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Review

# The Impact of Carbapenemase Producing Enterobacterales in African Countries: Evolution, Current Burden and Importance of Colonizations

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**Abstract:** Antimicrobial resistance (AMR) is a worldwide healthcare problem. Multidrug resistant organisms (MDRO) have the ability to spread quickly owing to their resistance mechanisms. Although colonized individuals are crucial MDRO dispensers, colonizing microbes have the potential to turn pathogenic under certain conditions, leading to symptomatic infections in carriers. Carbapenemase producing Enterobacterales (CPE) are among the most important MDRO involved in infections and colonizations, associating with multiple resistance mechanisms and virulence factors, causing infections with severe outcomes. All research papers identified in the most comprehensive online databases which contained information related to the topic of this article were analyzed, and relevant data was extracted and included. The first information on CPE could be traced back to the mid-2000s, but pertinent data for many African countries was established in the past 5-8 years. Information is presented chronologically for each country. Although no clear conclusions could be drawn for some countries, it was observed that CPE colonizations are present in most African countries and carbapenem-resistance levels are rising. The most common CPE involved are *Klebsiella pneumoniae* and *Escherichia coli*, and the most prevalent carbapenemases are NDM-type and OXA-48-type enzymes. Prophylactic measures, such as screening, are required to combat this phenomenon.

**Keywords:** Africa, Enterobacterales, Carbapenem resistance, Carbapenemase, CPE, Colonization

## 1. Introduction

The issue of antimicrobial resistance (AMR) in health care is intricate, dynamic, and ever-evolving globally [1,2]. Although resistance to antiviral, antifungal and antiparasitic medications poses significant challenges, bacterial resistance to antibiotics and chemotherapeutics seems to be the most troublesome, as bacterial infections are ubiquitous and extremely diverse. Resistance develops and spreads rapidly in different fields of activity, including human and veterinary medicine, and the food industry [1,3–6].

Although antimicrobial resistant organisms are known to cause severe healthcare associated infections, such bacteria are increasingly more common in community-acquired infections [7,8]. The silent spread of multidrug resistant organisms (MDRO), such as carbapenem-resistant organisms (CRO) including carbapenemase-producing Enterobacterales (CPE), extended spectrum  $\beta$ -lactamase (ESBL) producing Enterobacterales, methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin resistant *Enterococcus* (VRE) and others in carriers is concerning, as they disseminate in and between healthcare institutions, communities, even across borders and continents (e.g. travelers, diaspora, migrants) [7–17]. It has been demonstrated that chronic carriers are prone to developing severe, hard

to treat infections themselves, with important morbidity and mortality rates, as some colonizing bacteria tend to express their pathogenicity factors and become virulent in given circumstances: immunosuppression, imbalance of the bacterial flora, trauma, surgery, antimicrobial treatment, etc. [9,18–24].

Many bacterial genera and species presenting with varied mechanisms of resistance have been described and new mechanisms are constantly being discovered [25]. Enterobacterales is an order of Gram-negative bacteria, generally bacilli (GNB), which can associate with many complex resistance mechanisms, natural and acquired, constitutive and inducible. It is universally acknowledged that the improper exposure of microorganisms to antibiotics can selectively pressure the emergence of mutant, resistant bacterial strains. Mutations in genes encoding for structural proteins can lead to different adaptive modifications, such as permeability decrease, while acquisition and regulation of genes can lead to the development of efflux pumps and a decrease in the number of porins, respectively. However, enzymatic mechanisms are the most concerning, as their encoding genes are frequently located on mobile, transposable elements, which can be easily transmitted between bacteria, not only to descendants but also horizontally, between different strains, sometimes even species or genera [1,5,26,27].

Some of the most important enzymes associated with Enterobacterales are  $\beta$ -lactamases, which can inactivate a various number of  $\beta$ -lactam antibiotics.  $\beta$ -lactam antibiotics are very important therapeutic resources because of their bactericidal effect, often representing the first and the most effective treatment choice. Among  $\beta$ -lactamases, extended spectrum  $\beta$ -lactamases (ESBL), cephalosporinases (especially AmpC) and carbapenemases are the most significant [12,26,27]. Of these, carbapenemases are enzymes that can render most of, or the entire  $\beta$ -lactam group unsuitable for treatment and, associated with other mechanisms, can lead to the emergence of multidrug-resistant (MDR), extended drug-resistant (XDR) and pandrug-resistant (PDR) strains; it must be noted that not all carbapenemase-producing Enterobacterales (CPE) are actually resistant to carbapenems (CR), and not all carbapenem resistant Enterobacterales (CRE) are carbapenemase producers (CP) [27,28]. An important classification of the  $\beta$ -lactamases is the Ambler classification, with four major groups, noted from A to D, with carbapenemases being included in classes A (with various enzymes), B (metallo- $\beta$ -lactamases or MBL) and D (OXA-type carbapenemases). Classes A and D are also known as serine carbapenemases. [25,26] Carbapenemases are also associated with other pathogens (or opportunistic pathogens), such as non-fermentative GNB - *Pseudomonas* spp. and *Acinetobacter* spp. [26].

## 2. Materials and Methods

In order to extract the information for this non-systematic review, PubMed Central and Google Scholar databases have been accessed. From 71 research papers containing the keywords “carbapenemase” AND “colonization” AND “Africa”, published in English between 2011 and 2023, 37 relevant results were selected and included in this article.

As more data from the literature was needed for a robust review, supplementary published studies were selected from a pool of 309 research papers extracted using keywords such as: “carbapenem-resistant”, “carbapenemase”, “beta-lactamase”, “Enterobacterales”, “Enterobacteriaceae”, “Gram-negative”, “colonization”, “screening”, “travelers” associated with “Africa” or African regions and country names.

Additionally, a microbiology textbook and other articles published in English and French which included relevant information for the topic were addressed.

Inclusion criteria: Research papers presenting reports and data on carbapenemase producing Enterobacterales and colonization with such microorganisms from countries and regions located in Africa were prioritized. Articles describing cases of African origin patients, or people who were hospitalized or traveled in Africa were also accessed if data was relevant.

Exclusion criteria: Data from other regions and countries, data on resistance mechanisms other than carbapenemases and microorganisms other than Enterobacterales were generally excluded, if unrelated to the reviewed topic.

For reference management, Zotero version 6.0.27 was used.

## 3. Results

Although other CRE or even CPE might have been reported in Africa before, the authors of a 2010 article tracked down and published the first documented case of *Klebsiella pneumoniae* NDM-1 infection in Africa, originating in Kenya, 2007 [29]. The strain was very similar to the one first reported in 2008 Sweden in a patient previously hospitalized in India [29]. Another study, also published in 2010, described two strains of *Escherichia coli* and *Klebsiella pneumoniae*, isolated from Algerian patients in 2008, in which a novel VIM carbapenemase, VIM-19, was recorded [30].

Some of the first cases of CP non-Enterobacterales were reported in South Africa even sooner: a study published in 2001 described a case of *Pseudomonas aeruginosa* harboring GES-2, isolated from blood cultures [31], while another study published in 2005 described infections caused by *Acinetobacter baumannii* OXA-23 – authors suspected the emergence of these strains to be in 2002 [32]. Later, in 2008 and 2010, such strains isolated in 2005-2006 were also reported in Tunisia and Madagascar [33,34].

These findings suggest that CP microorganisms reached African countries a few years after they were first identified and described in GNB [25,35–37]. In the following years, CPE have been reported and described with an increasing frequency in many African healthcare units, in infected patients, and carriers.

**Algeria:** The first report regarding CPE infected Algerian patients was made in 2010 (described above) [30]. In a 2014 study, *E. coli* producing OXA-48 enzymes, sampled from an infected patient in 2012, was reported for the first time in Algeria [38]. Later, in 2015, OXA-48 or NDM-5 *E. coli* were reported in 5 of 200 (2.5%) pets screened for intestinal carriage [39]. A 2016 publication reported 14 carbapenemase-producing organisms (CPO) (OXA-48, NDM, OXA-23) among 32 carbapenem-resistant organisms (CRO). Two of them were the first *Enterobacter cloacae* strains with OXA-48 encoding genes (*bla*<sub>OXA-48</sub>) reported in Algeria [40], while in another study, among 186 GNB from clinical isolates, 161/186 were *Enterobacteriaceae*, 36/186 were CR-GNB and 2 of them *bla*<sub>OXA-48</sub> *K. pneumoniae* (1.2% CPE prevalence among *Enterobacteriaceae*) [41]. A 2017 study reported that, among 99 GNB isolated in 2014-2015 from stool samples and surfaces, 10 were CR-CPO. Two were *bla*<sub>OXA-48</sub> *Enterobacteriaceae* (1 *E. coli* and 1 *K. pneumoniae*). The other 8 were *Acinetobacter* spp. (7 *A. baumannii* and 1 *A. nosocomialis*), among which 4 *A. baumannii* and the *A. nosocomialis* were *bla*<sub>NDM-1</sub> and the remaining 3 *A. baumannii* were *bla*<sub>OXA-23</sub> [42]. A 2020 publication reported that among 42 colorectal cancer patients from 2019 screened for CPE fecal carriage, 1 patient was carrying OXA-48 producing *K. pneumoniae* [43]. In 2022 a strain of NDM-5 producing *K. pneumoniae* isolated in 2017-2018 was reported [44]. Overall, data on human CPE carriage is still scarce for Algeria, but CPE prevalence varied in studies from 1.2% to 2.5%.

**Angola:** A 2016 publication reported that, following a 2015 screening for CPE rectal colonization (rectal swabs were collected), 43/157 children (27.4%) carried *Enterobacterlaes* encoding for OXA-181 (an OXA-48-like enzyme) or NDM-1 [45]. This study was followed by another one, published by the same authors in 2018, where increased rates of CPE were reported (28/36 screened patients) and the emergence of NDM-5 was noted [46].

**Benin:** In a 2023 study, *blages* genes were identified in hospital wastewater and in water intended for handwashing [47]. Another 2023 study which evaluated 390 urine samples from 2021-2022 isolated 103 *Enterobacteriaceae* (*E. coli*, *Serratia* spp., *Klebsiella* spp., *Citrobacter freundii*, and *Enterobacter intermedius*). Although a low imipenem resistance rate was observed in 27.18% strains, no data on CP is available [48].

**Burkina Faso:** In a 2023 study, *blages*, *bla*<sub>IMP</sub>, *bla*<sub>NDM</sub>, *bla*<sub>OXA-48-like</sub>, *bla*<sub>OXA58-like</sub> and *bla*<sub>VIM</sub> genes were identified in Burkina Faso hospital wastewater [47]. Another 2023 study which evaluated 170 *E. coli* and *K. pneumoniae* strains isolated from 82/84 healthcare center wastewater samples identified 10 CPE, of which 6 NDM, 3 OXA-48 producers, and 1 NDM + OXA-48 co-producer [49].

**Botswana:** Relevant data was found in a 2021 study that evaluated the CRE colonization prevalence. Of 2469 participants recruited from different environments (hospital, clinic, and communities), 42 were colonized with CRE, 10 with multiple strains. The CRE species were *E. coli*, *K. pneumoniae*, and *E. cloacae*. Of all hospital subjects, 6.8% were colonized, while in clinics and communities only 0.7% and 0.2% tested positive for CRE [50].

**Cape Verde:** A study published in 2022 showed that 6 of 98 patients screened with rectal swabs carried *E. coli* and *K. pneumoniae* encoding for OXA-48-like enzymes [51].



**Djibouti:** A 2023 study revealed a prevalence of 1.9% CP-GNB (32/1650). The samples were collected from multiple sites: 1300 from humans (800 community, 500 hospital), and the others from animals, fish and water. Among the 32, 19 were *E. coli*, 5 *K. pneumoniae*, and 1 *Proteus mirabilis* associated with *bla*<sub>NDM</sub>, *bla*<sub>OXA-48</sub>, and *bla*<sub>OXA-181</sub> [52].

**Egypt:** A study from 2012 described some of the first infections caused by *K. pneumoniae* producing NDM-1 or OXA-163 [53]. A 2018 study reported MBL producing *Serratia marcescens* (VIM-2 and IMP-4) isolated from intensive care unit (ICU) patients in Cairo [54]. A 2019 study reported that out of 413 *Enterobacteriaceae* isolated from cultured rectal swabs (2015-2016), 100 (24%) were CRE. Eighty percent (80%) of CRE were CPE (19.4% overall CPE colonization). *bla*<sub>OXA-48</sub> and *bla*<sub>NDM-1</sub> were the most prevalent genes, while *E. coli* and *Klebsiella* spp. were the most prevalent species [55]. A 2020 study reported an *E. coli* NDM isolated from a patient with diarrheal disease [56]. A study published in 2023 reported among 150 isolates from 2019, 30 CR-GNB (20%), of which 26 (17.33%) were CRE. *K. pneumoniae* was the most prevalent CR species (10/30) and *bla*<sub>NDM</sub> was the most prevalent gene (15/30), frequently on plasmids. Twenty-one out of the thirty CR-GNB (21/30) harbored CP genes. Of these 21/30, 19 (12.66%) were Enterobacterales and 2 *P. aeruginosa*. Other CPE were *E. coli*, *E. cloacae*, *Citrobacter freundii*, while other genes were represented by *bla*<sub>VIM</sub>, *bla*<sub>IMP</sub> and *bla*<sub>KPC</sub> [57]. Another 2023 study described 150 Enterobacterales strains isolated from clinical samples (2019-2020), out of which fifty-three (53/150) were deemed CR by antimicrobial susceptibility (AST) screening and confirmed CPE by molecular methods (35.33% CPE prevalence). Genotypically, 30/53 isolates carried *bla*<sub>NDM-1</sub> and 41/53 carried *bla*<sub>OXA-48</sub> (18 isolates carrying both genes). *K. pneumoniae* was the most prevalent (37/53), followed by *E. coli* (15/53) and *K. oxytoca* (1/53) [58]. Overall, reported CPE prevalence ranged from 12.66% to 35.33%, but data on CPE colonization is still scarce for Egypt (one 19.4% report was found).

**Ethiopia:** In 2016, KPC and MBL *K. pneumoniae* strains isolated in 2012 from two colonized children were reported [59]. Larger studies reported prevalences of 2.73% (2015) [60] and 2% (2019) [61] CPE among isolated Enterobacterales, or even 12.2%, (although it is not clear if the isolates were CPE, or if CRE with other resistance mechanisms were also included, 2017) [62]. One study identified 16.2% CPO among 185 GNB isolated from 532 samples, 2019 [63]. In a 2021 study, 17 of 312 Enterobacterales isolated from clinical samples had potential CPE and 8 (2.6%) were phenotypically confirmed by mCIM. The 8 strains were *K. pneumoniae* (4), *E. coli* (3), and *Enterobacter* spp. (1); further testing revealed the presence of OXA-48, MBL, and KPC+OXA-48 [64]. In another 2021 study which screened 833 subjects, 141 GNB were isolated and 51 proved to be MDR. Eight passed as CPE (*Enterobacter* spp., *Klebsiella* spp. and *E. coli*) on Modified Hodge Test (MHT), resulting in an approximately 1% CPE colonization prevalence [65]. Many studies were published in 2022. In one of them, 301 *Enterobacteriaceae* isolated from 1416 patients were analyzed, ~7% (20/301 strains, *K. pneumoniae*, and *E. cloacae*) carried *bla*<sub>NDM</sub> and/or *bla*<sub>OXA-48</sub> genes [66], while in another one 8% isolated *Enterobacteriaceae* were CR, 6% confirmed by mCIM as CPE (*E. cloacae*, *K. pneumoniae* and *E. coli*) [67]. One study showed that, out of 290 stool samples collected from asymptomatic food handlers, 7 (2.4%) tested positive for CPE presence, especially *E. coli* and *K. pneumoniae* [68]. Another article reported that, out of 132 *K. pneumoniae* strains isolated from patients in previous years, 39 (29.6%) were CR and 28 (21.2%) CPE. Twenty six harbored *bla*<sub>NDM</sub>, of which 1 co-harbored *bla*<sub>KPC</sub> [69]. A 2023 study revealed that of 183 diarrheal pathotype *E. coli* isolated from children, 4 (2.2%) were CPE [70], while another study evaluating GNB isolated from blood cultures revealed a prevalence of 25.1% CP-GNB and 5.6% MBL among 231 GNB (179 Enterobacterales) [71]. A systematic review from 2023 reported an overall 5.44%, pooled prevalence of CPE in Ethiopia, ranging from 2.24% in 2015-2016 to 17.44% in 2017-2018, and from 1.65% in the Southern region to 6.45% in Central Ethiopia [72].

**Gabon:** A 2022 screening study evaluated 98 Enterobacterales isolated from diarrheal stools and reported 28 CRE [73]. In 2023 data on CP-GNB collected from 2016 to 2018 was published. 14/869 clinical isolates (1.61%) and 1/19 fecal samples presented CP-GNB, with higher rates among inpatients (2.98%) than outpatients (0.33%). The most prevalent GNB were *K. pneumoniae* (8/15) and *A. baumannii* (4/15), and the most prevalent gene was *bla*<sub>OXA-48</sub>, followed by *bla*<sub>NDM-5</sub> [74].

**Ghana:** In a study published in 2019, 26 out of 111 CR-GNB (including CPE), isolated in 2012-2014, presented NDM-1, OXA-48, and VIM-1 genes (VIM-1 only in *Pseudomonas* spp.) [75]. In a 2020 published study, MDR-GNB carriage was evaluated in 175/228 hospitalized neonates recruited from neonatal ICUs (NICU). Two hundred seventy-six (276) GNB were isolated, of which 115 *Klebsiella* spp.

18/115 (15.6%) *Klebsiella* spp. Expressed CR and harbored *bla*<sub>OXA-181</sub>. Sixteen of two hundred twenty-eight (16/228, 7%) neonates developed GNB bloodstream infection, and in 2 of them sequencing confirmed the colonizing MDRO to be responsible. The confirmed CPE carriage was of ~10% [76]. In a study from 2022, 26 *bla*<sub>NDM</sub> and 1 *bla*<sub>OXA-48</sub> harboring strains were isolated from 231 hospital surfaces. One strain was *K. pneumoniae*, and the rest *Acinetobacter* spp. [77]. Another study from 2022 revealed that in 410 nasopharyngeal samples collected in 2016 from small children, 57 GNB, especially *E. coli*, *K. pneumoniae*, and *E. cloacae* were isolated. Among the 57, 6 strains tested as carbapenemase producers on MHT (including *Acinetobacter* spp.). Nasopharyngeal CPO carriage was found in 1.46% screened children [78]. In a 2023 study, 181 GNB isolated from clinical samples were processed and 161 were identified as Enterobacterales. Among the 161, 31 were CRE, but only 4 encoded for carbapenemases: 1 *bla*<sub>OXA-48</sub> + *bla*<sub>KPC</sub> *E. coli*, 1 *bla*<sub>OXA-48</sub> + *bla*<sub>KPC</sub> *K. pneumoniae*, 1 *bla*<sub>NDM</sub> *K. pneumoniae*, and 1 *bla*<sub>NDM</sub> *Providencia vermicola*. This equaled to a CPE prevalence of 2.2 – 2.5% [79]. A 2023 study that evaluated stool samples for MDR colonization showed that, out of 736 healthy residents, 2 (0.3%) participants carried *bla*<sub>NDM-1</sub> *E. coli* [80]. Thus, the reported CPE carriage prevalence across studies ranged from 0.3% to 10% in Ghana.

**Kenya:** The first report regarding CPE in Kenya was dates to 2010 (described above) [29]. In an article from 2020, OXA-48 *Salmonella* isolated from a Kenyan patient with diarrheal disease was reported [56]. A study published in 2022 analyzed 89 *K. pneumoniae* strains isolated between 2015 and 2020 in Kenya and described 2 strains (2.24%) harboring *bla*<sub>NDM-1</sub> and *bla*<sub>OXA-181</sub> [81]. Another 2022 publication reported screening data from 2019: 300 mothers and their newborn babies were evaluated for MDR-GNB colonization. Two percent (2%) of mothers ( $n = 7/300$ ) had CRO isolated from vaginal secretions. For newborns, a 3% ( $n=8/300$ ) CRO rate was observed on admission and a fivefold increase was recorded (up to 14%,  $n = 29/218$ ) upon discharge. Among CRO, the most prevalent were *K. pneumoniae* and *E. coli* harboring *bla*<sub>NDM-1</sub>, *bla*<sub>NDM-5</sub> and *bla*<sub>NDM-7</sub>, but *bla*<sub>OXA-181</sub> and *bla*<sub>OXA-232</sub> were also identified. Furthermore, a 3% ( $n = 3/164$ ) CRO rate was reported in the hospital environment [82]. A surveillance report published in 2023 evaluated 119 stool samples and rectal swabs collected from 42 infants in 2018-2019. 18 infants were from Kenya, and 24 from Nigeria. Seven of eighteen (7/18) Kenyan infants tested positive for CPE colonization at some point during admission. The most prevalent gene was *bla*<sub>NDM</sub>, but *bla*<sub>OXA-48</sub> and *bla*<sub>VIM</sub> were also identified [22].

**Libya:** In 2011, a case of OXA-48 *K. pneumoniae* rectal carriage was reported in a patient transferred from Libya to Slovenia [83] and in 2012-2013 other *K. pneumoniae* and *E. coli* encoding for OXA-48 and NDM-1 enzymes were isolated from Libyan patients [84–86]. Later in 2016, more such strains isolated in Libya and Tunisia were described, with 11.4% of all studied strains being *K. pneumoniae* OXA-48 producers [87].

**Madagascar:** An article from 2015 reported community colonization with NDM-1 *K. pneumoniae* [88]. A 2020 study reported 6 cases of CPE originating from Madagascar, isolated between 2011 and 2016, and an increasing prevalence in all recruited countries (Madagascar, French Reunion, Mauritius, Seychelles, India, Mayotte/ Comoros) [89].

**Mauritius:** In 2012, a MDR strain of *K. pneumoniae* isolated from a patient in Mauritius, 2009, was reported to be *bla*<sub>NDM-1</sub> positive [90]. A 2020 study reported 11 more cases of CPE originating from Mauritius, isolated between 2011 and 2016 [89].

**Malawi:** A study published in 2019 described that 16 out of 200 (8%) Enterobacterales isolated in 2016-2017 in Malawi were *Klebsiella* spp. And *E. coli* producing KPC-2, NDM-5, and OXA-48 enzymes [91].

**Mali:** In 2017, an article reported an OXA-181 *E. coli*, probably the first CPE reported in Mali [92]. In 2023 was published a study that evaluated 526 patients with pleurisy between 2021 and 2022. 110 were diagnosed with enterobacterial pleuritis, mainly *E. coli*, *K. pneumoniae*, and *Proteus mirabilis*. Three isolates (2.72%), 1 *K. pneumoniae* and 2 *Providencia* spp. tested positive for *bla*<sub>NDM-1</sub> [93].

**Morocco:** In 2011, the emergence of NDM-1 producing *K. pneumoniae* was reported in Morocco [94]. In a study published in 2012 in which 463 Enterobacterales isolated in 2009-2010 were evaluated, 2.8% were CPE: OXA-48 or NDM-1, *Klebsiella* spp. or *Enterobacter cloacae* [95]. Later, more CPE were reported: OXA-48 and IMP-1 *E. coli*, 2013 [96]; OXA-48 and NDM-1 *K. pneumoniae*, 2015 [97]. A 2014 published study reported that in 2012, among 77 patients screened by rectal swabbing and culture on screening media followed by PCR, 10 OXA-48 CPE intestinal carriers (13%) were found. The prevalent species were *K. pneumoniae* and *E. cloacae* [98]. A 2017 study reported 3 CPE *bla*<sub>OXA-48</sub> among

169 *Enterobacteriaceae* isolates from 164 neonates evaluated for ESBL and CPE rectal carriage (1.8% CPE carriage) [99]. In a 2021 published study it was reported that 641 *Enterobacteriaceae* were isolated from 455 newborns and infants screened for intestinal colonization on admission (2013-2015). 8.7% were colonized with *bla*<sub>OXA-48</sub> CPE. During hospitalization, 207 newborns were included in a follow-up acquisition study, and it was observed that 12.5% have acquired *bla*<sub>OXA-48</sub> CPE during hospital stay. The majority of CPE consisted of *K. pneumoniae* and *E. coli* [100]. A 2022 study in which GNB isolated in 2018-2020 were analyzed, reported that out of 810 Enterobacterales, 210 were eligible for  $\beta$ -lactamase screening: 40 presented NDM and 39 OXA enzymes; 7 carried both OXA-48 and NDM-1. These findings indicate a ~10% CPE prevalence [101]. A study from 2023 which evaluated 195 CRE isolated from 18,172 clinical samples identified 190 CPE (~1%), of which 74 were biofilm-associated MBL producers. Sixty-two of seventy-four (62/74) presented *bla*<sub>NDM</sub> and 12 strains associated *bla*<sub>NDM</sub> and *bla*<sub>OXA-48</sub>. *K. pneumoniae* was the most prevalent species [102]. Another 2023 study evaluated 199 positive NICU blood cultures from 2019. Seventy-five of one hundred ninety-nine (75/199) were Enterobacterales, and 36/75 were CPE (especially *K. pneumoniae* and *Enterobacter* spp. Encoding for OXA-48 and/or NDM). Thus, CPE were responsible for 18% of 199 positive blood cultures [103]. One more 2023 study which included 38 MDR Enterobacterales, especially *E. coli*, *Klebsiella* spp. And *Enterobacter* spp. Isolated in 2016-2017 from clinical samples, identified 22 CPE positive for *bla*<sub>OXA-48</sub> and *bla*<sub>NDM</sub> [104]. The overall CPE colonizations in Morocco varied from 1% to 13%, but higher percentages were observed in symptomatic infections.

**Mozambique:** A 2021 published study reported the emergence of *E. coli bla*<sub>NDM-5</sub> [105].

**Namibia:** In a study published in 2022, among 13,673 positive urine cultures from 2016-2017, resistance to carbapenems was low and only 1 CPE was found [106].

**Nigeria:** In 2013-2014 reports, several strains isolated in Nigeria, evaluated with phenotypic assays, were CR suspected as CP ( $n = 9$  of 97 tested strains [107]) or confirmed CP ( $n = 10$  of 182 tested strains [108]). In 2015, a rectal swab was collected from a patient previously hospitalized in Nigeria, and the patient was found to be colonized with NDM-1 *K. pneumoniae*, OXA-181 *E. coli*, and VIM-2 *P. aeruginosa* [109]. In 2017, among 248 evaluated clinical isolates (140 *E. coli* and 108 *K. pneumoniae*), 191/248 were CR and 93/191 (41 *E. coli* and 52 *K. pneumoniae*) were identified as CPE by MHT. An increase in CPE prevalence was observed when compared to 2011 reports (from 11.9% to 39.2%) [110]. In 2019, an outbreak of 5 NDM-5 producing *Klebsiella quasipneumoniae* was reported [111]. Later, in a 2020 study, 397 Gram-negative bacterial strains (of which 293 Enterobacterales) isolated from patients were tested. Fifteen of three hundred ninety-seven (15/397) GNB (7/293 Enterobacterales, 2.38%) were Carba NP positive [112]. In a 2021 study, from a total of 134 *K. pneumoniae* strains isolated in 3 Nigerian hospitals, 11 (8.2%) were CPE: 8 *bla*<sub>NDM-1</sub>, 2 *bla*<sub>NDM-5</sub>, and 1 *bla*<sub>OXA-48</sub> [113]. A 2022 study on 107 *E. coli* clinical isolates revealed that 6 (5.6%) presented *bla*<sub>NDM-1</sub> and *bla*<sub>NDM-5</sub> [114]. In 2023, 33/49 strains of MDR Enterobacterales were identified as CPE associating *bla*<sub>NDM</sub> and *bla*<sub>OXA-48</sub>-like genes. It was observed that 3 strains were susceptible to meropenem [115]. In a 2023 study that also included Kenya, 20/24 Nigerian infants presented CPE colonization at some point during hospital admission. Especially *bla*<sub>NDM</sub>, but also *bla*<sub>OXA-48</sub> and *bla*<sub>VIM</sub> were identified [22]. More noteworthy recent data is found in a study on Sub-Saharan countries described below [116]. It is still difficult to draw a general conclusion regarding CPE colonization in Nigeria, as data strictly regarding this topic are scarce. However, overall CPE prevalence ranged from 2.38 to 39.2% or more.

**São Tomé and Príncipe:** In a 2018 study it was reported that, out of 50 patients screened for MDR-GNB presence, 34 CRE were isolated from 22 patients. The 34 strains were *E. coli* and *K. pneumoniae* which harbored *bla*<sub>OXA-181</sub>, resulting in 44% CR CPE colonization [117].

**Senegal:** In 2011, 8 *K. pneumoniae* strains and 1 *E. coli* isolated from Senegalese patients during 2008-2009, were PCR confirmed to have the *bla*<sub>OXA-48</sub> gene. As imipenem (and meropenem) were susceptible, such strains could pass undetected and the importance of routine AST was raised [118].

**Sierra Leone:** A 2013 study recorded strains of *K. pneumoniae*, *E. coli*, and *E. cloacae* presenting *bla*<sub>OXA-51</sub> and *bla*<sub>OXA-58</sub>, genes usually found in *Acinetobacter* spp., among 20 GNB isolated between 2010 and 2011 in a Sierra Leone hospital [119].

**South Africa:** In 2011, the first reports of NDM-1 and KPC-2 *K. pneumoniae* isolated from patients in South Africa, along with the first case of KPC in Africa, were published [120]. In 2013, a paper was published describing the emergence of OXA-48-like (including OXA-181) producing *K. pneumoniae* in hospitalized patients (2011-2012). One patient previously received a kidney transplant in Egypt



which was probably the first case of OXA-48 reported in South Africa [121]. Later, an article from 2019 characterized several OXA-48-like CPE, including OXA-181 [122], while another article reported an increase in CRE prevalence from 2.6% (2013) to 8.9% (2015) in a NICU. 22/26 CRE were *K. pneumoniae*, and 17/18 tested CRE presented NDM or VIM enzymes [123]. A study published in 2019 in which 439 patient samples collected in 2016 were screened for colonization, identified 12 CRE but only 1 *K. pneumoniae* harboring *bla*<sub>NDM-1</sub> (0.22%) [124]. In one of the 2020 studies, 5/263 (1.9%) rectal swabs and 5 other isolates from infected patients were confirmed as CR *K. pneumoniae*. All 10 isolates showed genotypic resistance, being *bla*<sub>NDM-1</sub> positive. Sequencing revealed genetic relatedness, with the same plasmid multilocus sequence type and capsular serotype, thus supporting the horizontal transfer of resistance genes and clonal dissemination [17]. Another study evaluated ESBL and CRE rectal colonization in a pediatric hospital. Although 1/200 patients presented a CR *E. cloacae* colonization, no common CP gene was found [125]. Other 2020 studies reported more OXA-48 and NDM *K. pneumoniae* strains isolated from clinical samples, such as blood cultures; similar strains were identified in carriers [126,127]. A study from 2021 which screened 31 ICU patients by collecting 97 rectal swabs which were cultivated on screening media, isolated 14 CR *K. pneumoniae*, and all were confirmed CPE through molecular testing (all harboring *bla*<sub>OXA-181</sub>) [128]. In a 2022 screening article, out of 587 collected from humans (230 rectal swabs), pigs (345 rectal swabs) and water (12), 19 samples (3.2% of total) presented CRE, of which 9 *K. pneumoniae*. Of the 19 samples, 4 were environmental and 15 from humans (resulting in 6.5% colonized humans). Sixteen of nineteen (16/19) also tested positive for OXA-181 (9/16), NDM-1 (4/16), but OXA-48, GES-5, and OXA-484 were also identified [129]. A 2022 publication of a large 2019-2020 surveillance reported 2144 patients with CRE bacteremia from multiple healthcare facilities. Out of 1082 studied strains, 863 (79.8%) were *K. pneumoniae*, followed by *E. cloacae*, *S. marcescens* and *E. coli* in close proportions. 915/1082 (84.6%) presented one carbapenemase gene, while 38 (3.5%) had 2 genes encoding for carbapenemases. The most common carbapenemase gene was *bla*<sub>OXA-48-like</sub> (761/991, 76.8%), followed by *bla*<sub>NDM</sub> (209/991, 21.1%), *bla*<sub>VIM</sub>, *bla*<sub>GES</sub>, and *bla*<sub>KPC</sub> [130]. In a 2023 study, 23/53 newborns that suffered infections in a neonatal unit had CRE positive cultures, and 15/33 newborns screened for CRE carriage tested positive. For 20 of the strains *bla*<sub>NDM</sub> and *bla*<sub>OXA-48</sub> genes were identified [131]. Another 2023 study revealed *bla*<sub>OXA-48-like</sub> genes in 18/39 CR *Serratia marcescens* isolated from patients during 2015-2020. It must be noted that a total of 1396 *S. marcescens* strains were identified, and only 21 of the 39 CR were also sequenced. 19 of the 21 patients were on antibiotics prior to isolation [132]. More noteworthy recent data is found in a recent study on Sub-Saharan countries described below [116]. Overall, CPE colonization in South Africa was found to range from 0 to 6.5% or more (close to 50% if studies on small lots are taken into account).

**Somalia:** Although data is very limited for Somalia, in a 2021 study that evaluated carbapenemase-encoding bacteria (CEB) isolated between 2014 and 2019, 11 Somali patients tested positive for CEB, with genes encoding for NDM, OXA-23 and VIM [133].

**Sudan:** In a 2018 study, 36.1% of 200 Gram-negative strains isolated in Sudan were MBL producers [134], while a 2020 study identified an important number of *K. pneumoniae* strains ( $n = 46$ ) isolated from infected patients, harboring genes that encoded for OXA-48, NDM, KPC, IMP [135]. A study from 2021 reported that, out of 206 CR-GNB, 171 were phenotypically confirmed CR and 121 harbored carbapenemase genes (including CPE, mostly *K. pneumoniae* and *E. coli*), such as *bla*<sub>NDM</sub> (107), *bla*<sub>IMP</sub> (7), *bla*<sub>OXA-48</sub> (5) and *bla*<sub>VIM</sub> (2), with 3 strains co-harboring *bla*<sub>NDM</sub> and *bla*<sub>OXA-48</sub>, 1 strain *bla*<sub>NDM</sub> + *bla*<sub>VIM</sub> and 1 strain *bla*<sub>NDM</sub> + *bla*<sub>IMP</sub> [136]. In a 2023 article, 86 *K. pneumoniae* hospital isolates (2016-2020) were evaluated. Thirty-five (35) were CR, and 3/35 were not CPE. However, the study indicates that among the total 86 sequenced strains, 37 were CPE, encoding for NDM-1, NDM-4, NDM-5, OXA-48, and OXA-232; 3 strains presented both NDM-5 and OXA-48 [137].

**Tanzania:** A study from 2014 showed that in Tanzania 80 of 227 (35.24%) MDR-GNB (among which 176 were Enterobacterales), presented one or more genes encoding for carbapenemases: IMP, VIM, OXA-48, KPC, NDM [138]. In a 2020 study, 244 Enterobacteriaceae were isolated from 194 HIV-positive patients screened by collecting rectal swabs. For 1 patient rectal colonization with CP *E. coli* was reported (0.4%) [139]. In 2023 a study reported a rate of 22.8% CPE isolated from hospital surfaces [140].

**Tunisia:** In 2010 the first warnings were released on OXA-48 *K. pneumoniae* in Tunisia [141]. In 2011, an outbreak of OXA-48 *K. pneumoniae* was reported, with 21 out of 153 CR strains testing



positive for this enzyme [142], followed by other reports of OXA-48 *K. pneumoniae* and *Citrobacter freundii* in 2012 [143] and the case of a Libyan patient infected with a *K. pneumoniae* co-harboring NDM-1 and OXA-48 in 2013 [86]. In 2015, 2 patients who underwent rectal swab screening in 2015 after being transferred from Tunisia to Poland had *bla*<sub>NDM-1</sub> *K. pneumoniae* and *bla*<sub>OXA-48</sub> *K. pneumoniae* colonization. Ten days after admission, *bla*<sub>NDM-1</sub> *K. pneumoniae* and *E. coli* were found in one patient, with a gene similar to the one isolated in the other patient [144]. Later papers reported KPC-2 *E. coli*, OXA-48, and VEB-8 *K. pneumoniae*, 2016-2017 [145,146]. A large study from 2019 phenotypically tested 2160 *K. pneumoniae* strains and reported 342 CR strains (15.8%), 203 being suspected of OXA-48-like enzymes and 17 of MBL (10% of *K. pneumoniae* strains were CP) [147]. Another 2019 study evaluated intestinal MDR-GNB carriage in 38 patients at admission and then weekly. During their stay, 14 of them were colonized with various MDR-GNB, among which 10 CR-GNB were identified. Among *Enterobacteriaceae*, 5 CPE (4 OXA-48 and 1 NDM) were identified [148]. A study from 2021 which characterized 19 *Klebsiella oxytoca* strains isolated in a Tunisian hospital (2013-2016) showed that all these strains presented the *bla*<sub>OXA-48</sub> gene [149]. In a 2022 study, out of 2135 stool samples collected from food handlers between 2012 and 2017, 7 (0.33%) were positive for CPE carriage (OXA-48 and NDM-1 *K. pneumoniae* and *E. coli*) [150]. Similar strains were described by other authors in 2022 [151]. Another 2022 study in which 227 hospitalized children were screened for MDR *Enterobacteriaceae* rectal colonization reported only 1 patient (0.44%) with CPE carriage (a strain of *bla*<sub>OXA-48</sub> *Klebsiella oxytoca*) [152]. In 2023, the first report of IMI-2 producing *Enterobacter bugandensis* isolated from the stool of a healthy volunteer in Tunisia was published [153]. Overall, although important rates of CPE were observed generally, CPE carriage seems to be under 1% in Tunisia.

**Uganda:** In a 2015 study it was reported that 56 of 658 (8.5%) Enterobacterales strains (especially *K. pneumoniae* and *E. coli*) isolated in 2013-2014 from Ugandan hospital encoded for carbapenemases (confirmed by RT-PCR). 11 of these 56 strains encoded for VIM and OXA-48 enzymes and presented phenotypically detectable resistance [154]. In a 2020 study, 15 of 69 GNB isolated from surgical site infections and identified as *K. pneumoniae*, were suspected as CPE [155]. Later in 2021, in a study where 227 virulent *K. pneumoniae* strains isolated from 4 hospitals in 2019 have been evaluated, and it has been shown that 23.3% of the strains were phenotypically CR, but the PCR analysis revealed that even more (43.1%) presented genes associated with CP, especially *bla*<sub>OXA-48-like</sub>, *bla*<sub>IMP</sub>, *bla*<sub>VIM</sub>, *bla*<sub>KPC</sub>, and *bla*<sub>NDM</sub> [156]. In a 2023 study, 95/192 (49.5%) *E. coli* strains isolated from the stool samples collected in equal amounts from humans (49/96) and their livestock (45/96) presented *bla*<sub>KPC</sub> on PCR evaluation, although not all were phenotypically resistant to carbapenems, and not all CRE were CPE [157]. In another 2023 study, multiple samples (swabs) were collected from 137 mothers and their 137 newborns, 67 health workers, and 70 frequently touched hospital surfaces. One hundred thirty-one (131) GNB were isolated from 21 mothers, 15 babies, 2 health workers, and 13 surfaces, of which 104/131 were *K. pneumoniae*, *E. coli*, and *Enterobacter* spp. Ten of one hundred four (10/104) strains were CR, 6/10 were confirmed as CPE by PCR (*bla*<sub>VIM</sub>, *bla*<sub>IMP</sub>, *bla*<sub>NDM</sub>) and 4/6 co-harbored more than one carbapenemase gene. The overall CPE prevalence was 1.46% in this study [158]. The difference between results regarding CPE colonization is significant: 1.46% for a study (maybe less if surfaces were excluded) and 49.5% for another study. More studies are necessary in order to draw a conclusion.

**Central Africa:** A systematic review from 2023 evaluated all publications from 2005 to 2020, including Gabon, Cameroon, Democratic Republic of Congo, Central African Republic, Chad, Republic of Congo, São Tomé and Príncipe, and Angola. Revealed data regarding CPE was still scarce for these countries, but nonetheless relevant. From clinical and carriage human isolates, in Angola were found NDM-1, NDM-5, OXA-181 producing strains and 26.4 - 78% CPE isolation rates (similar data to reports presented above); in Cameroon NDM-1 and NDM-4; in Chad NDM-5, OXA-181 and 2.5 - 6.5% CPE; in Gabon NDM-7, OXA-48 and 5.1% CPE (close findings to a study presented above); in Republic of Congo OXA-181 and 6.97% CPE; and in São Tomé and Príncipe OXA-181 and 44% CPE (the study was described above). For Democratic Republic of Congo, OXA-48, KPC, VIM, IMP, and NDM genes were found in wastewater and drinking water. No data was available for the other included countries [159].

**Sub-Saharan Africa:** A study from 2023 evaluated data on MDR-GNB from Cameroon, Ivory Coast, Nigeria, and South Africa. 5014 GNB isolates were included, of which 3905 Enterobacterales; among them 214 were CRE. *K. pneumoniae* was the most prevalent CRE (72.4%). Of the

Enterobacterales that underwent molecular characterization, 136 (3.5% of all Enterobacterales) carried a MBL (131 NDM, all CR, and 5 VIM). Most NDM strains were from Nigeria (87/512 characterized strains, 17%), followed by Cameroon (5/42, 11.9%), South Africa (37/444, 8.3%) and Ivory Coast (2/56, 3.6%). The 5 VIM isolates were from South Africa, while 25 NDM strains also carried OXA-48-like genes. 127 strains that were non-MBL CPE (3.3% of all Enterobacterales) included 125 OXA-48 group carriers (105 OXA-181, 15 OXA-48, 5 OXA-232) and 2 KPC. Including the 25 OXA-48 + MBL strains, OXA-48/OXA-48-like isolates were most prevalent in South Africa (129/444 molecular characterized strains, 29.1%), then Cameroon (5/42, 11.9%), Nigeria (15/512, 2.9%), and Ivory Coast (1/58, 1.8%). The 2 KPC strains were from South Africa [116].

In some regions OXA-48 and VIM-2 *Salmonella enterica* ser. Kentucky were reported in a study published in 2013 [160].

Also, reports of CP and CR *Acinetobacter* spp. and *Pseudomonas* spp. increased in number, with alarmingly high rates of resistance [161–165]. Even rare species of non-fermenters CP were reported [166].

#### 4. Discussions

It is hard to say with certainty when, where or how the CPE began to spread in Africa, as there are many factors involved, but it can be assumed that the first strains emerged in the mid or early 2000s and were disseminated through various ways, including asymptomatic carriers. It should be noted that some studies reported data from the same year the study was published, while others from previous years.

Limiting factors include: published data related only to MDRO and not all isolated bacteria, reported findings for all Gram-negatives without separating Enterobacterales from the others, analyzed just a part of isolates belonging to one species, lacked confirmation tests, and included a limited number of strains. However, there are important differences between countries, sometimes between healthcare units, screened population groups and/or clinical samples evaluated. Although CPE are more frequently associated with infections, colonization can happen in asymptomatic humans, both hospitalized and from the community. The most common CPE species involved in infections and colonization seem to be *K. pneumoniae* and *E. coli*, but also *Enterobacter* spp., while the most prevalent carbapenemases associated are NDM, OXA-48/OXA-48-like and to some extent VIM and KPC enzymes, results that match the existing literature [167–172].

In the past 5-6 years, reports of highly resistant CPE have become increasingly common, and CPE which associate multiple resistance mechanisms, including carbapenem and colistin resistance (e.g. *mcr-1*) or multiple carbapenemases, have emerged in: Tunisia, 2017 [173]; Egypt, 2021 [174]; Sudan, 2021 [136]; Ethiopia, 2021 [64]; Uganda, 2021 [156]; Ghana, 2023 [79]; Sudan, 2023 [137] etc. A 2019 report detailed a patient who was recently admitted to a Kenyan hospital and tested positive for both *Candida auris* and CPO [175]. These may be caused by the long-term rise in CPE prevalence and the rise in carbapenem prescriptions, which favors the selection of resistant strains; the rise in the accessibility of certain testing techniques, including phenotypic and molecular testing should also be considered [176]. Unfortunately, although carbapenems are already expensive and still difficult to access for the population in some countries, antimicrobial molecules active on CPE will be necessary in Africa [116,117,177].

Some studies have shown that molecular analysis might reveal even more CPE than phenotypic tests among strains with no expressed CR, which supported the concern that some CPE can be missed by usual screening methods and could disseminate silently [137,156]. Other studies revealed quite the opposite, showing that not all CRO are CP, and that carbapenem resistance can occur through other mechanisms, facts supported by EUCAST and different studies [27,79,136]. This aspect may be dependent on the type of carbapenemase, species and virulence of the strain [116].

Scarce or no published data regarding CR or CPE was found for some regions, especially for developing countries or countries where carbapenem access is limited [178,179]. For many countries, reported data on CPE carriage was inconclusive. As this study is not a systematic review, some reported data might have been omitted.

A method of surveillance for carriers with MDRO that could be accessible even for countries with limited resources is the use of screening culture media. Relevant clinical samples (e.g. rectal swabs or fecal matter for CPE, tegumentary swabs for MRSA etc.) can be collected periodically, or at

certain times (at the moment of admission into a hospital, during the hospital stay, before surgery, before release, on transfer to another healthcare facilities, etc.) and cultivated on selective and differential media specially designed for the identification of certain microorganisms. This method is easy to use and has proven effective as some studies show [23,45,98,128]. However, further phenotypic or molecular assays are necessary to confirm carbapenemase production in the isolates that grow on the screening media [23,27,180,181].

In addition to human colonization, MDRO (including CPE) can also be spread by contaminated surfaces, hands [182], money [183], contaminated food [4,184,185], soil, water, air [5,186–189], colonized animals [39], birds [190] including migratory species [191], and even insects (e.g. cockroaches, flies) [192–194].

Several other limitations regarding this review were identified:

- As English publications were mainly accessed in order to write this review, studies presenting relevant information published in French or other languages might have been overlooked;
- Although extensive research was performed in order to extract the information, studies not matching the searching criteria and keywords that could contain important data might have not been identified;
- It should be mentioned that this study did not extensively analyze data for other CP Gram-negatives, such as *Pseudomonas* and *Acinetobacter*, that may present with different enzymes and a different epidemiology.

## 5. Conclusions

Even if some studies fall short within the scope of this review, it can be concluded that the CRE, including CPE, are present in many African countries and their prevalence is on the rise.

Even if it first appears that resistant strains have come to Africa from other continents, the combinations that are developing there may be an escalating factor in the AMR phenomenon. Considering that antibiotic and chemotherapy treatments are not always based on rational criteria and stewardship rules, new MDR, XDR, and possibly even PDR strains may soon occur.

Towards this end, there are certain organizations around the world that contribute to the fight against the spread of AMR. One such example is the Pasteur Network [195], which is already present in some parts of Africa (ex. Cameroon, Niger, Côte d'Ivoire, Madagascar, etc.) and other parts of the world (Americas, Asia-Pacific, Euro-Mediterranean). Further collaborations between public health institutions and the Pasteur Network as well as other networks worldwide, will allow experts from around the world to come together and focus on addressing difficult issues including AMR. These partnership prospects are welcomed by international and national committees, including well-established representative institutions.

To summarize, this concerning phenomenon has a cost to patients and healthcare systems worldwide, necessitating early detection, correct and efficient antibiotic use, preventive measures (such as isolation and decontamination of patients infected or colonized with problematic microorganisms, as well as strict hygiene practices), and ongoing education.

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