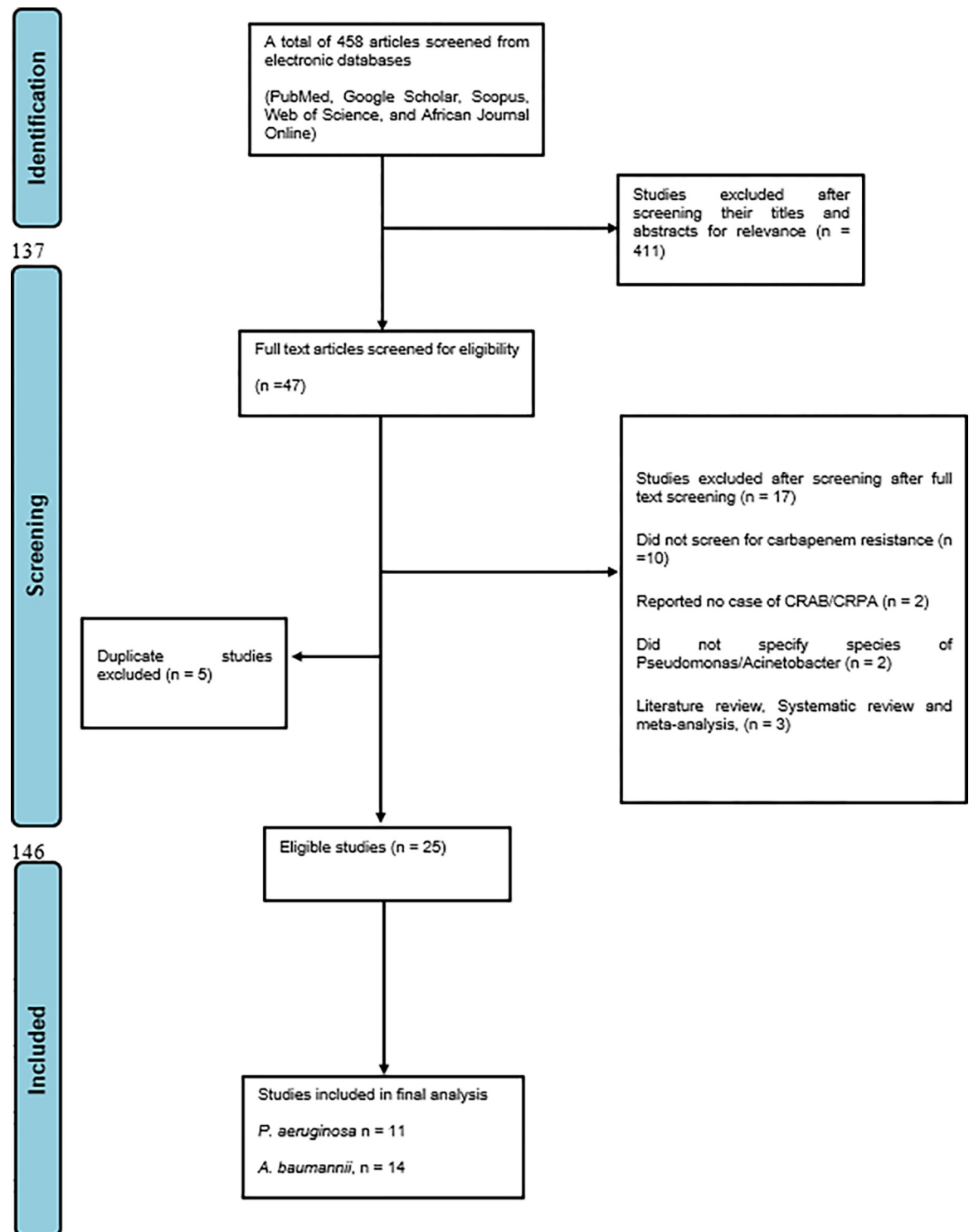


Fig 1. PRISMA flowchart for the search process.

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*P. aeruginosa* (CRPA) pooled prevalence of the present study was analyzed using the random-effect model while subgroup prevalence was considered based on the source of the reported studies. Cochran Q statistics and the  $I^2$  (inverse variance index) were used to analyze the

heterogeneity (low, 0–0.25; fair, 0.25–0.5; moderate, 0.5–0.75; and high, above 0.75). A p-value of <0.01 was considered significant. Publication bias and degree of heterogeneity was examined visually with the use of the funnel plot.

## Result

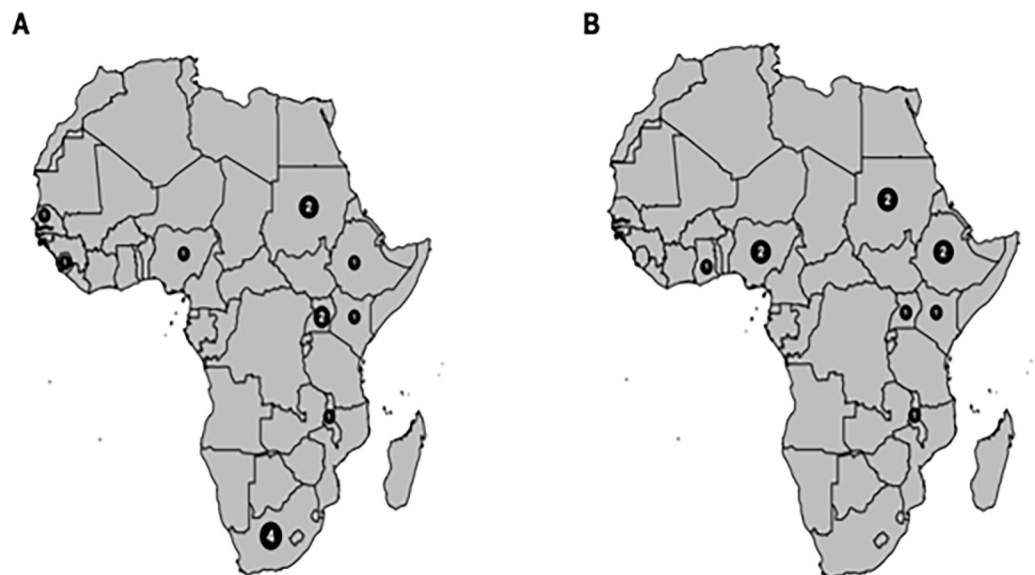
A total of 25 articles (CRAB, 14; CRPA 11) (Fig 2) were included in the final analysis after screening 458 articles from different electronic databases. These articles were from different countries and sub-regions of sub-Saharan Africa. Of the 14 articles analysed for the CRAB, South Africa had 4(28.6%), Sudan and Uganda had 2(14.3%) each, while Ethiopia, Senegal, Malawi, Kenya, Nigeria, and Sierra Leone had one each. For the CRPA analysis, Nigeria, Ethiopia, Uganda, and Sudan each had 2 eligible articles included in the final analysis while Malawi, Ghana, and Kenya each had just one eligible article (Tables 1 and 2).

### Meta-analysis of Carbapenem-resistant *A. baumannii*

The pooled prevalence of CRAB in the present study was estimated at 20% (95% Confidence Interval [CI]; 0.04–0.43;  $I^2 = 99\%$ ;  $P < 0.01$ ) (Fig 3). The funnel plot (Fig 4) and Q statistics show high heterogeneity ( $Q = 1452.57$ ,  $I^2 = 99\%$ ;  $P < 0.0001$ ) (S1 Fig) between the CRAB studies.

### Meta-analysis of carbapenem-resistant *P. aeruginosa*

The pooled prevalence of CRPA in the present study was estimated at 8% (95% CI; 0.02–0.17;  $I^2 = 98\%$ ;  $P < 0.01$ ) (Fig 5). Similarly, there was high heterogeneity between CRPA studies analysed as shown by the Q statistics ( $Q = 591.71$ ,  $I^2 = 98.9\%$ ;  $P < 0.0001$ ) and the funnel plot (Figs 6 and S2).



**Fig 2. Distribution of eligible articles included in the final analysis.** A. A total of 14 articles were analysed to determine the pooled prevalence of carbapenem-resistant *Acinetobacter baumannii*. A majority (4) were from South Africa, Sudan and Uganda had 2 each, while Ethiopia, Senegal, Malawi, Kenya, Nigeria, and Sierra Leone had one each. B. A total of 11 articles were analysed to determine the pooled prevalence of carbapenem-resistant *Pseudomonas aeruginosa*, 2 each from Ethiopia, Nigeria, and Sudan while Malawi, Ghana, Kenya, and Uganda had one each.

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Table 1. Data extraction table for carbapenem-resistant *A. baumannii* (CRAB) studies.

First author	Year	Study design	Study country	Study aim	Sample size	Sample source	<i>A. baumannii</i> prevalence	Carbapenem-resistant <i>A. baumannii</i> prevalence (%)	AST method	Carbapenem use
[13]	2021	cross-sectional study	Sudan	To assess the phenotypic and genotypic patterns of antimicrobial resistant strains of <i>Acinetobacter baumannii</i> at hospital settings, Khartoum, Sudan	36	Human	36	17 (47%)	Disc diffusion	Imipenem
[14]	2013	cross-sectional	South Africa	To evaluate and optimise multiplex polymerase chain reaction (M-PCR) assays for the rapid differentiation of the four subgroups of the OXA genes and the subgroups of the MBL genes of <i>A. baumannii</i> .	97	Human	97	61 (62.8%)	Vitek 2	Meropenem and Imipenem
[15]	2021	Longitudinal	Ethiopia	To detect and phenotypically characterize carbapenem-resistant Gram negative bacilli from Ethiopian public health institute	1337	Human	36	4 (0.3%)	Simplified carbapenem inactivation method	Meropenem
[16]	2016	cross sectional study	Uganda	To determine the prevalence of carbapenem-resistant <i>P. aeruginosa</i> and <i>A. baumannii</i> at Mulago Hospital in Kampala Uganda, and to establish whether the hospital environment harbours carbapenem-resistant Gram-negative rods	869	Human	29	9 (1.04%)	Disc diffusion	Imipenem
[17]	2015	cross-sectional study	South Africa	To determine the prevalence of $\beta$ -lactamase genes in multidrug-resistant (MDR) clinical <i>A. baumannii</i> isolates using Multiplex-PCR (M-PCR) assays.	94	Human	94	80 (85.1%)	Vitek 2	Meropenem and Imipenem
[18]	2019	cross sectional study	South Africa	To investigated the 28 genetic determinants of multi-drug resistant <i>A. baumannii</i> (MDRAB) at a teaching hospital in 29 Pretoria, South Africa.	100	Human	100	95 (95%)	Vitek 2	Imipenem and Meropenem
[19]	2012	longitudinal prospective study	Senegal	To identify the presence of <i>A. baumannii</i> carbapenem-resistant encoding genes in natural reservoirs in Senegal, where antibiotic pressure is believed to be low	717	Human	78	6 (0.8%)	Disc diffusion	Imipenem
[20]	2019	cross-sectional	Sudan	To characterize the genotypes and phenotypes associated with carbapenem-resistance in Gram-negative bacilli from patients in Sudan	367	Human	not stated	1 (0.3%)	Disc diffusion	Meropenem
[21]	2022	cross-sectional study	Malawi	To ascertain the antimicrobial resistance in clinical bacterial pathogens from in-patient adults in a tertiary hospital in Malawi	694	Human	26	4 (0.58%)	Disc diffusion	Meropenem
[22]	2021	cross sectional study	Kenya	To understand the antibiotic resistance profiles, genes, sequence types, and distribution of carbapenem-resistant gram from patients in six hospitals across five Kenyan counties.	48	Human	27	27 (56%)	Disc diffusion	Meropenem
[23]	2013	cross sectional study	Nigeria	To report the presence of carbapenem-encoding genes in imipenem-resistant <i>A. baumannii</i> among multidrug-resistant clinical isolates collected from the University College Hospital, Ibadan, south-western Nigeria.	5	Human	3	3 (60%)	Combined disc diffusion test (CDDT)	Imipenem

(Continued)

Table 1. (Continued)

First author	Year	Study design	Study country	Study aim	Sample size	Sample source	<i>A. baumannii</i> prevalence	Carbapenem-resistant <i>A. baumannii</i> prevalence (%)	AST method	Carbapenem use
[24]	2017	cross-sectional	Uganda	To determine the intra-species genotypic diversity among <i>P. aeruginosa</i> and <i>Acinetobacter baumannii</i> isolated from hospitalized patients and the environment at Mulago Hospital	736	Human	7	1 (0.14%)	Disc diffusion	Meropenem
[25]	2020	cross-sectional	Sierra Leone	To assess antibiotic resistance rates from isolates in the urine and sputum samples of patients with clinical features of healthcare-associated infections HAIs.	164	Human	16	2(1.2%)	Vitek 2	Meropenem and Imipenem
[26]	2018	retrospective descriptive study	South Africa	To determine prevalence of culture confirmed sepsis due to <i>A. baumannii</i> , antimicrobial susceptibility and case fatality rates (CFR) due to this organism	93527	Human	399	11 (0.01%)	Disc diffusion	Meropenem and Imipenem

CRAB = Carbapenem-resistant *Acinetobacter baumannii*.

AST = Antimicrobial Susceptibility Testing.

\*The percentage in the bracket is a fraction of the sample size.

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### Prevalence of carbapenem-resistant genes in *A. baumannii* and *P. aeruginosa* in Sub-Saharan Africa

The carbapenemase genes isolated from *A. baumannii* reported in the articles analysed include *bla*<sub>OXA23</sub>, *bla*<sub>OXA48</sub>, *bla*<sub>GES</sub>, *bla*<sub>NDM</sub>, *bla*<sub>VIM</sub>, *bla*<sub>OXA24</sub>, *bla*<sub>OXA58</sub>, *bla*<sub>OXA51</sub>, *bla*<sub>SIM-1</sub>, *bla*<sub>OXA40</sub>, *bla*<sub>OXA66</sub>, *bla*<sub>OXA69</sub>, *bla*<sub>OXA91</sub>. The most common carbapenemase gene in the studies analysed are the *bla*<sub>OXA23</sub> and *bla*<sub>VIM</sub>. On the other hand, the carbapenemase genes reported in *P. aeruginosa* from studies in Sub-Saharan Africa included in this analysis are *bla*<sub>NDM</sub>, *bla*<sub>VIM</sub>, *bla*<sub>IMP</sub>, *bla*<sub>OXA48</sub>, *bla*<sub>OXA51</sub>, *bla*<sub>SIM-1</sub>, *bla*<sub>OXA181</sub>, *bla*<sub>KPC</sub>, *bla*<sub>OXA23</sub>, *bla*<sub>OXA50</sub>. The most frequent among them are the *bla*<sub>VIM</sub> and *bla*<sub>NDM</sub> genes.

### Discussion

Carbapenems are important broad-spectrum antimicrobials of last-resort; hence, resistance to them signifies increased infection mortality, hospital stay duration, and cost of treatment [31]. This challenge is mostly common to infections associated with notorious clinical pathogens such as *A. baumannii* and *P. aeruginosa* [32]. These two Gram-negative pathogens have been linked to varieties of hospital-acquired infections and multidrug resistance.

Carbapenemase-resistant *A. baumannii* in Sub-Saharan Africa in this study was estimated at 20% (95% CI; 0.04–0.43;  $I^2 = 99\%$ ;  $P < 0.01$ ). [33] in their study on the occurrence and frequency of hospital-acquired (carbapenem-resistant) *A. baumannii* in Europe (EUR), Eastern Mediterranean (EMR) and Africa (AFR) stated similar results with a pooled incidence of Hospital Acquired-CRAB of 21.4 (95% CI 11.0–41.3) cases per 1,000 patients in the EUR, EMR and AFR WHO regions. On the other hand, our study revealed the pooled prevalence of CRPA in Sub-Saharan Africa to be 8% (95% CI; 0.02–0.17;  $I^2 = 98\%$ ;  $P < 0.01$ ). This value is relatively low compared to the prevalence of carbapenem resistance reported in Indonesia, India, Italy, China, Germany, and Spain [34]. An additional study from Asia recounted a

Table 2. Data extraction table for carbapenem-resistant *P. aeruginosa* (CRPA) studies.

First author	Year	Study design	Study country	Study aim	Sample size	Sample source	<i>P. aeruginosa</i> prevalence	Carbapenem-resistant <i>P. aeruginosa</i> prevalence (%)	AST method	Carbapenem used
[21]	2022	cross sectional	Malawi	To ascertain antimicrobial resistance (AMR) in clinical bacterial pathogens from in-hospital adult patients at a tertiary hospital in Malawi	694	Human	29	18 (2.5%)	Disc diffusion	Meropenem
[15]	2021	cross sectional	Ethiopia	To detect and phenotypically characterise carbapenemase non-susceptible Gram-negative bacilli at the Ethiopian Public health institute	1337	Human	36	4(0.2%)	Disc diffusion	Meropenem
[16]	2016	cross sectional	Uganda	To determine the prevalence of carbapenem-resistant <i>P. aeruginosa</i> and <i>A. baumannii</i> at Mulago Hospital in Kampala Uganda, and to establish whether the hospital environment harbours carbapenem-resistant Gram-negative rods	869	Human	42	9 (1.15%)	Disc diffusion	Imipenem
[27]	2019	cross sectional	Nigeria	To investigate the occurrence of MBL-producing bacteria in a healthcare facility in Nigeria.	110	Human	Not reported	13(11.8%)	Combined disc method	
[20]	2019	cross sectional	Sudan	To characterise the phenotypes and genotypes associated with carbapenems-resistant in gram-negative bacilli isolated	367	Human	Not reported	14(3.8%)	Disc diffusion	Meropenem
[28]	2019	cross sectional	Ghana	To apply phenotypic and genotypic methods to identify and characterise carbapenem-resistant (CR) Gram-negative bacteria from the hospital environment in Ghana.	111	Human	Not reported	51(45.9%)	Disc synergy	Edoripenem (75%), imipenem (66.7%) and meropenem (58%)
[22]	2021	Cross-sectional	Kenya	To understand the antibiotic resistance profiles, genes, sequence types, and distribution of carbapenem-resistant Gram negative bacteria from patients in six hospitals across five Kenyan counties by bacterial culture, antibiotic susceptibility testing and whole genome sequence analysis. Culture, antibiotic susceptibility testing, and whole-genome sequence analysis.	48	Human	14	14(29.2%)		Meropenem
[29]	2021	cross sectional	Nigeria	To determine the incidence and Molecular Characterization of Carbapenemase Genes in Association with Multidrug-Resistant Clinical Isolates of <i>Pseudomonas aeruginosa</i> from Tertiary Healthcare Facilities in Southwest Nigeria	430	Human	430	71(16.5%)	Disc diffusion	Meropenem and doripenem
[24]	2017	cross sectional	Uganda	To report the intra-species genotypic diversity among <i>P. aeruginosa</i> and <i>A. baumannii</i> isolated from hospitalized patients and the environment at Mulago Hospital, using repetitive elements-based PCR (Rep-PCR) genotyping.	736	Human	9	3(0.4%)		Meropenem

(Continued)



Table 2. (Continued)

First author	Year	Study design	Study country	Study aim	Sample size	Sample source	<i>P. aeruginosa</i> prevalence	Carbapenem-resistant <i>P. aeruginosa</i> prevalence (%)	AST method	Carbapenem used
[29]	2018	Cross sectional	Sudan	To detect (blaVIM, blaIMP and blaNDM) Metallo-β-lactamase genes in Khartoum state	200	Human	54	33(16.5%)	Disc diffusion	Meropenem and/or imipenem.
[30]	2019	Cross sectional	Ethiopia	To identify and determine multi-drug resistant, extended spectrum β-lactamase and carbapenemase producing bacterial isolates among blood culture specimens from pediatric patients less than five years of age from Tikur Anbessa Specialized Hospital using an automated BacT/Alert instrument.	340	Human	Not reported	4(1.1%)	Disc diffusion	Meropenem

CRPA = Carbapenem-resistant *Pseudomonas aeruginosa*.

AST = Antimicrobial Susceptibility Testing.

\*The percentage in the bracket is a fraction of the sample size.

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prevalence of 18.9% CRPA in the Asia-Pacific region. The unexpectedly lower prevalence reported in this study might be due to the absence data from many of the Sub-Saharan African countries. The high heterogeneity observed in this study is most likely not due to publication bias but a result of the different prevalence rates reported in the different studies analysed from different parts of Sub-Saharan Africa and the low number of eligible articles analysed in this study (Figs 5 and 6).

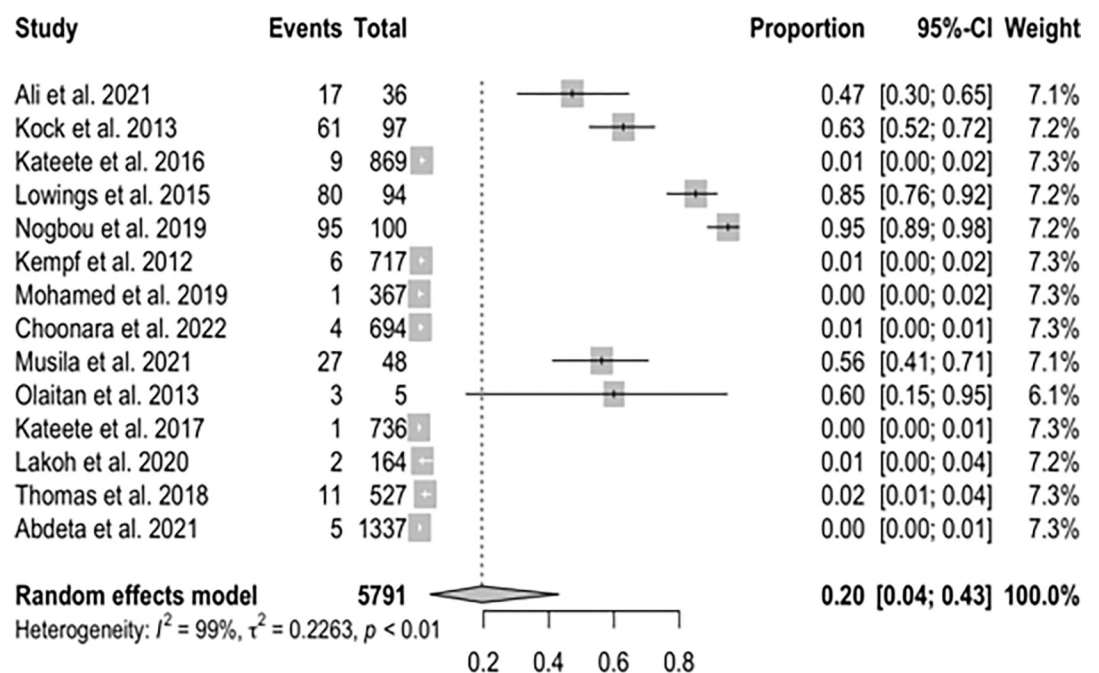


Fig 3. The Forest plots of random-effects meta-analysis show the pooled prevalence of carbapenem-resistant *Acinetobacter baumannii*. CI = Confidence interval.

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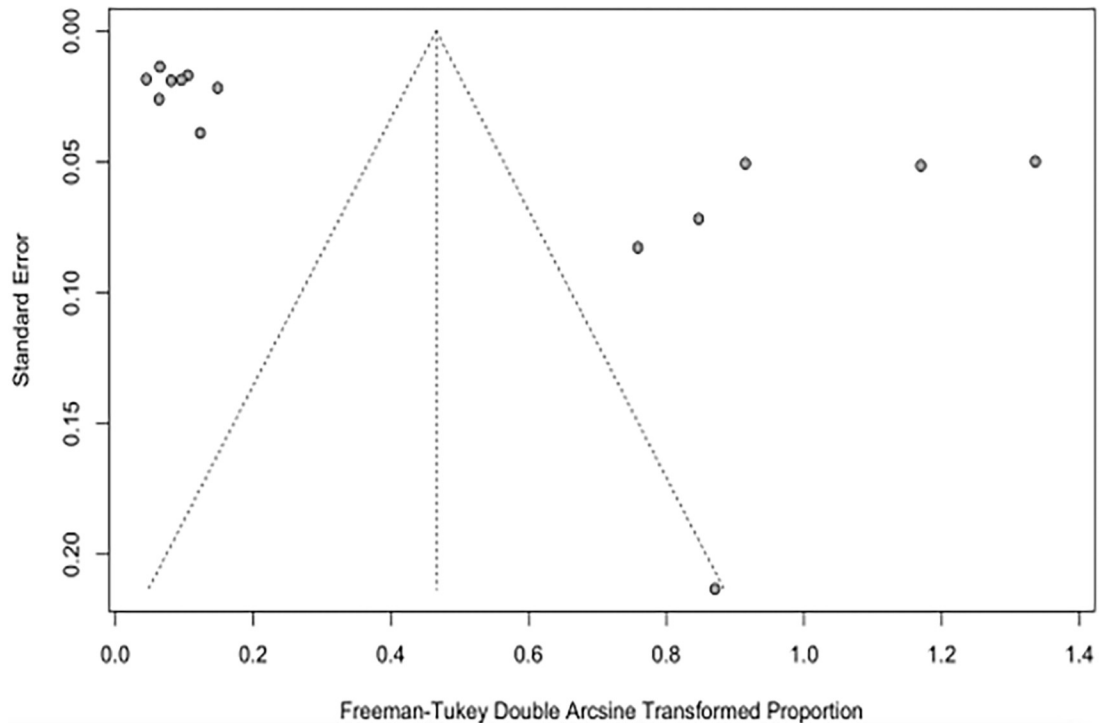


Fig 4. The Funnel plot of CRAB studies shows the publication bias of the study sample.

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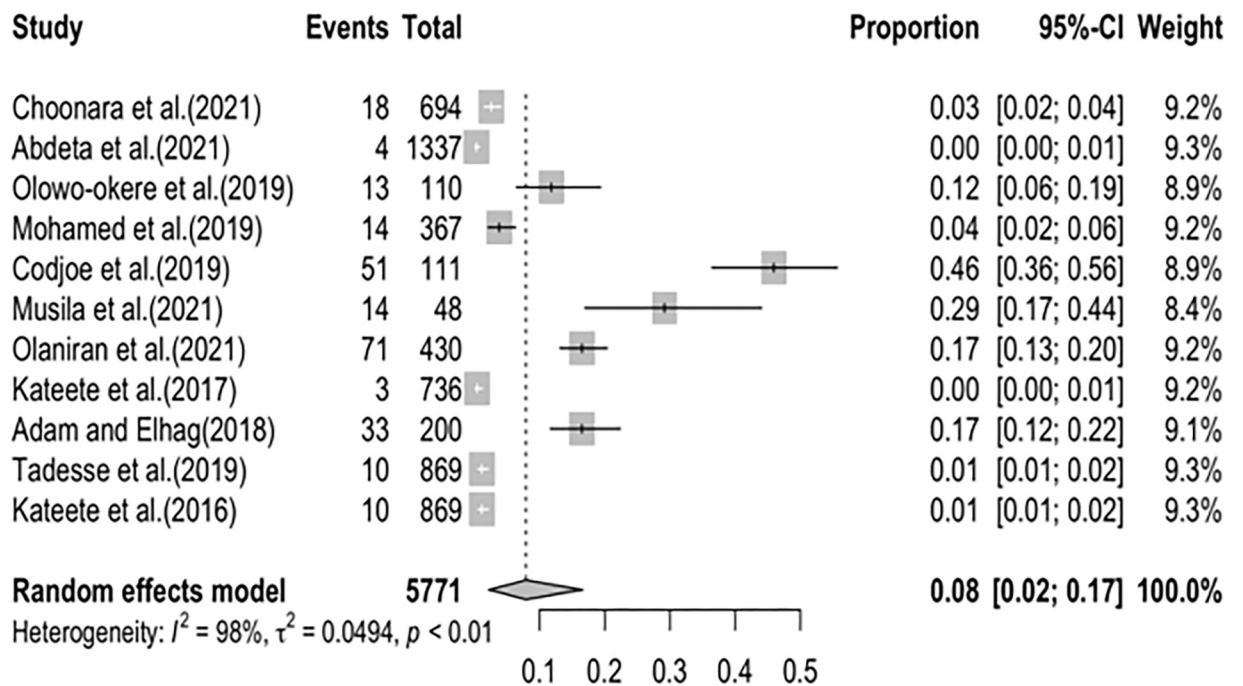
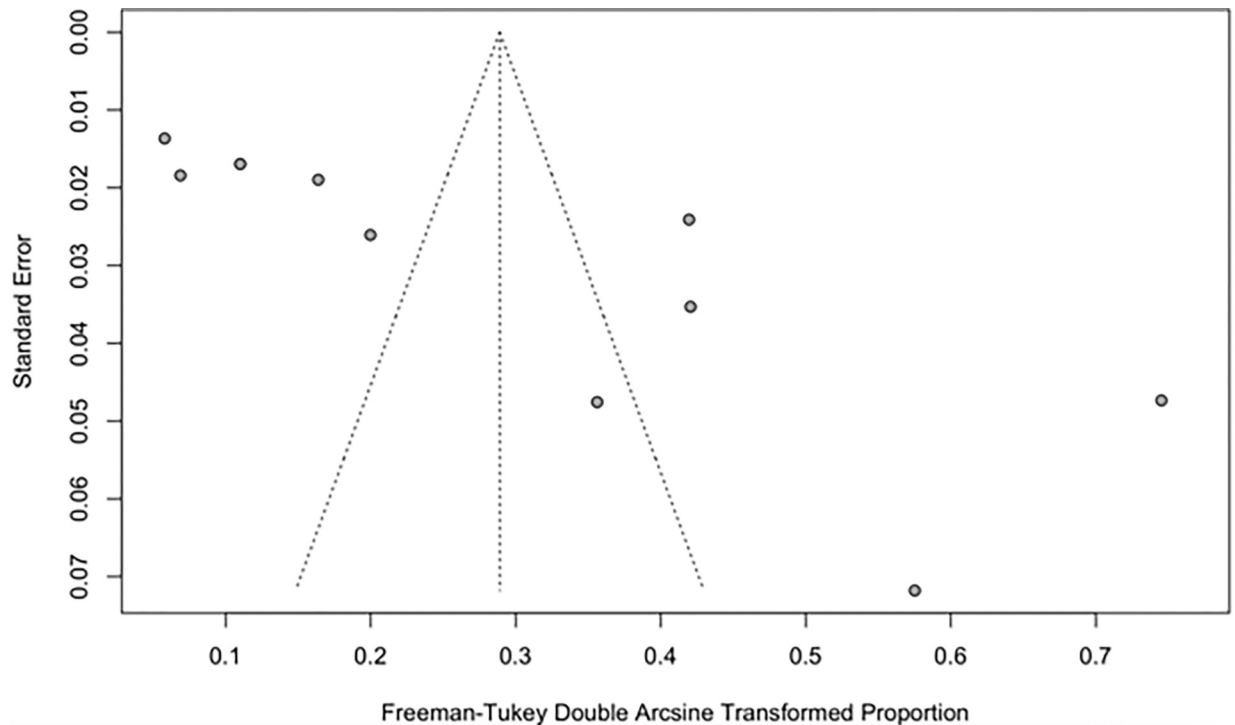


Fig 5. Forest plot showing the pooled prevalence of carbapenem-resistant *Pseudomonas aeruginosa* in Sub-Saharan Africa.

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**Fig 6.** The Funnel plot of CRPA studies shows the publication bias of the study sample.

<https://doi.org/10.1371/journal.pone.0287762.g006>

The most common carbapenem-resistant genes in *P. aeruginosa* in the compared studies in this analysis are the NDM and VIM genes. In the reports of [34] the *bla*<sub>VIM</sub> and *bla*<sub>IMP</sub> were the most prevalent carbapenemase genes in *P. aeruginosa* in Italy and Indonesia. The dominance of OXA-23 genes in CRAB isolates in many of the studies is not surprising as this gene has been associated with carbapenem resistance in this organism since the 1980s [35]. Furthermore, an earlier study indicated that the existence of plasmid encoding OXA-23 alone in *A. baumannii* is sufficient to confer resistance to carbapenem in *A. baumannii* [36]. Even though some of the studies analysed reported carbapenemase genes, many of them did not report the molecular basis of carbapenem resistance in their study. This might be a result of low resources for molecular techniques in many Sub-Saharan African labs.

The pooled prevalence during 2012–2022 should maximally reflect the current status of antibiotic resistance (Tables 1 and 2). Thus, we believe that the current prevalence of antibiotic resistance in *A. baumannii* infection is similar in the Sub-Saharan countries where these studies were carried out, most of which are facing the same degree of severity of antibiotic resistance. Most published studies have concentrated on the hospital epidemiology of these organisms and animal healthcare settings making it difficult to demonstrate the extra-hospital origin of *A. baumannii*. Thus, although antibiotic resistance has long been considered as a modern phenomenon, it predates the concept of selective antibiotic pressure due to clinical antibiotic usage [37].

Over the last few decades, the intensive use of antibiotics in humans and as growth-promoting and as prophylactic agents in livestock have resulted in serious environmental and public health problems since this enhances antimicrobial selective pressure [38]. According to a study by [39], it was discovered that *A. baumannii* isolated from various environmental locations has been linked to nosocomial spread. The resistant bacteria from the extra-hospital

environments may be transmitted to humans, to whom they cause diseases that are difficult to treat with conventional antibiotics.

A major strength of our study is that we included studies comprising both in-patients and out-patients and from a range of different samples, which ensured the representativeness of our estimates for these institutions. However, our study has some limitations. Firstly, the country representativeness of the individual studies is unclear in most cases, limiting our findings' external validity. Secondly, studies are not evenly distributed across the Sub-Saharan regions. Some countries have more studies included in the analysis while there were no studies from others. Consequently, possible differences in CRAB and CRPA incidence and prevalence between the countries may be masked by geographical proximity. Thirdly, due to the relatively low number of hospital-wide studies, our hospital-wide estimates of hospital-acquired *A. baumannii* infections are unlikely to be generalizable.

## Conclusion

*Acinetobacter baumannii* and *Pseudomonas aeruginosa* are two important public health pathogens due to their increasingly multidrug-resistant nature. The prevalence of CRAB and CRPA reported in Sub-Saharan Africa indicates a serious threat to the Sub-Saharan African populace. Sensitization on the dangers of self-medication and poor antibiotics stewardship should be intensified as well as advocacy for the reduction in the use of antibiotics for growth promotion and prophylactics in animals. There is a need for urgent and comprehensive surveillance studies including both hospital environments and communities to determine the true prevalence of these drug-resistant pathogens in sub-Saharan Africa. Moreover, finally, infection control policies promoting personal and environmental hygiene, and appropriate administration of antibiotics by clinicians and veterinarians should be made and enforced to facilitate the reduction of CRAB in the region.

## Supporting information

**S1 Fig. Analysis summary for CRAB.**

(PDF)

**S2 Fig. Analysis summary for CRPA.**

(PDF)

**S1 File.**

(DOCX)

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## References

1. Prestinaci F, Pezzotti P, Pantosti A. Antimicrobial resistance: a global multifaceted phenomenon. *Pathogens and Global Health*. 2015; 109:309–318. <https://doi.org/10.1179/2047773215Y.0000000030> PMID: 26343252
2. O' Neill J. Tackling drug-resistant infections globally: final report and recommendations. *Review on Antimicrobial Resistance*. 2016; 84.
3. Murray CJ, Ikuta KS, Sharara F. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *The Lancet*. 2022; 399:629–655. [https://doi.org/10.1016/s0140-6736\(21\)02724-0](https://doi.org/10.1016/s0140-6736(21)02724-0) PMID: 35065702
4. Armstrong T, Fenn SJ, Hardie KR. JMM Profile: Carbapenems: a broad-spectrum antibiotic. *Journal of Medical Microbiology*. 2021 <https://doi.org/10.1099/jmm.0.001462> PMID: 34889726
5. Ma CW, Ng KKH., Yam BHC. Rapid Broad Spectrum Detection of Carbapenemases with a Dual Fluorogenic-Colorimetric Probe. *Journal of the American Chemical Society*. 2021; 143:6886–6894. <https://doi.org/10.1021/jacs.1c00462> PMID: 33909441
6. Meletis G. Carbapenem resistance: overview of the problem and future perspectives. *Therapeutic Advances in Infectious Disease*. 2016; 3:15–21. <https://doi.org/10.1177/2049936115621709> PMID: 26862399
7. Santajit S, Indrawattana N. Mechanisms of Antimicrobial Resistance in ESKAPE Pathogens. *Biomed Res Int*. 2016:2475067. <https://doi.org/10.1155/2016/2475067> PMID: 27274985
8. Vivo A, Fitzpatrick MA, Suda KJ, Jones MM, Perencevich EN, Rubin MA et al. Epidemiology and outcomes associated with carbapenem-resistant *Acinetobacter baumannii* and carbapenem-resistant *Pseudomonas aeruginosa*: a retrospective cohort. *BMC Infectious Diseases*. 2022; 22:291. <https://doi.org/10.1186/s12879-022-07436-w> PMID: 35610601
9. Whiteside A, Zebryk N. New and Re-Emerging Infectious Diseases in Sub-Saharan Africa. 2017;299–313.
10. Zerbo A, Delgado RC, González PA. Water sanitation and hygiene in Sub-Saharan Africa: Coverage, risks of diarrheal diseases, and urbanization. *Journal of Biosafety and Biosecurity*. 2021; 3:41–45. <https://doi.org/10.1016/j.jobb.2021.03.004>
11. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Systematic Review*. 2021; 10:89. <https://doi.org/10.1186/s13643-021-01626-4> PMID: 33781348
12. Zhanel GG, Simor AE, Vercaigne L. Imipenem and Meropenem: Comparison of In Vitro Activity, Pharmacokinetics, Clinical Trials and Adverse Effects. *Canadian Journal of Infectious Diseases*. 1998; 9:215–228. <https://doi.org/10.1155/1998/831425> PMID: 22346545
13. Ali KM, Ali AH, Ali MA, Hamza SH, Hassan SM, Osman WA, et al. Phenotypic and Genotypic Patterns of Antimicrobial Resistant Strains of *Acinetobacter baumannii* at Hospital Settings, Khartoum State, Sudan. *EC Microbiology*. 2021; 17(3):44–54.
14. Kock MM, Bellomo AN, Storm N, Ehlers MM. Prevalence of carbapenem resistance genes in *Acinetobacter baumannii* isolated from clinical specimens obtained from an academic hospital in South Africa. *South African Journal of Epidemiology Infection*. 2013; 28(1):28–32.
15. Abdeta A, Bitew A, Fentaw S, Tsige E, Assefa D, Lejisa T, et al. Phenotypic characterization of carbapenem non-susceptible Gram-negative bacilli isolated from clinical specimens. *PLoS ONE*. 2021; 16(12): e0256556. <https://doi.org/10.1371/journal.pone.0256556> PMID: 34855767
16. Kateete DP, Nakanjako R, Namugenyi J, Erume J, Joloba ML, Najjuka CF. Carbapenem resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii* at Mulago Hospital in Kampala, Uganda (2007–2009). *Springer Plus*. 2016; 5:1308.

17. Lowings M, Ehlers MM, Dreyer AW, Kock MM. High prevalence of oxacillinases in clinical multidrug-resistant *Acinetobacter baumannii* isolates from the Tshwane region, South Africa—an update. *BMC Infectious Diseases*. 2015; 15:521.
18. Nogbou ND, Phofa DT, Nchabeleng M, Musyoki AM. Genetic determinants of multi-drug resistance in *Acinetobacter baumannii* at an academic hospital in Pretoria, South Africa. *International Journal of Infectious Diseases*. 2020; 101(1):35–60. <https://doi.org/10.1016/j.ijid.2020.09.125>
19. Kempf M, Rolain JM, Diatta G, Azza S, Samb B, Mediannikov O, et al. Carbapenem Resistance and *Acinetobacter baumannii* in Senegal: The Paradigm of a Common Phenomenon in Natural Reservoirs. *PLoS ONE*. 2012; 7(6):e39495. <https://doi.org/10.1371/journal.pone.0039495> PMID: 22745768
20. Mohamed MEA, Ahmed AO, Kidir ESB, Sirag B, Ali MA. Phenotypic and genotypic characterization of carbapenems-resistant clinical Gram-negative bacteria from Sudan. *Edorium Journal of Microbiology*. 2019; 5:100011M08MM2019.
21. Choonara FE, Haldorsen BC, Ndhlovu I, Saulosi O, Maida T, Lampiao F et al. Antimicrobial susceptibility profiles of clinically important bacterial pathogens at the Kamuzu Central Hospital in Lilongwe, Malawi. *Malawi Medical Journal* 2022; 34 (1):9–16. <https://doi.org/10.4314/mmj.v34i1.3> PMID: 37265833
22. Musila L, Kyany'a C, Maybank R, Stam J, Oundo V, Sang W. Detection of diverse carbapenem and multidrug resistance genes and high-risk strain types among carbapenem non-susceptible clinical isolates of target gram-negative bacteria in Kenya. *PLoS ONE*. 2021; 16(2):e0246937. <https://doi.org/10.1371/journal.pone.0246937> PMID: 33617559
23. Olaitan AO, Berrazeg M, Fagade OE, Adelowo OO, Alli JA, Rolain JM. Emergence of multidrug-resistant *Acinetobacter baumannii* producing OXA-23 carbapenemase, Nigeria. *International Journal of Infectious Diseases*. 2013; 17:e469–e470.
24. Kateeta DP, Nakanjako R, Okee M, Joloba ML, Najjuka CF. Genotypic diversity among multidrug resistant *Pseudomonas aeruginosa* and *Acinetobacter* species at Mulago Hospital in Kampala, Uganda. *BMC Research Notes*. 2017; 10:284–294. <https://doi.org/10.1186/s13104-017-2612-y> PMID: 28705201
25. Lakoh S, Li L, Sevalie S, Guo X, Adekanmbi O, Yang G et al. Antibiotic resistance in patients with clinical features of healthcare-associated infections in an urban tertiary hospital in Sierra Leone: a cross-sectional study. *Antimicrobial Resistance and Infection Control*. 2020; 9:38–48. <https://doi.org/10.1186/s13756-020-0701-5> PMID: 32087751
26. Thomas R, Wadula J, Seetharam S, Velaphi S. Prevalence, antimicrobial susceptibility profiles and case fatality rates of *Acinetobacter Baumannii* sepsis in a neonatal unit. *The Journal of Infection in Developing Countries*. 2018; 12(4):211–219. <https://doi.org/10.3855/jidc.9543> PMID: 31851629
27. Olowo-okere A, Abdullahi MA, Ladidi BK, Suleiman S, Tanko N, Ungokore HY et al. Emergence of Metallo- $\beta$ -Lactamase Producing Gram-negative Bacteria in a Hospital with no History of Carbapenem Usage in Northwest Nigeria. *Ife Journal of Science*. 2019; 21(2):323–332. <https://doi.org/10.4314/ijfs.v21i2.6>
28. Codejoe FS, Donkor ES, Smith TJ, Miller K. Phenotypic and Genotypic Characterization of Carbapenem-Resistant Gram-Negative Bacilli Pathogens from Hospitals in Ghana. *Microbial Drug Resistance*. 2019; 25(10):1449–1457. <https://doi.org/10.1089/mdr.2018.0278> PMID: 31237486
29. Olaniran OB, Adeleke OE, Donia A, Shahid R, Bokhari H. Incidence and Molecular Characterization of Carbapenemase Gene in Association with Multidrug-Resistant Clinical Isolates of *Pseudomonas aeruginosa* from Tertiary Healthcare Facilities in Southwest Nigeria. *Current Microbiology*. 2022; 79:27–41. <https://doi.org/10.1007/s00284-021-02706-3> PMID: 34905085
30. Adam MA, Elhag WI. Prevalence of metallo- $\beta$ -lactamase acquired genes among carbapenems susceptible and resistant Gram-negative clinical isolates using multiplex PCR, Khartoum hospitals, Khartoum Sudan. *BMC Infectious Diseases*. 2018; 18:668–674. <https://doi.org/10.1186/s12879-018-3>
31. Tadesse MM, Matebie ZA, Tullu KD. Multi-drug resistant, extended spectrum beta-lactamase and carbapenemase-producing bacterial isolates among children under five years old suspected of blood-stream infection in a specialized Hospital in Ethiopia: Cross- Sectional Study. *Research Square*. 2019; 1–14. <https://doi.org/10.21203/rs.2.149521/v1>
32. Friedman ND, Temkin E, Carmeli Y. The negative impact of antibiotic resistance. *Clinical Microbiology and Infection*. 2016; 22:416–422. <https://doi.org/10.1016/j.cmi.2015.12.002> PMID: 26706614
33. Olaniyi A, Niklas W, Thomas H, Iruka NO, Tim E, Robby M. The incidence and prevalence of hospital-acquired (carbapenem resistant) *Acinetobacter baumannii* in Europe, Eastern Mediterranean and Africa: a systematic review and meta-analysis. *Emerging Microbes and Infections*. 2019; 8(1):1747–1759.
34. Wang MG, Liu ZY, Liao XP. Retrospective Data Insight into the Global Distribution of Carbapenemase-Producing *Pseudomonas aeruginosa*. *Antibiotics*. 2021; 10:548. <https://doi.org/10.3390/antibiotics10050548> PMID: 34065054

35. Evans BA, Amyes SGB. OXA  $\beta$ -Lactamases. *Clinical Microbiology Reviews*. 2014; 27:241–263. <https://doi.org/10.1128/cmr.00117-13> PMID: 24696435
36. Heritier C, Poirel L, Lambert T, Nordmann P. Contribution of acquired carbapenem-hydrolyzing oxacillinases to carbapenem resistance in *Acinetobacter baumannii*. *Antimicrobial Agents of Chemotherapy*. 2005; 49:3198–3202.
37. D'Costa VM, King CE, Kalan L, Morar M, Sung WW. Antibiotic resistance is ancient. *Nature*. 2011; 477:457–461. <https://doi.org/10.1038/nature10388> PMID: 21881561
38. Anane AY, Apalata T, Vasaikar S, Okuthe GE, Songca S. Prevalence and molecular analysis of multi-drug-resistant *Acinetobacter baumannii* in the extra-hospital environment in Mthatha, South Africa. *Brazilian Journal of Infectious Diseases*. 2019; 23(6):371–380.
39. Gros M, Petrovic M, Barcelo D. Multi-residue analytical methods using LC-tandem MS for the determination of pharmaceuticals in environmental and wastewater samples: a review. *Analytical and Bioanalytical Chemistry*. 2006; 386:941–952. <https://doi.org/10.1007/s00216-006-0586-z> PMID: 16830112