Genetic support of carbapenemases: a One Health systematic review and meta-analysis of current trends in Africa

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Abstract

Antimicrobial resistance (AMR) is a public health threat globally. Carbapenems are β-lactam antibiotics used as last-resort agents for treating antibiotic-resistant infections. Mobile genetic elements (MGEs) play an important role in the dissemination and expression of antimicrobial resistance genes (ARGs), including the mobilization of ARGs within and between species. The presence of MGEs around carbapenem-hydrolyzing enzymes, called carbapenemases, in bacterial isolates in Africa is concerning. The association between MGEs and carbapenemases is described herein. Specific plasmid replicons, integrons, transposons, and insertion sequences were found flanking specific and different carbapenemases across the same and different clones and species isolated from humans, animals, and the environment. Notably, similar genetic contexts have been reported in non-African countries, supporting the importance of MGEs in driving the intra- and interclonal and species transmission of carbapenemases in Africa and globally. Technical and budgetary limitations remain challenges for epidemiological analysis of carbapenemases in Africa, as studies undertaken with whole-genome sequencing remained relatively few. Characterization of MGEs in antibiotic-resistant infections can deepen our understanding of carbapenemase epidemiology and facilitate the control of AMR in Africa. Investment in genomic epidemiology will facilitate faster clinical interventions and containment of outbreaks.

Keywords: antimicrobial resistance; carbapenemase; mobile genetic elements; Africa; horizontal gene transfer; One Health

Introduction

Infectious diseases are caused by disease-causing pathogens, which are responsible for most morbidities and mortalities in low- and middle-income countries.[1-3] Tuberculosis (TB) and human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) are the most common infectious diseases with the highest toll on human health worldwide, together accounting for more than 2 million deaths annually.[4-6] However, infections caused by Gram-negative bacteria (GNB) are increasingly becoming a clinical challenge owing to the emergence and spread of antimicrobial resistance genes (ARGs).[7, 8] By acquiring ARGs, bacteria are able to grow in the presence of therapeutic concentrations of administered antimicrobials. Hence, infections caused by these bacteria become untreatable, putting patients and animals at risk of fatal morbidities and complicated sequelae or death.[1, 7, 8] Moreover, common surgical operations and childbirth may lead to increased death as a result, as there will be no effective antibiotics to prevent bacterial infections arising from such procedures and common infections.[3] It has been estimated that antimicrobial resistance (AMR) will cause up to 10 million deaths annually by 2050 and push 24 million people into extreme poverty by 2030 if nothing is done to stem the tide of increasing AMR.[9]

Several international reports have pointed out the problem of AMR and its consequences on healthcare and economic levels.[1, 10] Notably, this threat is not only limited to humans, animals—in particular, food animals raised in large-scale livestock/industrial farms—are also prone to bacterial and viral infections.[10, 11] The current coronavirus (COVID-19) pandemic has underlined the interrelatedness of human and animal medicine, as well as shown the need for effective antimicrobial therapeutics. First, it demonstrates that animal infections can be transmitted to humans, either directly through contact and animal food products, or, indirectly, through the environment. Second, the world will be unable to contain any large-scale outbreak of any infectious disease without effective therapeutics, be it medicines or vaccines.[12] This interrelationship between humans, animals, and the environment, through the food chain, wastewater from farms and communities, industrial and hospital effluents, and surface and groundwater, has necessitated the need to coordinate research into these three areas: a concept called One Health.[13, 14] One Health involves the investigation of AMR through a combination of human, animal (including animal products), and environmental (including agriculture, aquaculture, surface and ground water, soils, and effluents) samples to identify the spread of ARGs and pathogens between these three domains.[10, 15, 16]

AMR has been more pronounced among GNB than Gram-positive bacteria owing to the latter's elaborate cell envelope (capsules, outer membrane, peptidoglycan, and cytoplasmic membrane) that prevents antimicrobial molecules from passing into their cytosols.[17] Among GNB, Enterobacterales are commonly implicated in multidrug-resistant (MDR) infections in humans and animals.[7, 8] Furthermore, GNB are able to exchange plasmids (between the same and different species), enabling them to expand on their ARGs repertoire. GNB have been associated with MDR infections mediated by resistance plasmids.[7, 8, 18]

To maintain the edge over pathogens, use of some antimicrobials is reserved only for fatal or difficult-to-treat pathogens. However, many GNB have managed to acquire or develop resistance to even these reserved antibiotics, specifically carbapenems and polymyxins (e.g., colistin).[3, 19] This makes AMR in GNB particularly concerning, especially because AMR cannot be limited to any one country.

The varied socioeconomic, infrastructure, health, sanitary, and skilled labor challenges in Africa complicate AMR on this continent. Specifically, the absence of medical insurance and surveillance programs,[20] poor sanitation and unhygienic practices (such as littering, open defecation, open gutters, and open refuse dumps), the dearth of wastewater and sewage treatment plants,[15] and the presence of substandard antimicrobial agents make the AMR situation in Africa very challenging.[21, 22] Africa's geographical location, moreover, attracts many travelers, labor, and cargo, which increases AMR dissemination.[23] Self-medication and over-the-counter prescription of antibiotics in Africa are common, while regulations on the prescription-only sale of antimicrobials (comparable to the United States, for example) are absent.[24-26] The gap between legislation and practice has resulted in the emergence of extensive drug resistance and pandrug resistance,[27] including resistance to colistin.[28-30] Furthermore, the high prevalence of HIV/AIDS and TB in Africa, which, among other things, cause depletion of $CD4^+$ T lymphocytes and compromise immunity,[6, 31-33] predisposes many Africans to MDR pathogens.[34, 35]

Carbapenems and carbapenem resistance

β-Lactams are one of the most popular antimicrobial agents used for treating bacterial infections. They interfere with the cell wall synthesis of susceptible bacteria by binding to penicillin-binding proteins (PBPs), located in the cytoplasmic membrane and involved in the synthesis of the cell wall, leading to cell death.[19, 36] β-Lactams include penicillins, cephalosporins, carbapenems, and monobactams.[37] Carbapenems are characterized by the presence of carbon instead of sulfur in the β-lactam ring.[38] Carbapenems include imipenem, meropenem, doripenem, and ertapenem. They differ in their chemical structure and, consequently, their activity and pharmacokinetics.[39] Carbapenems are the last-resort β-lactams for treating serious bacterial infections. Resistance to carbapenems may lead to worse outcomes owing to limited therapeutic options for carbapenem-resistant (CR) infections; or owing to high toxicity that is caused by other non–β-lactam antimicrobials.[40] Carbapenem resistance may be attributed to one or more of the following mechanisms: alterations in PBPs, porin mutations, efflux pumps; extended-spectrum β-lactamase overexpression; and carbapenemase production. Porin mutations inhibit the entry of carbapenems into the bacterial cells, while efflux pumps expel them from the cells.[19, 41, 42]

β-Lactamases (βL) are classified as either serine β-lactamases (SβLs), in which a serine residue is present at the active site, or metallo-β-lactamases (MβLs), which have divalent zinc at their active site.[37] βL are further distinguished by one of two schemes: the Ambler molecular classification and the Bush–Jacoby–Medeiros functional classification. The Ambler classification categorizes βL into molecular classes, namely, A, B, C, and D, according to the sequence of the amino acids.[37] Classes A, C, and D are SβLs, whereas class B includes MβLs.[43] On the other hand, the updated Bush–Jacoby–Medeiros scheme classifies βL according to the hydrolysis profile into three groups, with multiple subgroups in each main group.[44] Carbapenemases are βL that hydrolyze carbapenems, leading to decreased susceptibility or resistance.[45] Carbapenemases may be either intrinsic (naturally occurring), that is, carried on chromosomes, or acquired, that is, are carried on plasmids. As one example, *Acinetobacter* spp. have several naturally occurring ($bla_{\text{OXA-51}}$) and acquired carbapenemases ($bla_{\text{OXA-23}}$).[46, 47] Several MβL variants, namely, bla_{NDM}, bla_{VIM}, and bla_{IMP}, are plasmid-encoded and found in Enterobacterales, *Pseudomonas* spp., and *Acinetobacter* spp.[48]

Despite the diverse plethora of carbapenemases identified globally, extensive attention is directed to five carbapenemases because of their dissemination worldwide and different variantsa :[49] *Klebsiella pneumoniae* carbapenemase (KPC; *bla*$_{KPC}$), *bla*$_{OXA-48-like}$, New Delhi MβL (*bla*$_{NDM}$), Verona integron–encoded MβL (*bla*$_{VIM}$), and imipenemase MβL (*bla*$_{IMP}$).[37] KPC belongs to Ambler class A and functional group 2; OXA-48 belongs to class D and functional group 2d; and NDM, VIM, and IMP belong to Ambler class B and functional group 3.

The dissemination of carbapenemases is mostly associated with mobile genetic elements (MGEs), such as plasmids, integrons, and transposable elements (insertion sequences [IS] and transposons [Tn])[50] (see Appendix S1 (A), online only, for further details).

Evidence before this review

Systematic reviews and meta-analyses describing the MGEs facilitating the dissemination of carbapenemases in Africa are nonexistent. The earliest systematic[51] or narrative[36] reviews on carbapenemases in Africa were published in 2015 and 2016, respectively. Moreover, these two articles did not include a One Health component. According to our knowledge, our review here is the first work to describe the genetic environments of carbapenemases systematically and statistically from a One Health perspective in Africa.

Methods

Literature search strategy

The literature selection criteria were according to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[52] The selected articles were retrieved from PubMed. They described MGEs in the environments of carbapsenemase genes in GNB. The following keywords were applied: (“antibiotic” OR “anti-microbial resistance” OR “carbapenemases”); (“carbapenem” OR “imipenem” OR “meropenem” OR “ertapenem” OR “doripenem”); (“mobile genetic elements” OR “plasmid” OR “transposon” OR “integrons” OR “insertion sequences” OR “genetic environment” OR “genetic context”); (“Africa” OR “northern Mediterranean countries”). The search was conducted in a factorial fashion. The last literature search was performed on December 4, 2020 and was restricted to articles that were published in the English language (full research articles, short communications, or case reports) with the exclusion of review articles. There was no restriction for the studied microorganisms or the origin of isolates. Also, publications in which carbapenemases were not associated with MGEs are not reported herein as they fall outside the scope of this review.

Statistical analysis

The extracted data were organized into contingency tables in Microsoft Excel and analyzed with GraphPad Prism® version 9.0.2. One sample *t*-test was used to determine the significance of the association between the different variables: country, sample sources, species, clones, carbapenemase types, and MGEs. Means, medians, and variance (standard deviation) were determined using columns and descriptive statistics. The contingency tables were used to generate charts and maps.

Results and discussion

The literature search yielded 56,732 publications. The elimination of duplicates, review articles, and non-African studies resulted in 535 manuscripts. Examination of the full texts resulted in the inclusion of 80 eligible studies (Fig. S1, online only). The included studies were from 15 African countries: Algeria, Angola, Egypt, Ghana, Ivory Coast, Kenya, Libya, Mali, Morocco, Nigeria, São Tomé and Príncipe, Senegal, South Africa, Tunisia, and Uganda (Fig. 1).

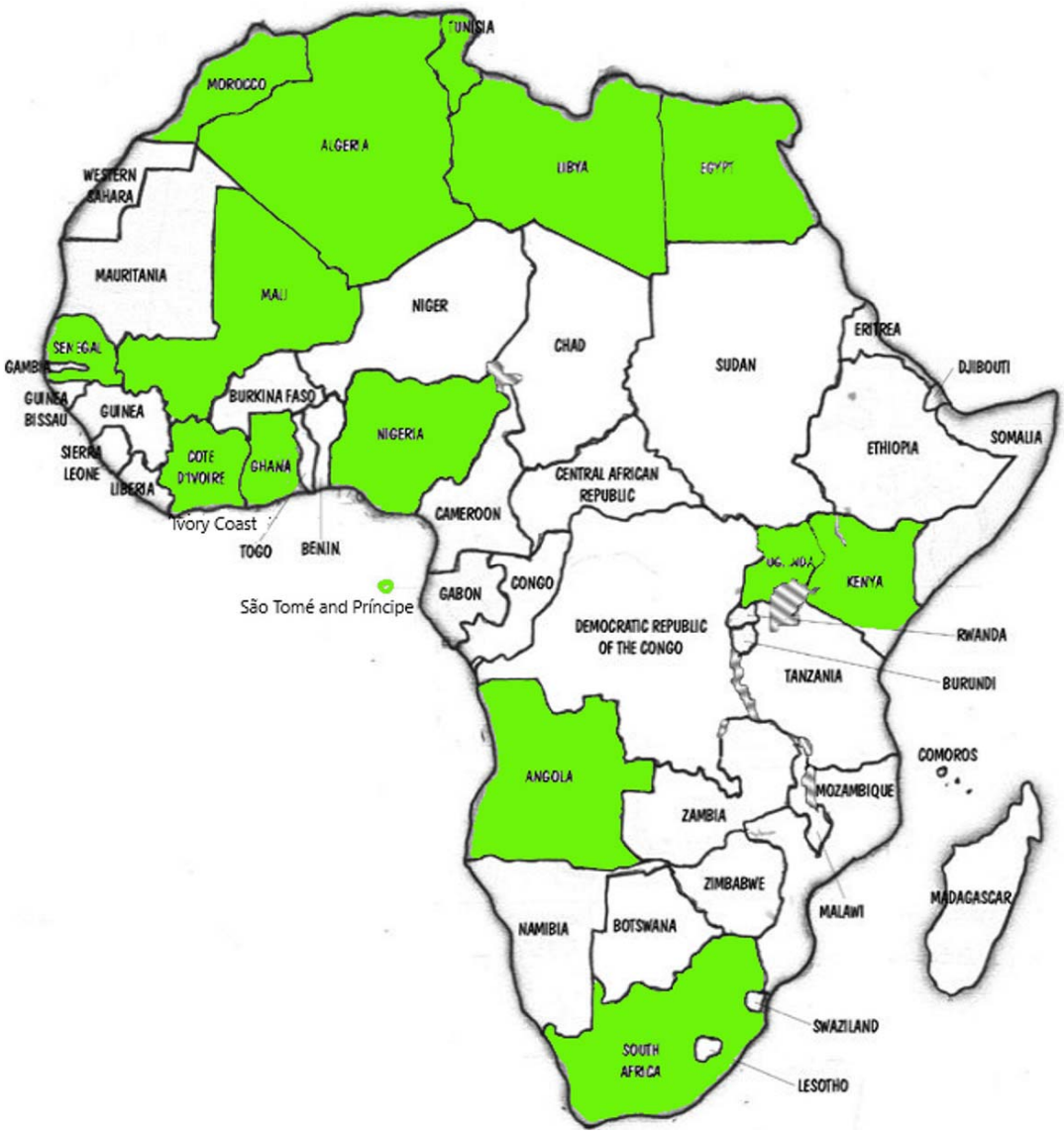


Figure 1. African countries from where the included studies were conducted.

Carbapenemase-positive species and clones

Carbapenemase-positive (CP) species in Africa were mainly GNB belonging to *Acinetobacter baumannii*, *Acinetobacter junii*, *Acinetobacter nosocomialis*, *Citrobacter*

freundii, *Escherichia coli*, *Enterobacter* spp., *K. pneumoniae*, *Klebsiella oxytoca*, *Klebsiella quasipneumoniae*, *Klebsiella michiganensis*, *Morganella morganii*, *Proteus* spp., *Providencia rettgeri*, *Providencia stuartii*, *Pseudomonas aeruginosa*, *Pseudomonas putida* group, *Salmonella enterica* serotype Kentucky, and *Serratia marcescens*, making them "critical priority pathogens" as per the World Health Organization's classification.[53, 54] Among the 15 countries, CP-GNB diversity was higher in Algeria (*n* = 6 species), Egypt (*n* = 5), Morocco (*n* = 6), and Tunisia (*n* = 6) (in northern Africa), Nigeria (*n* = 9) (in West Africa), Angola (*n* = 5), and South Africa (*n* = 8) (in southern Africa) (Fig. 2). Overall, while the detection of CP-GNB in Africa was relatively low, several CP-GNB species (*n* = 18) were reported. The presense of CP-GNB data from only 15 African countries likely does not represent a low prevalence of these critical priority pathogens but rather limited research, surveillance, and molecular epidemiology studies in Africa. In addition, inadequate investment into molecular laboratories and a dearth of skilled diagnostic technicians in molecular microbiology explain the fewer reports of CP-GNB in Africa.[8]

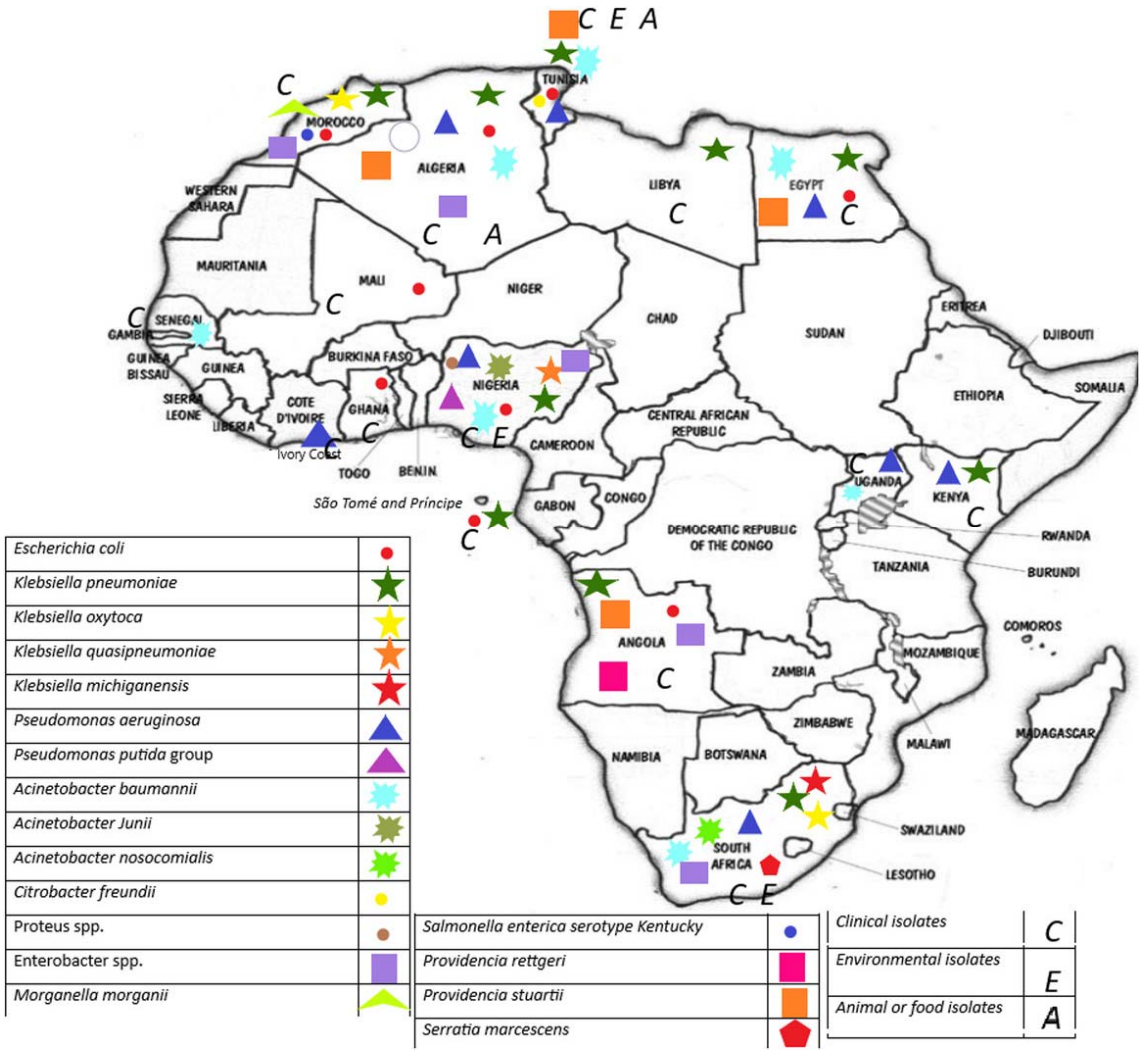
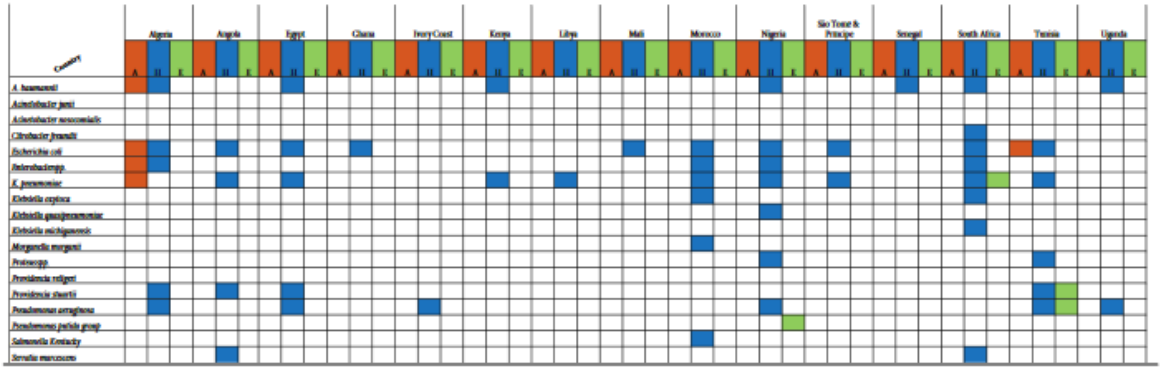


Figure 2. Distribution and origin of isolates in the investigated countries.

CP *E. coli* and *K. pneumoniae* have been reported in eight countries, Algeria, Angola, Egypt, Morocco, Nigeria, São Tomé and Príncipe, South Africa, and Tunisia, while CP *K. oxytoca, K. quasipneumoniae*, and *K. michiganensis* have been isolated in Morocco, Nigeria, and South Africa, respectively. *P. aeruginosa* has been isolated in Algeria, Egypt, Ivory Coast, Kenya, Nigeria, South Africa, Tunisia, and Uganda; *P. putida* was detected in Nigeria; *A. baumannii* was detected in Algeria, Egypt, Kenya, Nigeria, Senegal, South Africa, Tunisia, and Uganda; and *A. junii* and *A. nosocomialis* have been isolated in Nigeria and South Africa, respectively. Other species have also been reported: *C. freundii* in Tunisia; *Proteus* spp. in Nigeria and Tunisia; *Enterobacter* spp. in Angola, Algeria, Egypt, Morocco, Nigeria, and South Africa; *P. rettgeri* in Angola; *P. stuartii* in Algeria and Egypt; *S. enterica* serotype Kentucky, *M. morganii*, and *S. marcescens* in Morocco and South Africa (Fig. 2).

CP-GNB have been isolated from clinical, animal, and environment samples, demonstrating the broad distribution and diverse sampling sources of these MDR species (Table 1 and Fig. 2). Among the studies (n = 80), most isolates were from clinical samples (n = 75, 92.6%), followed by animal or food sources (n = 3, 3.7%), environmental samples (n = 2, 2.5%), and clinical and environmental samples (n = 1, 1.2%). The distribution of CP-GNB species isolated from animals, humans, and the environment per country is summarized in Table 1. Clinical specimens are the most common sources of carbapenemases in Africa; the number of isolates in the investigated studies was 3439, with isolates having KPC (n = 13, 0.38%), NDM (n = 272, 7.90%), VIM (n = 266, 7.73%), IMP (n = 11, 0.32%), OXA-48-like (n = 300, 8.72%), OXA-23-like (n = 687, 19.98%), OXA-24/40-like (n = 20, 0.58%), OXA-51-like (n = 883, 24.22%), OXA-58-like (n = 46, 1.34%), OXA-235 (n = 1, 0.01%), SIM (n = 15, 0.44%), GES-5 (n = 8, 0.23%), and GES-14 (n = 7, 0.20%) being detected (Dataset 1, online only). By comparison, carbapenemases from environmental isolates, including KPC (n = 1, 0.01%), NDM (n = 2, 0.06%), VIM (n = 10, 0.29%), OXA-48-like (n = 17, 0.49%), and OXA-51-like (n = 1, 0.01%), and those from food/animal sources, including KPC (n = 1, 0.01%), OXA-48-like (n = 12, 0.35%), OXA-23-like (n = 2, 0.06%), and OXA-51-like (n = 2, 0.06%), were fewer.

Table 1. Distribution of carbapenemase-positive GNB species across animal, human, and environmental samples from African countries



CP-GNB clones

Bacteria are typed into clones/strains to enable easy identification and tracking of infections from their source to their intermediary hosts.[55] Several bacterial typing schemes have been developed to classify bacterial strains into clones, see (Appendix S1 (B), online only) for

further details. From our analysis, several clones (sequence types) in CP-GNB species were described, including *A. baumannii* with 61 sequence types (STs), followed by *K. pneumoniae* (*n* = 46 STs), *E. coli* (*n* = 19 STs), and *P. aeruginosa* (*n* = 15 STs) (see Table S1, online only). These clones were isolated from various sources in Africa, reflecting their wide circulation and, hence, the possibility of disseminating ARGs vertically. In particular, the detection of carbapenemase genes in the same clones (i.e., same STs) found in different hosts (animals, humans, or environment) and countries shows the possible dissemination of such genes in clonal strains.

Clinical *A. baumannii* STs were found in Egypt[56] and were shared among other countries, including Nigeria[57] (ST1 and ST10), Kenya[58] (ST2), and Algeria[59] and Tunisia[60] (ST85). In addition, *A. baumannii* ST25 was identified in Algeria[59] and Kenya,[58] ST113 in Kenya[58] and Nigeria,[57] and ST208 in South Africa[61] and Egypt;[62, 63] *K. pneumoniae* ST11 was identified in Libya,[64] Morocco,[65] and Tunisia,[66] while ST14 was found in Tunisia[66] and two South African studies;[67, 68] *K. pneumoniae* ST17 was found in Egypt[69] and South Africa,[18] while ST196 was detected in Morocco[65] and Tunisia;[66] *K. pneumoniae* ST307 was identified in Morocco,[70] South Africa,[18] and Tunisia,[71] while ST392 occurred in Morocco[65] and Tunisia;[72] and *E. coli* ST410 was found in clinical isolates in Egypt,[73] Ghana,[74] and São Tomé and Príncipe.[75] Interestingly, both *E. coli* and *K. pneumoniae* showed relatively high dissemination of certain STs among the same and different countries at different timeframes, suggesting their persistence within those countries. The wide distribution of *K. pneumoniae* ST15, ST101, and ST147, and of *E. coli* ST167 indicates that they can be high-risk clones. For example, *K. pneumoniae* ST15 was identified in clinical samples in Angola,[76] Kenya,[77] Morocco,[65, 78] and Tunisia,[66] and in environmental samples in South Africa.[79] In addition, *K. pneumoniae* ST101 was identified in Algeria,[80] Libya,[81] Morocco,[65] South Africa,[68] and three different Tunisian studies;[66, 72, 82] *K. pneumoniae* ST147 was identified in Algeria,[83] Egypt,[69] Libya,[64] and five different Tunisian studies.[71, 72, 82, 84, 85]

The three predominant *K. pneumoniae* STs—ST15, ST101, and ST147—were associated with *bla*$_{\text{NDM-1}}$, *bla*$_{\text{OXA-48}}$, *bla*$_{\text{OXA-204}}$, and *bla*$_{\text{OXA-232}}$. These STs have also been isolated in non-African countries, for example, ST15 has been recorded in Hungary,[86] ST101 in Japan,[87] and ST147 in Pakistan[88] and Germany.[89] In addition, *K. pneumoniae* ST15, ST101, and ST147 have been associated with *bla*$_{\text{KPC}}$ in Bulgaria (ST15),[90] India (ST101),[91] and Portugal (ST147).[92]

E. coli ST167 was present in clinical isolates in Angola,[76] Egypt,[73] São Tomé and Príncipe,[75] and South Africa,[68] and in isolates from mussel samples in Tunisia;[93] this clone harbored *bla*$_{\text{OXA-181}}$, *bla*$_{\text{NDM-1}}$, *bla*$_{\text{NDM-5}}$, and *bla*$_{\text{KPC-3}}$, and has been reported in Italy.[94, 95]

By contrast to the above, clones of *P. aeruginosa, E. cloacae*, *E. asburiae*, *E. kobei*, *E. hormaechei*, *E. cloacae* complex, *Enterobacter* spp., *C. freundii*, *K. michiganensis*, and *S. enterica* serovar Kentucky were not as widespread across African countries and samples as those of *A. baumannii, E. coli*, and *K. pneumoniae* (Fig. 3). This reflects the variations in the detected species as well as the unavailability of ST determination in all studies that investigate this topic. Statistical analysis of clonality data was impossible owing to the absence of data in all articles we evaluated.

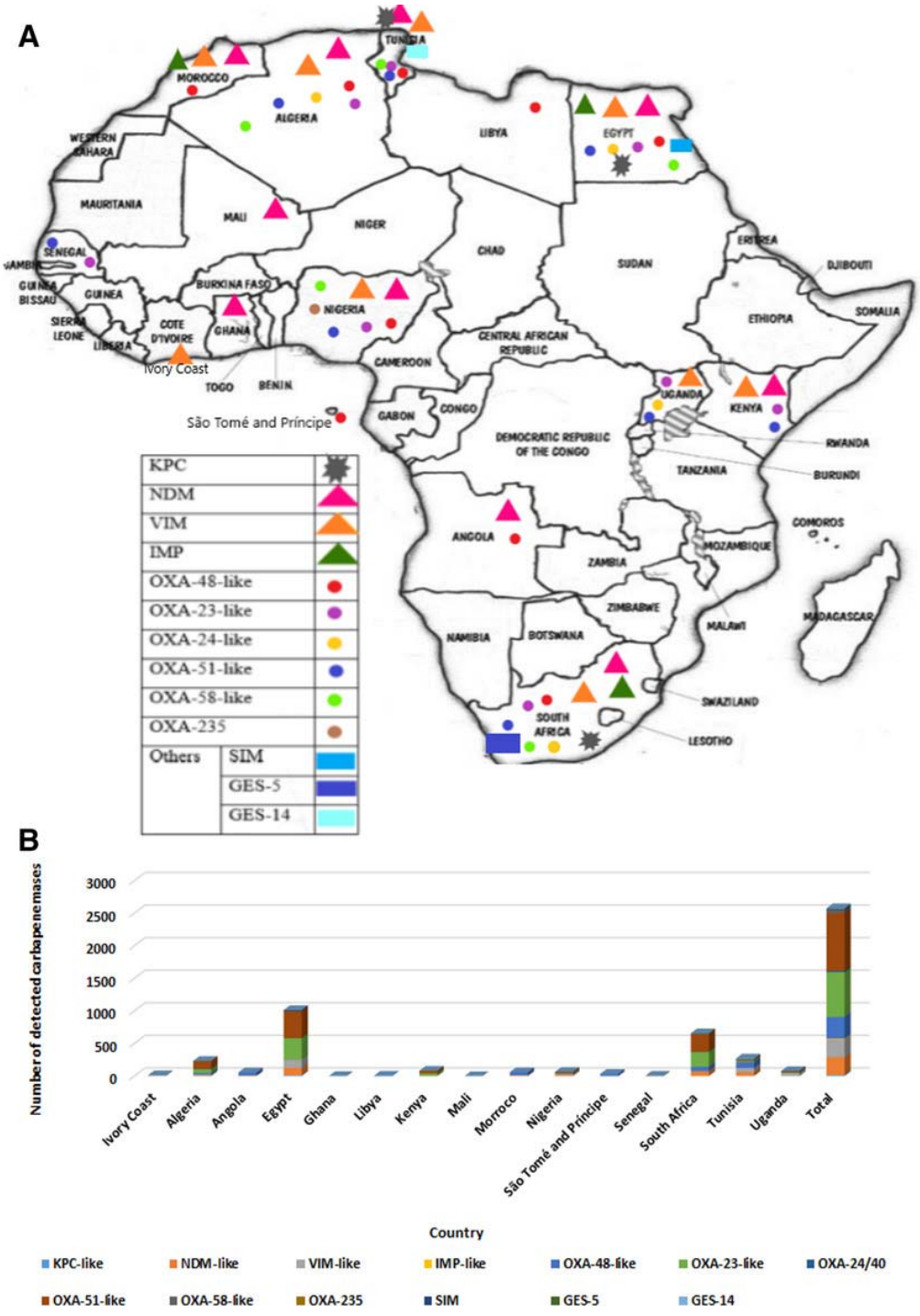


Figure 3. Distribution of carbapenemases in the investigated countries.

Prevalence of carbapenemases in African countries

The most common carbapenemases were *bla*$_{\text{NDM-like}}$, *bla*$_{\text{OXA-48-like}}$, *bla* $_{\text{OXA-23-like}}$, *bla*$_{\text{OXA-51-like}}$, and *bla*$_{\text{VIM-like}}$, with *bla*$_{\text{NDM-like}}$, *bla*$_{\text{OXA-48-like}}$, and *bla*$_{\text{VIM-like}}$ being reported from clinical, animal, and environmental specimens (Fig. 3). Other carbapenemases, such as *bla*$_{\text{KPC-like}}$, *bla*$_{\text{GES-like}}$, *bla*$_{\text{IMP-like}}$, *bla*$_{\text{SIM}}$, *bla*$_{\text{OXA-24/40}}$, *bla*$_{\text{OXA-58-like}}$, and *bla*$_{\text{OXA-235}}$, were relatively rare.

SβLs

Clinical isolates with *bla*$_{KPC}$ were identified in *K. pneumoniae* in Tunisia[66] and *A. baumannii* in Egypt;[96] *bla*$_{KPC}$ was detected in *K. pneumoniae* from environmental samples in South Africa;[79] and *E.coli* isolates from animal sources harbored *bla*$_{KPC}$ in Tunisia.[93] The presence of KPC in animals and the environment suggests they are being transferred by humans and animals, and that the environment can serve as reservoirs of this ARG (Fig. 3).

The most common carbapenemase reported was oxacillinase, with the *bla*$_{OXA-48}$ variant identified in clinical *K. pneumoniae* in Algeria,[80, 97, 98] Egypt,[99] Libya,[64, 81] Morocco,[65, 70, 100-102] Nigeria,[103] South Africa,[18] and Tunisia;[66, 71, 72, 82, 84, 85, 104, 105] it was also identified in environmental isolates in South Africa.[79] *E. coli* harboring *bla*$_{OXA-48}$ was identified in clinical isolates in Algeria,[98, 106] Morocco,[70, 101, 107] Nigeria,[103] and Tunisia;[66] other species, such as *K. oxytoca* in Morocco,[65] *M. morganii* in Morocco,[101] and *Enterobacter* spp. in Algeria,[98] Morocco,[65, 70] and Nigeria[103] also harbored this variant. Other *bla*$_{OXA-48-like}$ variants, such as *bla*$_{OXA-181}$, were detected in *K. pneumoniae* in Angola,[76] São Tomé and Príncipe,[75] and South Africa;[18, 67, 79] *K. oxytoca* in South Africa;[67] *E. coli* in Angola,[76] Egypt,[73] and São Tomé and Príncipe;[75] and *E. cloacae* in Angola.[76] Additionally, *bla*$_{OXA-204}$ was detected in clinical *K. pneumoniae* in Tunisia;[72, 82, 105, 108] *bla*$_{OXA-232}$ was found in clinical *K. pneumoniae* in South Africa[68] and Tunisia;[85] and *bla*$_{OXA-505}$ was found in environmental isolates of *K. pneumoniae* in South Africa.[79] Also, *bla*$_{OXA484}$ was detected in clinical *E. coli* in Egypt.[109]

In addition, *bla*$_{OXA-23-like}$, *bla*$_{OXA-24-like}$, *bla*$_{OXA-51-like}$, *bla*$_{OXA-58-like}$, and *bla*$_{OXA235}$ were detected mostly in clinical *Acinetobacter* spp. In particular, *bla*$_{OXA-23-like}$ was detected in Egypt[56, 96, 110] and South Africa,[61, 111] and specifically reported in clinical *A. baumannii* in Algeria,[59, 112, 113] Egypt,[62, 63, 99, 114] Kenya,[58, 115] Nigeria,[57] Senegal,[116] South Africa,[117, 118] Tunisia,[119, 120] and Uganda;[121] *bla*$_{OXA-23}$ was detected in clinical *P. aeruginosa* in Tunisia;[122] *bla*$_{OXA-24-like}$ ARGs were detected in clinical *A. baumannii* in Algeria,[59] Egypt,[99] South Africa,[111] and Uganda;[121] *bla*$_{OXA-40}$ was detected in Egypt;[62] *bla*$_{OXA-72}$ was detected in Algeria;[112] and *bla*$_{OXA-51-like}$ ARGs were detected mostly in clinical *A. baumannii* in Egypt,[56, 96, 110, 123] Kenya,[58] and South Africa.[61, 111] Other *bla*$_{OXA-51-like}$ variants were specifically identified in clinical *A. baumannii* in Algeria,[59, 112] Egypt,[99, 114] Senegal,[116] South Africa,[118] and Uganda;[121] *bla*$_{OXA-66}$ in clinical isolates in Kenya[58] and Tunisia;[120] and *bla*$_{OXA-94}$ in clinical isolates in Tunisia.[60] Worryingly, *bla*$_{OXA-98}$ was identified in environmental *K. pneumoniae* in South Africa.[79]

Two Egyptian studies, by Al-Hassan *et al*. and Lopes *et al*.,[62,63] Nigerian study, Ogbolu *et al*.,[57] reported a remarkable variety of the *bla*$_{OXA-51-like}$ genes. Al-Hassan *et al*. detected *bla*$_{OXA-64}$, *bla*$_{OXA-65}$, *bla*$_{OXA-66}$, *bla*$_{OXA-69}$, *bla*$_{OXA-71}$, *bla*$_{OXA-78}$, *bla*$_{OXA-89}$, and *bla*$_{OXA-94}$, while Lopes *et al*. reported *bla*$_{OXA-51}$, *bla*$_{OXA-64}$, *bla*$_{OXA-66}$, *bla*$_{OXA-68}$, *bla*$_{OXA-69}$, and *bla*$_{OXA-100}$. Ogbolu *et al*. detected *bla*$_{OXA-51}$, *bla*$_{OXA-67}$, *bla*$_{OXA-68}$, *bla*$_{OXA-69}$, *bla*$_{OXA-91}$, *bla*$_{OXA-130}$, *bla*$_{OXA-64}$, *bla*$_{OXA-180}$, and *bla*$_{OXA-203}$. *Bla*$_{OXA-58-like}$ was detected in clinical *A. baumannii* in South Africa,[61, 111] while *bla*$_{OXA-58}$ was specifically detected in Algeria,[59] Egypt,[62, 99] and Nigeria;[57] *bla*$_{OXA-97}$ was detected in Tunisia;[124] and *bla*$_{OXA235}$ was detected in Nigeria.[57]

MβLs

In various studies in Egypt, *bla*$_{IMP}$ was detected in clinical *A. baumannii* and *P. aeruginosa;*[96, 125] it was also reported in *K. pneumoniae* and *E. cloacae* isolates in Morocco[101] and in *A. baumannii* isolates in South Africa[111] (Fig. 3). In addition, *bla*$_{NDM}$ was identified in *A. baumannii*, *K. pneumoniae*, *P. aeruginosa*, *E. coli*, and *P. mirabilis*,

particularly in Egypt, South Africa, and Tunisia; specifically, *bla*$_{NDM}$ was detected in clinical *K. pneumoniae*,[87, 91] *P. aeruginosa*,[125] *E. coli*,[73, 109, 126] *A. baumannii*,[56, 63, 96, 114, 123] and *P. stuartii*[73] in Egypt. In South Africa, *bla*$_{NDM}$ was detected in clinical[18, 127] and environmental *K. pneumoniae*,[79] and in clinical *A. baumannii*.[111, 118] Pedersen *et al*. detected *bla*$_{NDM}$ in clinical *K. pneumoniae*, *K. michiganensis*, *E. coli*, *C. freundii*, and *Enterobacter* spp.[68] isolates. In Tunisia, *bla*$_{NDM}$ was reported in clinical *K. pneumoniae*, *A. baumannii*, and *P. mirabilis;*[60, 71, 72, 84, 128] in clinical *K. pneumoniae* in Morocco;[78, 102] in *A. baumannii* and *K. pneumoniae* in Algeria[59, 83] and Kenya;[58, 77] in *K. pneumoniae* and *K. quasipneumoniae* in Nigeria;[129, 130] in *A. baumannii* in Senegal;[116] in *E. coli* in Ghana[74] and Mali;[131] and in *K. pneumoniae*, *E.coli*, *P. rettgeri*, and *P. stuartii* in Angola[76] (Fig. 3).

The other MβL commonly identified in Africa was *bla*$_{VIM}$. A relatively high count of *bla*$_{VIM}$ was detected in Egypt in clinical *A. baumannii*,[63, 96, 110, 114] *P. aeruginosa*,[73, 125] and *E. hormaechei*.[132] In Tunisia, *bla*$_{VIM}$-positive clinical *P. aeruginosa*[122, 133, 134] and clinical and environmental *P. aeruginosa*[135] were reported. The widespread distribution of *bla*$_{VIM}$ transcended from North Africa throughout the continent: Algeria (clinical *E. coli*, *K. pneumoniae*, *P. stuartii*, and *P. aeruginosa*),[136, 137] Ivory Coast (clinical *K. pneumoniae* and *P. aeruginosa*),[138] Morocco (clinical *S. enterica* serotype Kentucky),[139] Nigeria (clinical *E. coli*, *K. pneumoniae*, *P. aeruginosa*, and *P. mirabilis*),[129] South Africa (clinical *K. pneumoniae*),[111, 140] and Uganda (clinical *A. baumannii* and *P. aeruginosa*).[121] Additionally, *bla*$_{VIM}$ was detected in the *P. putida* group (*P. plecoglossicida* and *P. guariconensis*) from environmental sources[141] (Fig. 3), suggesting that these clinically important ARGs can have environmental reservoirs.

Other MβL and SβL carbapenemases, such as Seoul imipenemase (*bla*$_{SIM}$) and Guiana extended spectrum β-lactamase (*bla*$_{GES}$), that is, *bla*$_{GES-5}$ and *bla*$_{GES-14}$ (which were proved to be true carbapenemases),[142] were detected in clinical isolates from limited studies. In Egypt, *bla*$_{SIM}$ was detected in the clinical isolates of *A. baumannii;*[96] *bla*$_{GES-5}$ was detected in *K. pneumoniae* isolates in South Africa;[68] and *bla*$_{GES-14}$ was detected in *A. baumannii* isolates in Tunisia.[143] There was a statistically significant association between some carbapenemases and the investigated countries (Dataset S1, online only); *bla*$_{OXA-48-like}$ and *bla*$_{OXA-24/40}$ were significantly associated with the countries in which they were reported (P = 0.011 and P = 0.0425), respectively.

Carbapenemase-associated MGEs

Plasmids

Plasmid exchange is the main mechanism of carbapenemase distribution within and between GNB species. Although chromosomal carbapenemases have been reported, plasmid-based carbapenemase genes are the rule rather than the exception.[18, 144] Notably, specific plasmid replicons have been associated with specific carbapenemases, internationally as well as in specific countries. In Africa, IncF plasmids are very common, particularly in South Africa, where they were found in environmental[79] or clinical[18, 68, 127] *K. pneumoniae* with *bla*$_{NDM-1}$; similarly, clinical *K. pneumoniae* from Tunisia,[72, 84] Mexico,[145] and Iran[146] had the same plasmid type with *bla*$_{NDM-1}$. Additionally, *bla*$_{KPC-like}$ has been reported on IncF plasmids in South Africa, where *bla*$_{KPC-2}$ occurs in environmental *K. pneumoniae*,[79] and in Tunisia, where *bla*$_{KPC-3}$ was found in *E.coli* isolated from depurated mussels.[93] IncF plasmids have also been detected with *bla*$_{KPC-2}$ in environmental *Citrobacter* isolates in China[147] and clinical *K. pneumoniae* in Portugal.[148]

A/C plasmids have also been isolated with *bla*$_{NDM-1}$ in clinical *K. pneumoniae* from South Africa[18] and in clinical *E. coli*, *K. pneumoniae*, and *P. stuartii* from Egypt,[73] findings from our study which corroborates another one from South America.[149] Isolates from Tunisia host A/C plasmids with *bla*$_{OXA-48}$[105] and *bla*$_{OXA-204}$;[72, 82, 105, 108] the localization of *bla*$_{OXA-48}$ and *bla*$_{OXA-204}$ on A/C plasmids has also been confirmed in Taiwan[150] and France,[151] respectively, showing the importance of specific plasmids in disseminating carbapenemases across species, different hosts, and borders.

Two other replicons, IncR and IncX$_3$, harbor different carbapenemases. IncR was detected in clinical *K. pneumoniae* with *bla*$_{NDM-1}$ in Algeria[83] and Egypt,[69] in agreement with findings from Kocsis *et al*. in clinical *K. pneumoniae* and *C. koseri* from Croatia.[152] IncX$_3$ was associated with *bla*$_{OXA-181}$ in clinical *K. pneumoniae, E. coli*, or *E. cloacae* in studies from Angola,[76] Egypt,[73] and São Tomé and Príncipe;[75] *bla*$_{NDM-5}$ was carried on IncX$_3$ in *E. coli* in South Africa;[68] and similar findings in Mali showed *E. coli* harbored *bla*$_{NDM-5}$,[131] in agreement with some Chinese studies that confirmed the existence of *bla*$_{OXA-181}$ or *bla*$_{NDM-5}$ on IncX$_3$ plasmids in *K. pneumoniae* or *E. coli* isolates.[153-155]

Several studies we evaluated showed the association between ARGs and either IncL/M or IncL incompatibility groups, which have been divided into subgroups, namely, IncL, IncM$_1$, and IncM$_2$, depending on newly investigated molecular factors.[156, 157] Studies from Algeria,[80, 97] Libya,[64, 81] Morocco,[70] South Africa,[18] and Tunisia[82] showed that *bla*$_{OXA-48}$ was located on L/M plasmids in clinical *K. pneumoniae*; Jesumirhewe *et al*. found similar results in *E. coli*, *E. cloacae*, and *K. pneumoniae* in Nigeria;[103] *bla*$_{OXA-48}$ was localized on IncL in two Tunisian studies;[72, 84] studies from Iran,[146] Ireland,[158] Palestine,[159] and the United States[160] found *bla*$_{OXA-48}$ on IncL or IncL/M; Soliman *et al*. found *bla*$_{NDM-5}$ on an IncI1-Iγ–type plasmid in clinical *E. coli* in Egypt;[126] and IncH has been associated with *bla*$_{NDM-1}$ in *E. coli* isolates in Ghana,[74] as well as in clinical *K. pneumoniae* in India.[161]

Rare carbapenemases, such as *bla*$_{GES-5}$, were disseminated by an IncQ-type plasmid in clinical *K. pneumoniae* in South Africa,[68] and the GR6 plasmid replicon was associated with *bla*$_{GES-14}$ in clinical *A. baumannii* in Tunisia.[143] Interestingly, IncQ-borne *bla*$_{GES-5}$ and GR6 plasmid–borne *bla*$_{GES-14}$ have been found, respectively, in *E. cloacae* isolated in Canada[162] and *A. baumannii* from Kuwait[163] and various European countries.[164] Col-type plasmids were found harboring *bla*$_{OXA-181}$ and *bla*$_{OXA-232}$ in clinical *K. pneumoniae* in two South African studies,[18, 68] as well as in Germany,[89] China,[165] and the United States.[160] These observations suggest that specific plasmids shuttle specific carbapenemases across different species and countries, both in Africa and globally. Interestingly, different *bla*$_{VIM}$ variants have been found on different plasmids; specifically, *bla*$_{VIM-1}$ on IncF (in clinical *K. pneumoniae* from South Africa)[140] and *bla*$_{VIM-2}$ on IncW (in clinical *S. enterica* serotype Kentucky from Morocco)[139] and on IncH (in clinical *E. hormaechei* from Egypt).[132] However, different *bla*$_{VIM-like}$ variants from other continents were carried on other replicons; for example, *bla*$_{VIM-1}$ was carried on IncH in *E. cloacae* from Spain,[166] on IncW in *S. liquefaciens* and *K. oxytoca* from Greece,[167] and on IncR in *K. pneumoniae* from Greece.[168] Moreover, *bla*$_{VIM-4}$ has also been shown to be carried on IncW in *E. coli* from Russia.[169]

In South Africa, the application of whole-genome sequencing (WGS) has enabled the recognition of several plasmid replicons in GNB. Ekwanzala *et al*. identified IncFIB, IncFII(K), IncFII, IncFII(pCoo), IncHI1B, IncL/M, IncR, IncX3, and Col replicons (ColKP3, ColRNAI, and Col4401) in CR *K. pneumoniae* using WGS, with each isolate hosting three to nine plasmid replicons.[79] Kopotsa *et al*. identified multireplicon plasmids in 75% of the

investigated isolates (n = 6), with the highest combination of replicons being detected in two isolates; one harbored *bla*$_{\text{OXA-48}}$ (with six replicon groups) and the other harbored *bla*$_{\text{NDM-1}}$ (with seven replicon groups).[18] Additionally, Ramsamy *et al*. found *bla*$_{\text{NDM-1}}$ on multireplicon plasmids in South Africa;[127] in Nigeria, Ogbolu and coworkers found different Col plasmids (Col, Col-pvc, and ColMG828) in *A. baumannii* isolates harboring *bla*$_{\text{NDM}}$;[57] and *bla*$_{\text{NDM}}$ was further identified on IncP[128] and IncF[71] plasmids, as well as on the other Inc groups, in Tunisia. Despite the variation of the replicons among the investigated countries, only IncL/M had a statistically significant association with countries (P = 0.021313) (Fig. 4; and Dataset S1).

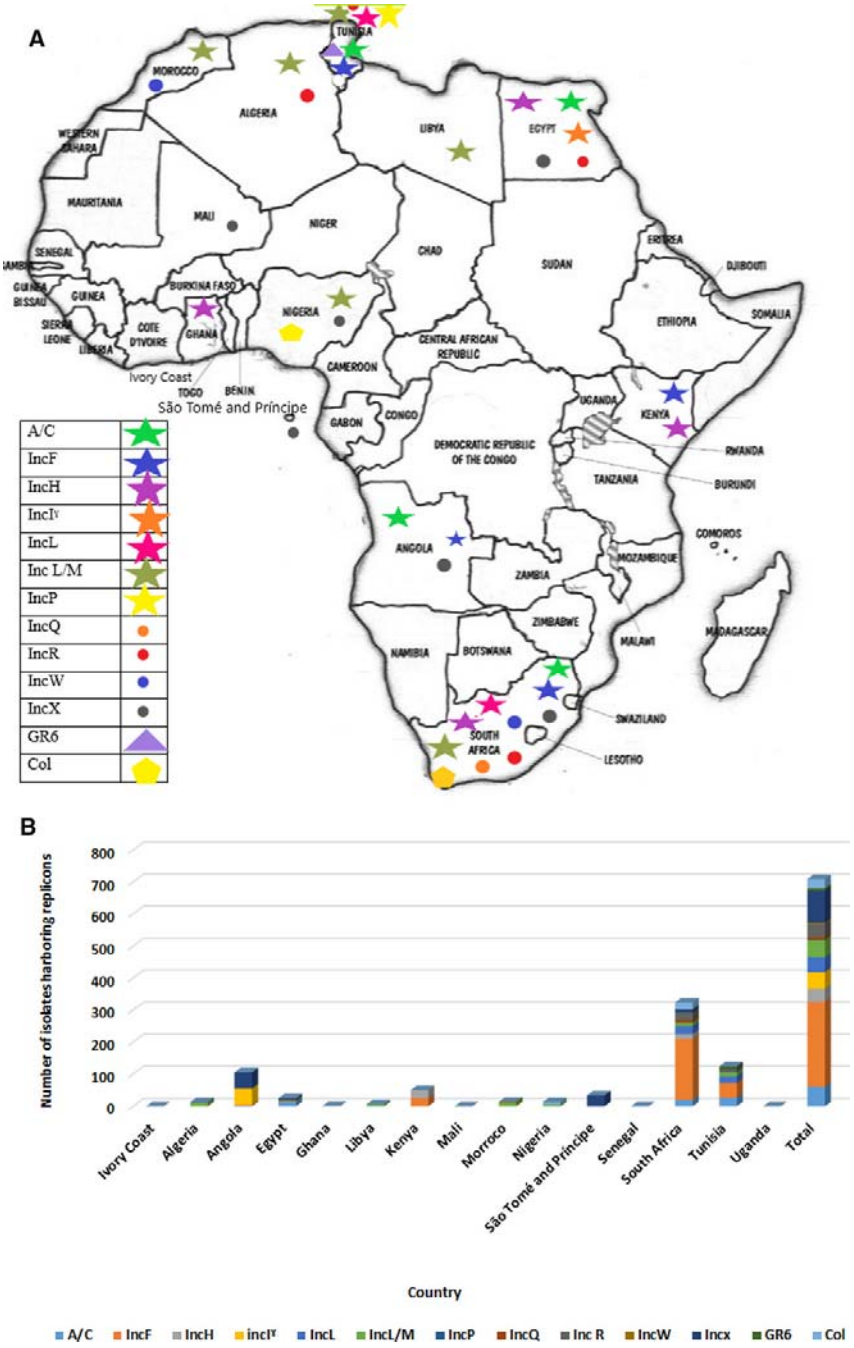


Figure 4. Distribution of plasmid replicons in the investigated countries.

Carbapenemases are usually found on mobile plasmids that exchange between different species and clones.[144, 170, 171] Conjugation or transformation assays are common techniques that were used to determine the mobility of plasmids, and a limited number of studies (in Africa) have shown the immobility of the gene encoding the carbapenemase, depicting its location on immobile plasmids or chromosomes. For example, in a Tunisian study by Mansour *et al*., *bla*$_{\text{VIM-2}}$–positive *P. aeruginosa* did not give positive results with electroporation, suggesting a chromosomal location of *bla*$_{\text{VIM-2,}}$ particularly in the absence of signals (by Southern hybridization) from plasmids of such isolates;[134] a chromosomal localization was similarly inferred for *bla*$_{\text{OXA-23}}$ in *A. baumannii*.[119]

In a study by Lahlaoui *et al*., two techniques, conjugation and transformation, were applied to *K. pneumoniae* isolates harboring *bla*$_{\text{OXA-232}}$; conjugation failed to transfer activity, while transformation succeeded.[85] Charfi-Kessis *et al*. investigated the genetic environment of *bla*$_{\text{OXA-23}}$ in two *A. baumannii* isolates and concluded that it was chromosomally located in one isolate, owing failure of conjugation, but was plasmid-borne in another isolate from which it was successfully transferred.[120] The same observation was made by Saïdani *et al*., in which *bla*$_{\text{OXA-48}}$ failed to transfer by conjugation in *C. freundii*, suggesting a chromosomal or immobile plasmid location. Yet, in Tunisia, *bla*$_{\text{OXA-48}}$ was transconjugated successfully from *K. pneumoniae* harboring an A/C replicon[104] and from an *E.coli* in Morocco.[107] Furthermore, in an Algerian study, conjugation proved the chromosomal location of *bla*$_{\text{NDM}}$ in one isolate, while a plasmid location in another isolate.[59] Robin *et al*. concluded *bla*$_{\text{VIM-19}}$ to be on a plasmid via several transconjugants and transformants.[136] However, transconjugation or transformation assays alone cannot confirm the presence of ARGs on chromosomes, unless whole-genome or whole-plasmid sequencing is done. Most instances of successful conjugation involve *K. pneumoniae*, considered a challenging pathogen owing to the presence of a unsually high plasmid load that provides an interesting point for further investigation.b [172]

Integrons

Compared to other integron classes, class 1 integrons are more predominantly associated with carbapenemases in Africa (Fig. 5): only *intI1* showed a significant association with the investigated African countries (P = 0.0309039) and was commonly found in clinical GNB isolates compared with environmental and animal/food isolates (*intI2* was found in Tunisia, where it was associated with clinical *P. mirabilis*).[128]

In Nigeria, a WGS study on the *P. putida* group (*P. plecoglossicida* and *P. guariconensis*) isolated from two wetlands showed the localization of *bla*$_{\text{VIM-5}}$ in three novel *intI1* structures (*aadB-bla*$_{\text{VIM-5}}$*-bla*$_{\text{PSE-1}}$, *aadB-bla*$_{\text{VIM-5}}$*-aadB-bla*$_{\text{PSE-1}}$, and *bla*$_{\text{VIM-5}}$*-aadB-tnpA-bla*$_{\text{PSE-1}}$*-smr2-tnpA*) among the investigated species.[141] These findings support the role of integrons in capturing cassettes harboring the gene *bla*$_{\text{VIM-5}}$ and disseminating the ARGs among different species from various sampling points. Also, in Tunisia, Chairat *et al*. identified *bla*$_{\text{VIM-2}}$ in *P. aeruginosa* localized in two different genetic arrangements; one of them was the novel In1183 (*bla*$_{\text{OXA-10}}$*-aadB-bla*$_{\text{VIM-2}}$*-aadB-bla*$_{\text{OXA-10}}$) (accession number: KT362173).[134] In general, novel integron names are assigned by the INTEGRALL database,c which curates novel integron sequences.[173]

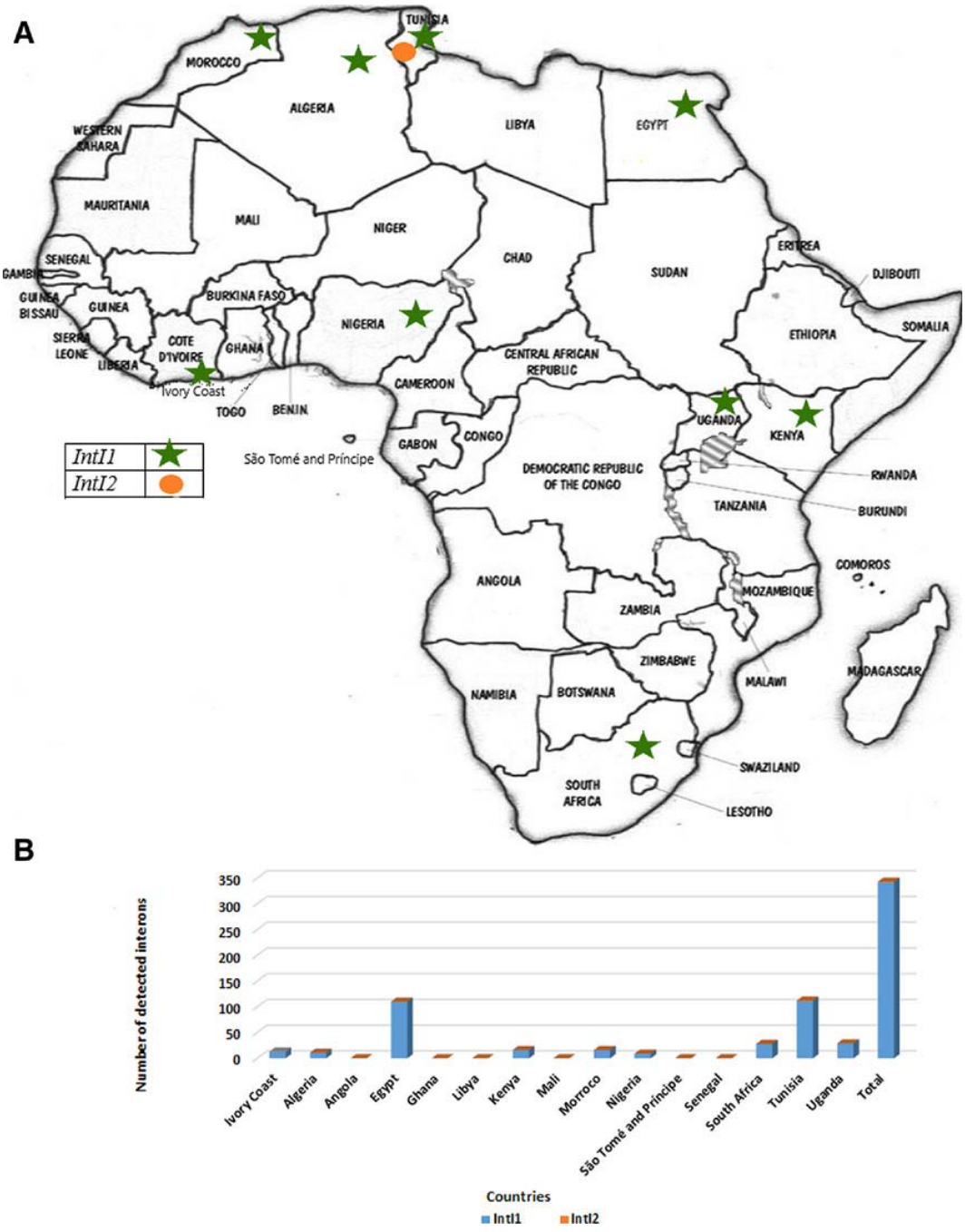


Figure 5. Distribution of integrons in the investigated countries.

Additionally, in the study by Belotti *et al*., despite the suggested chromosomal location of *bla*VIM-2, the integron that harbored *bla*VIM-2 also carried other β-lactam and non–β-lactam resistance determinants.[135] Belotti *et al*. showed that this integron carried quinolone resistance–encoding gene cassette (*qnrVC1*) and an uncommon group IIC-attC intron, emphasizing the emergence of other resistance patterns. In Iran, MDR *A. baumannii* showed a notable prevalence of class 1 over class 2 integrons, and carbapenemase genes were found in a genetic context of the two classes; class 3 integrons were not detected among isolates.[174]

Transposable elements

Tn and ISs are commonly associated with *bla*$_{\text{NDM-like}}$ and oxacillinases (*bla*$_{\text{OXA-48-like}}$, *bla*$_{\text{OXA-23-like}}$, *bla*$_{\text{OXA-24-like}}$, *bla*$_{\text{OXA-51-like}}$, and *bla*$_{\text{OXA-58-like}}$) and are mainly reported in North and South Africa. The genetic context of *bla*$_{\text{NDM}}$ is commonly flanked by IS*Aba125* and a bleomycin resistance gene (*ble*$_{\text{MBBL}}$); this structure was described for different variants, such as *bla*$_{\text{NDM-1}}$, which was detected in clinical *A. baumanii* and *K. pneumoniae* in Tunisia.[60, 71] IS*Aba125*-NDM-1(*ble*$_{\text{MBL}}$) was also detected in various strains isolated in Egypt, *E. coli*, *K. pneumoniae*, and *P. stuartii*;[69, 73] it was also associated with *bla*$_{\text{NDM-5}}$ in studies that investigated *E. coli* isolates from Egypt[73] and Mali.[131]

Other studies focused on one or both transposable elements: IS*Aba125* and Tn*125* in Tunisia[72, 84] and Ghana.[74] Studies describing IS*Aba125* and/or Tn*125* in the genetic context of *bla*$_{\text{NDM-like}}$ have been reported in Bulgaria,[175] India,[161] Oman,[176] and Poland.[177] In Tunisia, Jaidane *et al*. found an additional insertion sequence, IS*Aba14*, flanking the genetic environment of *bla*$_{\text{NDM}}$;[60] a similar observation was made in isolates from European countries;[178] and *bla*$_{\text{NDM-1}}$ was associated with a Tn*1548-like* structure delineated by IS*26* in South Africa.[68] In other studies, Tn*1548* has been associated with aminoglycoside resistance determinants.[179]

In South Africa, several ISs were detected among 10 investigated *K. pneumoniae* isolates harboring *bla*$_{\text{NDM-1}}$, reflecting the variation in the genetic backbone of *bla*$_{\text{NDM-1}}$; the ISs included IS*3*, IS*4*, IS*5*, IS*6*, IS*21*, IS*66*, IS*256*, IS*481*, IS*1182*, IS*1595*, IS*L3*, IS*Lre2*, and IS*NCY*.[127] In another study, *bla*$_{\text{NDM-1}}$ was associated with IS*1*, IS*5*, IS*3*, and IS*Kpn*26 in South Africa.[18]

For carbapenem-hydrolyzing oxacillinases, there was a notable variation in the types of ISs and Tns flanking *bla*$_{\text{OXA-48-/181/-like}}$. For example, the genetic context of *bla*$_{\text{OXA-48}}$ included Tn*1999* and IS*1999* in studies from Tunisia,[71, 72, 82, 84, 104] Algeria,[106] Libya,[64, 81] Morocco,[65, 100] and Egypt;[180] the same observations were made in Turkey[181] and the United States.[160] In addition, Hays *et al*. showed the existence of IS*1R*, besides IS*1999*, flanking *bla*$_{\text{OXA-48}}$; IS*1R* acted as an additional promotor to increase the expression of *bla*$_{\text{OXA-48}}$.[65] In a later study, IS*1R* was detected by Power *et al*. in clinical *K. pneumoniae* in Ireland.[158]

Another variant of *bla*$_{\text{OXA-48}}$, *bla*$_{\text{OXA-181}}$, has been associated with different ISs. Kieffer *et al*. showed that *bla*$_{\text{OXA-181}}$ was flanked by IS*Kpn19* and IS*Ecp1*, with IS*Ecp1* being truncated by IS*3000*, in *E. coli*, *K. pneumoniae*, and *E. cloacae*.[76] Other studies on *E. coli* or *Klebsiella* spp. showed that *bla*$_{\text{OXA-181}}$ was associated with IS*Kpn19*, as described in São Tomé and Príncipe,[75] or IS*Ecp1* from South Africa.[67] The association of these two ISs (IS*Kpn19* and IS*Ecp1*) with *bla*$_{\text{OXA-181}}$ was also reported in China.[182]

Moreover, IS*Ecp1* and Tn*2016* were associated with *bla*$_{\text{OXA-204}}$ in *K. pneumoniae* from Tunisia,[72, 82, 108] Potron *et al*. showing that IS*Ecp1* was truncated by IS*Kpn15*.[108] A similar finding for *bla*$_{\text{OXA-204}}$ was in a study from France.[151]

It was also reported that *bla*$_{\text{OXA-23-like}}$ and *bla*$_{\text{OXA-51-like}}$ are flanked by IS*Aba1* in isolates in Tunisia,[60] Algeria,[112] Kenya,[58, 115] Senegal,[116] Egypt,[56, 62, 63, 96, 99] and South Africa.[61, 111, 117, 118] Al-Hassan *et al*. described the prevalence of oxacillinases among *A. baumannii* isolates, in which IS*Aba1* and IS*Aba2* were upstream of *bla*$_{\text{OXA-23}}$ and *bla*$_{\text{OXA-89}}$, respectively; each gene was flanked by a single copy of the IS; furthermore, *bla*$_{\text{OXA-58}}$ was flanked by two copies of

IS*Aba3*.[62] IS*Aba1* was found flanking *bla*$_{\text{OXA-23-like}}$ and *bla*$_{\text{OXA-51-like}}$, while IS*Aba3* flanked *bla*$_{\text{OXA-58}}$ in *A. baumannii* in Argentina,[183] while IS*Aba2* was missing. IS*Aba8* was identified in the genetic context of *bla*$_{\text{OXA-97}}$ (*bla*$_{\text{OXA-58-like}}$).[124]

Other studies showed that *bla*$_{\text{OXA-23}}$ was flanked by other transposons, such as Tn*2006* in Algeria[113] and Tn*2008* in Tunisia.[60] Tn*2006*- or Tn*2008*-*bla*$_{\text{OXA-23}}$ structures have been reported in various *A. baumannii* isolates from different countries worldwide.[184, 185] However, relatively few *bla*$_{\text{VIM-like}}$ genes were found within transposable elements in Africa. In two studies that investigated *P. aeruginosa* harboring *bla*$_{\text{VIM-2}}$ found that it was associated with IS*Pa7* in Tunisia,[122] whereas IS*pa58* and Tn*3*/Tn*21* were found flanking the same gene in Ivory Coast.[138]

IS*pa21* was shown to be part of the genetic context of *bla*$_{\text{VIM-4}}$ in *E. hormaechei* isolated from Egypt.[132] Limited reports from countries worldwide described the existence of such ISs in the genetic environments of *bla*$_{\text{VIM-like}}$. In particular, IS*Pa7* was shown to flank *bla*$_{\text{VIM-1}}$ in clinical *P. aeruginosa* in Italy,[186] whereas IS*Pa21* was found to flank *bla*$_{\text{VIM-4}}$ in two studies on clinical *E. cloacae* isolated in the United Arab Emirates.[187]

Other transposable elements have been identified in GNB in Africa; in Nigeria, Tn*5403* truncated IS*3000* in *K. quasipneumoniae* isolates;[130] interestingly, this genetic structure was also detected in *bla*$_{\text{NDM-7}}$–positive *E. coli* isolated from a food sample in Pakistan.[188] Also, in South Africa four transposable elements were detected, namely, TniB NTP–binding protein; TniA putative transposase, resolvase, or integrase; TinR protein; and TniQ in *K. pneumoniae*.[79] Conversely, in a recent study from South Africa, *TniA* and *TniB* were found in an environmental *E. coli* isolate that showed resistance to antimicrobial classes other than carbapenems.[189] However, none of the investigated transposable elements (transposons and insertion sequences) had a statistically significant association with the investigated species or countries, except for IS*Aba1* ($P = 0.0313$; Dataset S1, online only). The distribution of the detected Tn and ISs in Africa is shown in Figures 6 and 7, respectively; we conclude that ISs and Tns facilitate the dissemination of carbapenemases in GNB in Africa and globally.

Some studies have pointed out the probable role of international mobility and the history of hospitalization in the dissemination of carbapenemases within Africa and among Africa and other continents. Kaase *et al*. and Chavda *et al*. found isolates from patients who had a history of travel and/or hospitalization in Egypt.[123, 132] Furthermore, Kocsis *et al*. isolated CP-GNB from an injured Libyan refugee.[81] Also, Abderrahim *et al*. investigated a patient who was hospitalized more than once and, consequently, the authors suggested that hospitalization facilitated the acquisition of MDR bacteria.[83] In general, the use of carbapenems in Africa is relatively low. Thus, the consumption of carbapenems is not the only explanation for the spread of carbapenemases. Other factors, such as the selection of carbapenemases by cross-selection with other antibiotics, might be perhaps considered.

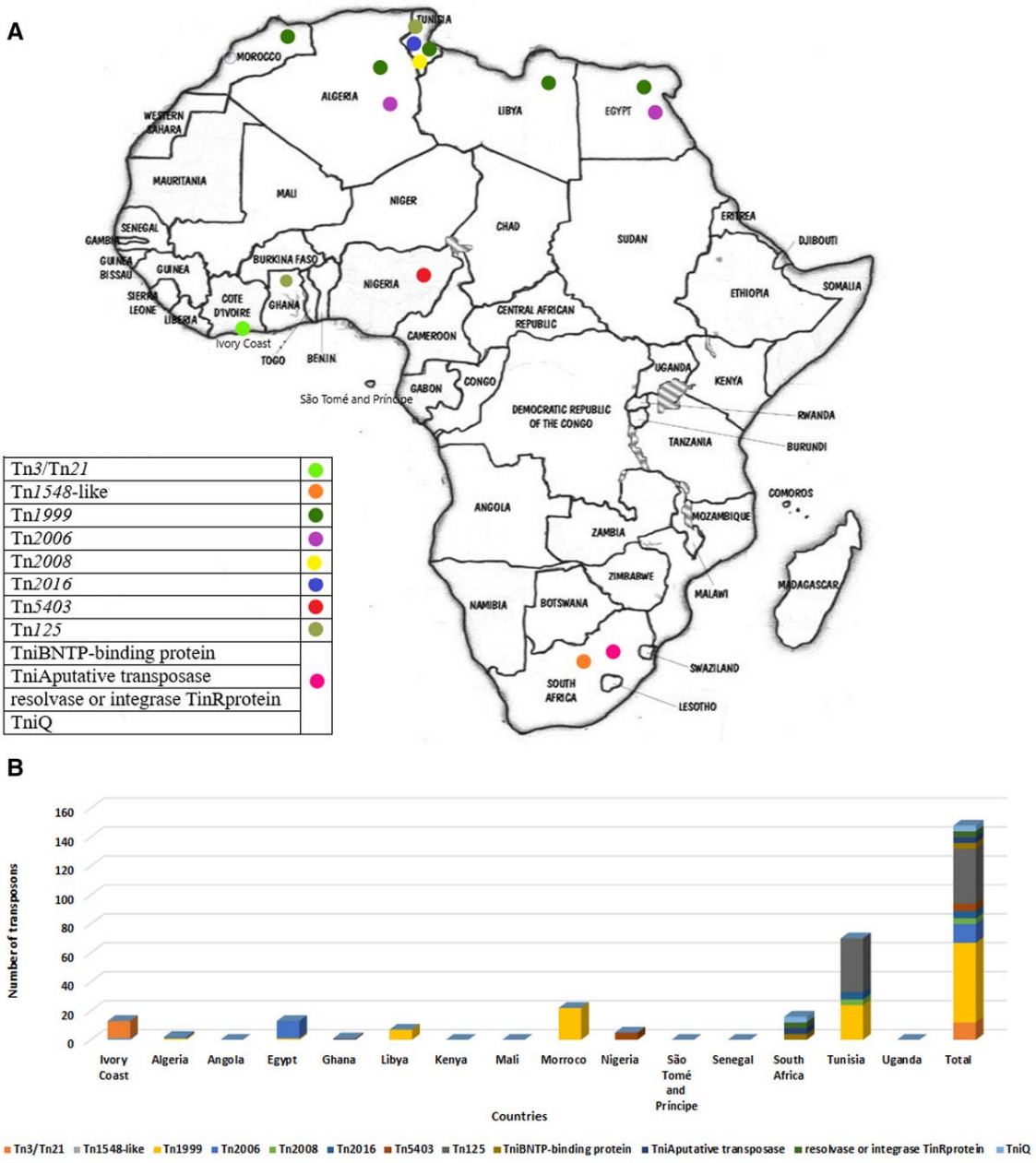


Figure 6. Distribution of transposons in the investigated countries.

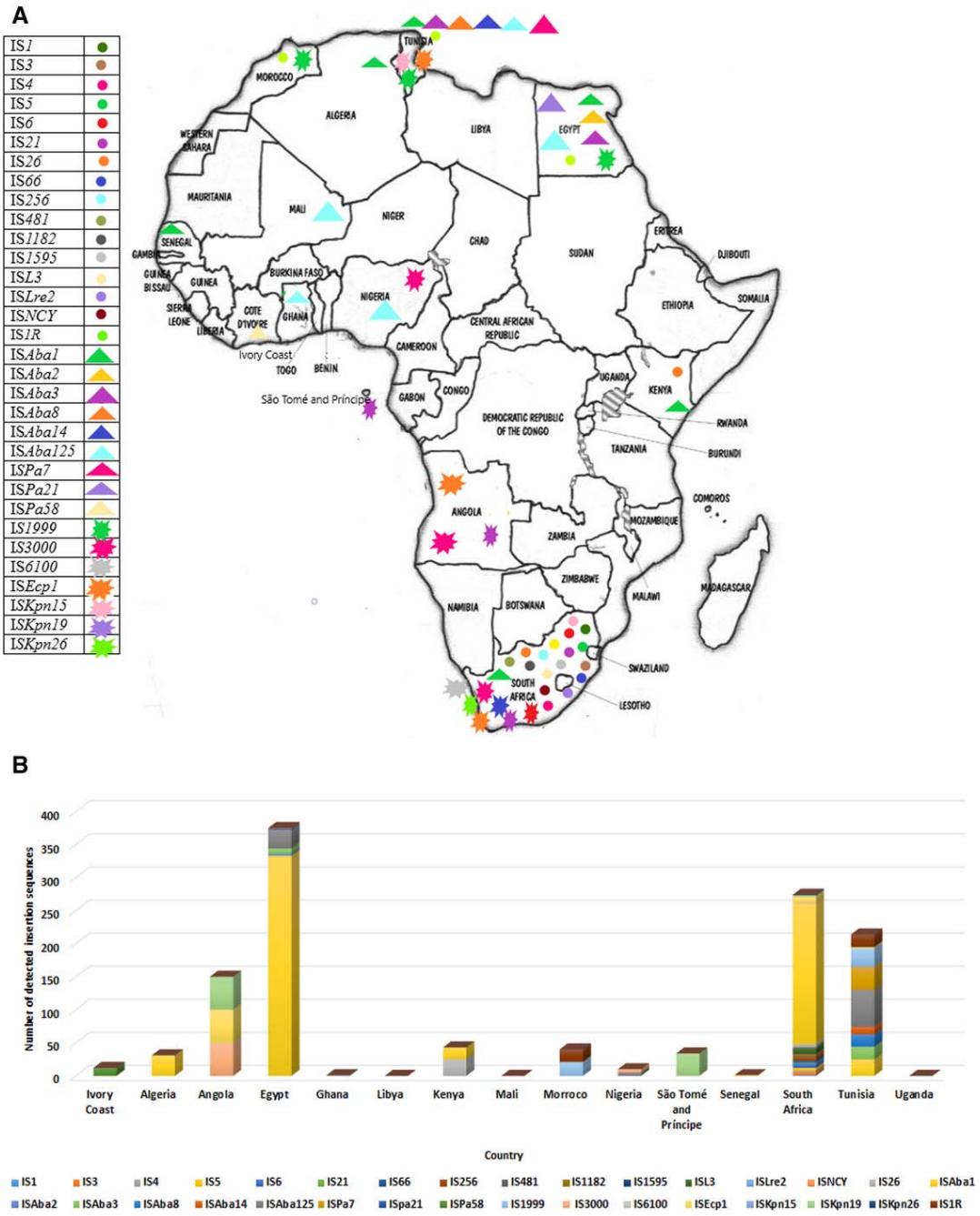


Figure 7. Distribution of insertion sequences in the investigated countries.

Conclusion, limitations, and future perspectives

In this work, we show that carbapenemases are mainly transmitted among African countries through MGEs in GNB. Notably, most of these CP-GNB have been isolated from clinical samples rather than animal or environmental samples and had similar genetic environments as the isolates of the same or different species from different countries. This demonstrates the importance of MGEs in driving AMR in GNB in animals, humans, and the environment. There is clearly a need to study MGEs and their role in the inter- and intraspecies dissemination of ARGs. Among other things, future studies must transcend the screening or

determination of plasmid transfer. The use of therapeutic molecules to target MGEs—including CRISPR to cure plasmids and carbapenemases[190, 191]—may combat the dissemination of ARGs. Other mechanisms may prove to be useful; for example, antiplasmid action of essential oils has recently been reported.[192]

In reference to the work from Africa we evaluated, differences in technological skills and laboratory equipment affect the type and quality of work undertaken by several research groups; this influences the conclusions of these studies. Most studies conducted in Africa depend on polymerase chain reaction (PCR) and Sanger sequencing to detect and confirm the existence of MGEs. In general, standard PCR is a simple molecular tool for screening carbapenemases in a large number of isolates.[193] And because most PCR-based studies used primers that target conserved regions, the determination of specific carbapenemase variants depended mainly on subsequent sequencing (which, at any rate, was not performed in all studies).

The application of WGS provides comprehensive data, including identification of clonality (multilocus sequence typing (MLST)), ARG determinants, plasmid replicons, and virulence genes.[194] Four studies each from Nigeria[57, 103, 130, 141] and South Africa[18, 68, 79, 127] applied WGS in epidemiological studies of carbapenemases; isolates from other countries, such as Tunisia[60, 85, 93] and Ghana,[74] also used WGS. In 2017, Henson *et al*. applied WGS to imipenem-susceptible *K. pneumoniae* and found a plasmid with a genetic architecture similar to a known plasmid that carried $bla_{\text{NDM-1}}$.[77] These studies show the superior resolution of WGS in providing epidemiological and genetic analyses of AMR, strongly supporting the adoption of WGS in all epidemiological studies.

Finally, there should be a continuously updated epidemiological database network among different African countries to monitor the prevalence and dissemination of ARGs. Detailed data sharing is an important pillar in epidemiological studies to preempt the dissemination and ARGs. A common bioinformatics platform for all African countries, technical exchanges among laboratories, capacity building, and training will be necessary to facilitate the easy standardization and analysis of AMR data. Governments must also invest in molecular and genomic laboratories to analyze and disseminate AMR data from CP-GNB.

Author contributions

S.M.R. conducted literature selection/screening, quality assessment, data extraction, data organization in a meaningful manner, generation of frequency charts and maps, and write-up of the manuscript. U.G. reviewed the manuscript. J.O.S. designed, supervised, and undertook the study, searched the literature, undertook all statistical analyses, image design, and write-up, revision, and formatting of the manuscript for publication.

Competing interests

The authors declare no competing interests.

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