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CARBAPENEM-RESISTANT ENTEROBACTERIACEAE IN PAEDIATRIC BLOODSTREAM INFECTIONS IN SUB-SAHARAN AFRICA

Osigwe CA [1, *], Nwakaeze EA [1], Egbuna NR [1], Ikegbunam C [1], Oli AN [2] and Iroha IR [3]

[1] Department of Pharmaceutical Microbiology and Biotechnology, Faculty of Pharmaceutical Sciences, Chukwuemeka Odumegwu Ojukwu University, Igbariam, Anambra State, Nigeria.
[2] Department of Pharmaceutical Microbiology and Biotechnology, Nnamdi Azikiwe University, Awka, Agulu Campus, Anambra State, Nigeria.
[3] Department of Applied Microbiology, Faculty of Sciences, Ebonyi State University, Ebonyi State, Nigeria.
* Corresponding Author

ORCID Details
Osigwe CA: https://orcid.org/0009-0007-4988-1354
Emmanuel Amobi Nwakaeze: https://orcid.org/0000-0002-7624-2984
Nneka Roselyn Egbuna: https://orcid.org/0000-0002-6647-436X
Chidozie. Ikegbunam: https://orcid.org/0000-0002-9096-7420
Angus Nnamdi Oli: https://orcid.org/0000-0001-8519-2555
Ifeanyichukwu Romanus Iroha: https://orcid.org/0000-0002-8198-3955

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ABSTRACT

Background: Carbapenem-resistant Enterobacterales (CRE) are a WHO critical-priority threat, and children in sub-Saharan Africa (SSA) carry a disproportionate share of the burden. Carbapenems are the last reliable β-lactams for multidrug-resistant Gram-negative sepsis, so resistance leaves few, often unavailable, options for sick children.

Aim: To synthesise evidence on the epidemiology, resistance mechanisms, risk factors, clinical consequences, laboratory detection and management of CRE bloodstream infections (BSIs) in children in SSA, with emphasis on Nigeria.

Main findings: Gram-negative organisms, led by *Klebsiella pneumoniae*, *Escherichia coli* and *Enterobacter* spp., cause a large share of paediatric and neonatal BSIs in SSA. Across studies, carbapenem resistance ranges from under 10% in some general paediatric series to over 40% of Gram-negative isolates in some tertiary neonatal units. Metallo-β-lactamases, particularly NDM variants, and OXA-48-like enzymes (including OXA-181) dominate in the region, while KPC is uncommon. Neonates, especially preterm and very-low-birth-weight infants in intensive care, are most affected; prior antibiotic exposure, prolonged admission, invasive devices and gut colonisation are key risk factors. CRE BSI is associated with higher crude mortality, prolonged admission and heavy reliance on toxic or unavailable reserve drugs. Phenotypic tests such as the modified Hodge test miss many NDM producers, and molecular confirmation is rarely available outside research settings.

Conclusion: Paediatric CRE BSI in SSA is an established, under-measured problem driven largely by nosocomial transmission of MBL-producing clones. Priorities are sustained paediatric surveillance with molecular typing, affordable carbapenemase detection, neonatal infection prevention, carbapenem stewardship, and access to paediatric-appropriate reserve antibiotics.

Keywords: Carbapenem-Resistant Enterobacterales; Bloodstream Infection; Neonatal Sepsis; Children; Carbapenemase; NDM; OXA-48; Sub-Saharan Africa; Nigeria

1 INTRODUCTION

Infections caused by antimicrobial-resistant bacteria were estimated to kill about 700,000 people a year, with projections of up to 10 million annual deaths by 2050 [59]. Carbapenem-resistant Enterobacterales (CRE) sit at the top of the WHO priority pathogen list alongside carbapenem-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa* [59]. Carbapenems were introduced in the 1980s as a last line of defence against multidrug-resistant Gram-negative bacteria, but carbapenemase-mediated resistance had spread widely among Enterobacterales by the early 2000s [31,25].

Early CRE studies focused on adults, yet CRE now cause severe bloodstream infections (BSIs), sepsis and neonatal sepsis in children worldwide. A paediatric referral centre in Argentina reported CRE BSIs predominantly among children with underlying conditions, with *K. pneumonia* being the most frequently isolated organism and KPC the predominant carbapenemase [42]. In Taiwan, 8.4% of pediatric Enterobacterales bacteraemia episodes were carbapenem-resistant, with 14-day mortality of 12.5% versus 3.6% for non-CRE episodes [24].

Sub-Saharan Africa (SSA) is estimated to have the world's highest death rate attributable to antimicrobial resistance, and children bear much of it [58,21]. Neonatal sepsis in the region is dominated by Gram-negative bacteria, and carbapenems are increasingly used as empirical or escalation therapy because first-line WHO regimens fail [43,41]. At the same time, laboratory capacity to detect carbapenemases is limited, reserve antibiotics are scarce, and paediatric data are fragmented [47,30].

This review synthesizes current evidence on CRE BSIs in children in SSA, with particular reference to Nigeria. It covers the burden and aetiology of pediatric BSI, mechanisms of carbapenem resistance, regional epidemiology, risk factors and transmission, clinical consequences, laboratory detection, treatment, and priorities for prevention and research.

1.1 Review approach

This is a narrative review developed from the literature review of a doctoral study on the molecular characterisation of CRE from pediatric blood cultures in Onitsha, south-east Nigeria. Sources included peer-reviewed primary studies, systematic reviews and guidance documents on CRE, pediatric BSI and neonatal sepsis, with priority given to studies conducted in SSA and in children aged 0–17 years. Because the review is narrative, study selection was not systematic and pooled estimates were not calculated; figures are reported as given by the original authors.

1.2 Terminology

"*Enterobacteriaceae*" was reclassified as the order Enterobacterales in 2016; this review uses "Enterobacterales" except when quoting older definitions. Following the US Centers for Disease Control and Prevention, CRE are Enterobacterales resistant to at least one carbapenem (meropenem, imipenem or doripenem MIC ≥4 μg/mL, or ertapenem MIC ≥2 μg/mL) or producing a carbapenemase [53]. Carbapenemase-producing CRE (CP-CRE) are distinguished from non-carbapenemase-producing CRE (non-CP-CRE), whose resistance arises from other mechanisms.

2 BLOODSTREAM INFECTIONS IN CHILDREN: BURDEN AND AETIOLOGY IN SUB-SAHARAN AFRICA

BSIs are a leading cause of pediatric morbidity and mortality, especially among neonates, infants and children with underlying conditions. Their epidemiology differs from adults because of immune immaturity, age-specific exposures and differences in healthcare practice. In high-income settings, pediatric BSI incidence is estimated at 5–15 per 1,000 admissions, with the highest rates in neonates [39,54].

2.1 Culture positivity and pathogen spectrum

Among children with suspected sepsis, reported blood culture positivity typically lies between about 13% and 28%, including roughly 22% in Nigeria [20,18]. The balance of Gram-positive and Gram-negative organisms varies by site, but several African series report Gram-negative predominance [20,33].

The pathogen spectrum differs by age and setting:

- Neonates: Group B *Streptococcus* and *E. coli* are classic causes of early-onset sepsis in high-income settings, but in SSA *Klebsiella* spp., *E. coli*, *Enterobacter* spp. and *Acinetobacter* spp. dominate both early- and late-onset disease [33,43].
- Older children: community-acquired BSI in children are commonly caused by organisms such as *Streptococcus pneumoniae*, non-typhoidal *Salmonella spp.,* and *Staphylococcus aureus,* although the relative distribution varies according to geographic location and clinical setting. [39].
- Hospitalized or immunocompromised children: healthcare-associated BSIs increasingly involve multidrug-resistant Enterobacterales, including CRE [25].

2.2 Why Enterobacterales matter in SSA

In the BARNARDS study of neonatal sepsis across seven low- and middle-income countries, including Ethiopia, Nigeria, Rwanda and South Africa, the main Gram-negative pathogens were antimicrobial-resistant *Klebsiella*, *E. coli* and *Enterobacter* spp. [43]. In the Neo OBS global neonatal cohort, Gram-negative pathogens such as *Klebsiella* and *Acinetobacter* were common and highly resistant, and escalation from WHO first-line regimens was most often to a carbapenem [41].

A 2024 meta-analysis of 122 studies on Enterobacterales infections in children in SSA found a pooled third-generation cephalosporin resistance of 84.9% among *Klebsiella* isolates [21]. With cephalosporins largely lost for *Klebsiella*, carbapenems become the default empirical escalation, creating strong selective pressure for carbapenem resistance.

3 CARBAPENEMS AND MECHANISMS OF CARBAPENEM RESISTANCE

3.1 Carbapenems

Carbapenems (imipenem–cilastatin, meropenem, ertapenem and doripenem) have the broadest spectrum of any β-lactam class. Their bicyclic core, a β-lactam ring fused to a pyrroline ring with carbon replacing sulphur at position 1, gives stability against most β-lactamases, including extended-spectrum β-lactamases (ESBLs) and AmpC enzymes [24]. They bind penicillin-binding proteins and block peptidoglycan cross-linking, and continued autolysin activity then lyses the cell [36].

Imipenem is given with cilastatin to prevent renal dehydropeptidase-I degradation. Meropenem is stable to this enzyme and is the carbapenem most used in children, including for meningitis. Ertapenem has weak activity against *P. aeruginosa* and *Acinetobacter* but allows once-daily dosing [61]. As ESBL-producing Enterobacterales spread after 2000, carbapenem use rose sharply, and that selective pressure drove the emergence of carbapenemases [51].

3.2 Resistance mechanisms

Carbapenem resistance in Enterobacterales arises through three routes, alone or combined [28,25]:

- Enzymatic hydrolysis by carbapenemases. This is the most important mechanism because the genes sit on plasmids, transposons and integrons that transfer between species.
- Reduced permeability. Loss or alteration of outer-membrane porins, such as OmpK35 and OmpK36 in *K. pneumoniae*, combined with ESBL or AmpC production, can confer carbapenem resistance without a carbapenemase; ertapenem is affected first [13].
- Efflux. Over expressed multidrug efflux pumps, such as AcrAB-TolC, add to resistance, usually alongside the other mechanisms.
- The distinction matters. CP-CRE spread rapidly between patients and species, whereas non-CP-CRE mostly arise within a patient under antibiotic pressure. Non-CP-CRE account for over half of adult CRE isolates in the United States and may also predominate in children there [17,10,23]. In SSA, the limited molecular data point the other way, with most characterized CRE carrying carbapenemase genes [34,43].

3.3 Carbapenemase classes

Carbapenemases fall into Ambler classes A, B and D. Classes A and D are serine enzymes; class B are zinc-dependent metallo-β-lactamases (MBLs) inhibited by EDTA but not by clavulanate, sulbactam or tazobactam [38].

Table 1: Classification of β-lactamases

Ambler class	Main enzymes in Enterobacterales	Key properties	Relevance in SSA
A (serine)	KPC (KPC-2, KPC-3); GES, IMI, SME less often	Hydrolyse all β-lactams; KPC carried on transposon Tn*4401*; inhibited by avibactam, vaborbactam, relebactam	Uncommon; first reported in South Africa in 2012 [Brink *et al*, 2012]
B (metallo-β-lactamase)	NDM (NDM-1, NDM-5, NDM-7), VIM, IMP	Hydrolyse all β-lactams except aztreonam; not inhibited by any licensed β-lactamase inhibitor	Dominant in Nigeria, South Africa, Kenya and neonatal cohorts [Manenzhe*et al*., 2015; Jamal *et al*., 2022]
D (OXA)	OXA-48, OXA-181, OXA-232	Weak carbapenem hydrolysis, spare extended-spectrum cephalosporins; hard to detect phenotypically; inhibited by avibactam	Common, often co-produced with NDM [Poirel*et al*., 2012; Olalekan *et al*., 2020]

Carbapenemase genes are usually co-located with determinants of resistance to other classes, including CTX-M-15 ESBLs, aminoglycoside-modifying enzymes and 16S rRNA methyltransferases, fluoroquinolone resistance and *sul*/*dfr* genes. The result is a multidrug-resistant phenotype that removes most oral and parenteral options [12,25].

4 EPIDEMIOLOGY OF CRE IN SUB-SAHARAN AFRICA

4.1 Regional picture

Most African countries have no active CRE surveillance, so the regional picture is assembled from single-centre studies, research networks and meta-analyses [27]. Early reports from Morocco, Kenya and South Africa identified NDM-1 as the dominant carbapenemase [37]. South Africa reported its first NDM-1 and KPC-2 producers in 2012 [7]. In Ghana, 111 carbapenem-resistant Gram-negative isolates carried *bla*NDM-1 (*A. baumannii*), *bla*VIM-1 (*Pseudomonas*) and *bla*OXA-48 (*K. pneumoniae*), but no KPC [11].

A 2024 meta-analysis of 60 West African studies found an average *bla*NDM prevalence of 10.6%, with carbapenem resistance highest in *A. baumannii* (18.6%) and lower in *K. pneumoniae* (5.8%) and *E. coli* (4.1%) [46]. The pattern across SSA is consistent: MBLs, especially NDM, and OXA-48-like enzymes dominate, and KPC is rare, in contrast to North America and southern Europe.

4.2 CRE in children and neonates

Paediatric data remain sparse but show a clear signal, concentrated in neonatal units. Table 1 summarises key studies.

Table 2: Selected studies of carbapenem resistance in paediatric and neonatal infections in sub-Saharan Africa.

Study	Setting and population	Key CRE findings
Ballot *et al*., 2019	Tertiary neonatal unit, Johannesburg, South Africa; 465 MDR Enterobacterales infections, 2013–2015	CRE rose from 2.6% to 8.9% of MDR Enterobacterales; most were NDM producers; all-cause mortality 33.3%
Sands *et al*., 2021 (BARNARDS)	Neonatal sepsis, 12 sites in 7 countries incl. Ethiopia, Nigeria, Rwanda, South Africa	Resistant *Klebsiella*, *E. coli*, *Enterobacter* predominated; *bla*NDM and *bla*OXA-48-group genes detected; high-risk *K. pneumoniae* ST307 in Rwanda and Nigeria
Edwards *et al*., 2023	Neonatal units in Kenya and Nigeria	Widespread gut colonisation with carbapenemase- and ESBL-producing organisms
Russell *et al*., 2023 (NeoOBS)	Global neonatal sepsis cohort incl. Kenya, Uganda, South Africa	*Klebsiella* and *Acinetobacter* common and highly resistant; escalation mostly to carbapenems; some infants needed colistin

Kowalski *et al*., 2024	Meta-analysis, 122 studies of Enterobacterales infections in children 0–18 years in SSA	Pooled third-generation cephalosporin resistance of 84.9% in *Klebsiella*
Ruef *et al*., 2024	Meta-analysis of Enterobacterales carriage in children in SSA	Pooled CRE carriage 3.6% (95% CI 0.7–16.4%)
Johannesburg neonatal cohort, 2026	Prospective, 353 infants <90 days with Gram-negative BSI or meningitis, 2021–2023	43% had carbapenem-resistant organisms, mainly *A. baumannii* and *K. pneumoniae*; crude 28-day mortality 31% vs 17%

The South African neonatal data show the trajectory most clearly. In one Johannesburg unit, CRE among multidrug-resistant Enterobacterales rose more than threefold in three years, driven by NDM [3]. A later prospective cohort in a Johannesburg tertiary neonatal unit found carbapenem-resistant organisms in 43% of infants with Gram-negative sepsis or meningitis, including 38% of early-onset Gram-negative cases (PMID 42466448, 2026). Not all neonatal units are equally affected: a Zambian NICU found ESBLs in 99.0% of *K. pneumoniae* isolates but carbapenemases in only 2.7% (PLOS Global Public Health, 2026).

4.3 Nigeria

Nigeria, Africa's most populous country, has the largest body of CRE data in West Africa, but it is uneven by region and rarely paediatric-specific. A 2024 systematic review and meta-analysis of 57 studies from Nigeria reported pooled resistance among carbapenem-resistant Enterobacterales (CRE) of 11.2% to imipenem, 13.5% to meropenem, 17.0% to ertapenem and 37.9% to doripenem, with very high heterogeneity across the estimates (1^2>85%, $p < 0.001$). [1]. Most studies came from the South-West. The South-South had the highest resistance (imipenem 28.4%, meropenem 37.2%, ertapenem 46.5%), and resistance increased over time [1]. The South-East, where the present authors work, is under-represented.

Single-centre studies tell a similar story:

- Rising resistance in Kano State: imipenem resistance among *E. coli*, *K. pneumoniae* and *P. aeruginosa* was reported to range from 6–9% in 2011 [60], subsequently, a study conducted in two tertiary hospitals reported overall resistance of 36.6% for imipenem and 40.3% for meropenem among *E. coli* and *K. pneumoniae* isolates, suggesting an increase in carbapenem resistance over time. [60].
- Blood as a high-yield specimen: In Kano, [60] reported carbapenemase production in 30.6% of blood isolates, highlighting blood as an important clinical specimen for detecting carbapenemase-producing organisms. Subsequent studies in kano also reported a high prevalence of the blaNDM-1 gene among blood isolates.
- Regional variation: Marked regional variation in carbapenem resistance has been reported in Nigeria, with reported prevalence estimates of 14.9% in Kano [52], 10.5% in Sokoto [52], 12.5% in Maiduguri [52] and 36.8% among clinical isolates from four tertiary hospitals in south-western Nigeria. [52].
- Molecular profile: among 175 ESBL-producing *E. coli* and *K. pneumoniae*, 27.4% were carbapenem-resistant; of these, 62.5% carried *bla*NDM alone, 20.8% *bla*NDM plus *bla*OXA-181, 4.2% *bla*OXA-181 alone and 2.1% *bla*NDM plus *bla*OXA-48 [34]. The isolates clustered in *E. coli* ST410 and *K. pneumoniae* ST147 and ST395, all internationally successful high-risk clones.
- Cross-country comparison: CRE prevalence was 8.0% in Nigeria versus 14.0% in Kuwait; *bla*NDM-7 was the commonest carbapenemase gene in Nigerian isolates, and 14.2% of Nigerian CRE were resistant to both colistin and to tigecycline [19].

Paediatric blood-culture data from south-east Nigeria are almost absent. This gap, and the dominance of NDM and OXA-181 in adult and mixed-age Nigerian series, motivates molecular surveillance of paediatric BSI isolates in the region.

5 RISK FACTORS, COLONISATION AND TRANSMISSION IN CHILDREN

5.1 Host and healthcare risk factors

Risk factors for CRE acquisition overlap with those for other multidrug-resistant Gram-negative infections: immunosuppression, intensive care admission, mechanical ventilation, prior antimicrobial exposure, transplantation and prolonged hospital stay [15]. In a multicentrepaediatric study, the strongest risk factors for CRE colonisation or infection were anti-pseudomonal antibiotic exposure in the preceding three months, prior surgery and mechanical ventilation [10].

Children-specific risk groups include:

- Preterm and very-low-birth-weight neonates in intensive care, with immature immunity, central lines, parenteral nutrition and frequent empirical antibiotics. In Johannesburg, prematurity, lower birth weight and maternal HIV infection were associated with multidrug-resistant Enterobacterales sepsis [3].
- Children with cancer. Malignancy, intensive chemotherapy with neutropenia, gastrointestinal mucositis and prolonged admission predispose to CRE bacteraemia, and treatment failure and delayed active therapy are common in febrile neutropenia [8]. Mortality in paediatric CRE BSI has been reported at 25–34% in some series, highest among immunocompromised children [26].
- Children with chronic conditions or devices, such as congenital heart disease, chronic kidney disease or indwelling catheters, who have repeated admissions.
- Malnourished children, who in SSA are at high risk of Enterobacteralesbacteraemia and routinely receive broad-spectrum antibiotics on admission.
- In SSA, these host factors are amplified by system factors: non-prescription sales, self-medication, weak regulation, inappropriate prescribing, and inadequate diagnostic capacity [5,1].

5.2 Gut colonisation as the precursor to BSI

Gastrointestinal colonisation is usually the first step towards invasive CRE infection [10]. In neonates, risk factors for CRE gut colonisation include longer admission, nasogastric tube feeding, formula instead of breast milk, ventilation and antibiotic exposure [45]. Molecular surveillance in neonatal units in Kenya and Nigeria found widespread colonisation with carbapenemase-producing organisms, making the neonatal gut a reservoir for onward transmission and later sepsis [14].

Across SSA, pooled CRE carriage among children is modest at 3.6%, but ESCR-E carriage is common. Over half of children who were ESCR-E negative on admission acquired it in hospital, and recent antibiotic treatment tripled the odds of carriage (OR 3.20) [40]. These findings point to the hospital as the main amplifier.

5.3 Nosocomial transmission and clonal spread

CRE spread readily within neonatal and paediatric units, where infants are close together, handled often and exposed to shared equipment [25]. Genomic studies in SSA neonatal units show that most Gram-negative infections belong to transmission clusters. In a Zambian NICU, 95.6% of *K. pneumoniae* infections fell within probable transmission clusters of 2 to 202 patients (PLOS Global Public Health, 2026). Environmental sampling in BARNARDS neonatal wards found carbapenemase-producing bacteria on surfaces, most often near sink drains, with higher carbapenemase prevalence in Ethiopia than in the other African sites, and some clones related to strains causing sepsis [4,43].

Carbapenemase genes on plasmids also move between species and clones, so a single unit can harbour an outbreak of a plasmid rather than a single strain. Improper injection practice, inadequate skin disinfection, and poor hand hygiene have been proposed as routes by which CRE reach the bloodstream in Nigerian hospitals [52].

6 CLINICAL CONSEQUENCES OF CRE BLOODSTREAM INFECTION IN CHILDREN

CRE BSI in children is associated with higher crude mortality, more organ dysfunction and longer admissions than carbapenem-susceptible infection. Whether this excess is caused by resistance itself or by the underlying illness of affected children is not fully resolved.

6.1 Mortality

In the multinational PANORAMA cohort of Enterobacterales BSI in low- and middle-income countries, carbapenem resistance was associated with worse outcomes [47]. Paediatric data follow the same direction:

In Taiwan, 14-day mortality was 12.5% in paediatric CRE bacteraemia versus 3.6% in non-CRE episodes [24].

In a multicenter study of very preterm infants in China, 13.0% of Enterobacteriaceae-associated late-onset sepsis episodes were caused by carbapenem-resistant Enterobacteriaceae (CRE). CRE-associated sepsis was associated with higher in-hospital mortality and substantial treatment failure, highlighting the serious clinical consequences of CRE infections in this vulnerable population [22].

In Johannesburg, crude 28-day mortality was 31% with carbapenem-resistant organisms versus 17% with susceptible organisms (OR 2.22), although carbapenem resistance was not an independent predictor after adjustment (PMID 42466448, 2026).

In the same city, all-cause mortality among neonates with multidrug-resistant Enterobacterales sepsis was 33.3%, predicted by low birth weight, necrotising enterocolitis and mechanical ventilation [3].

The adjusted Johannesburg result is a useful caution. In SSA neonatal units, CRE largely affect the sickest, smallest infants, so crude comparisons overstate the effect of resistance alone. Even so, resistance delays effective therapy, and delay is a well-established driver of sepsis mortality.

6.2 Sepsis, septic shock and organ dysfunction

Gram-negative endotoxin drives the systemic inflammatory response that can progress to septic shock and multiorgan dysfunction, with hypotension, poor perfusion and injury to kidneys, liver and lungs [16]. Children with CRE septic shock need intensive care, vasopressors and ventilation, resources that are scarce in many SSA hospitals [57].

6.3 Therapeutic failure and drug toxicity

Because CRE resist most β-lactams, initial empirical therapy is often inactive. The reserve agents available in SSA, polymyxins, aminoglycosides and tigecycline, carry nephrotoxicity and neurotoxicity and have uncertain paediatric dosing [9]. Resistance to these last agents is emerging too: 14.2% of Nigerian CRE isolates were resistant to colistin and to tigecycline [19].

6.4 Longer-term and system effects

Survivors of severe sepsis may have neurodevelopmental impairment, growth faltering and reduced quality of life. Prolonged admission and expensive second-line drugs place heavy costs on families, many of whom pay out of pocket. Broad-spectrum treatment also disrupts the gut microbiota, favouring secondary infections with other resistant organisms and *Candida* [25]. Each CRE-infected or colonised child is also a source for further transmission within the unit.

7 LABORATORY DETECTION IN RESOURCE-LIMITED SETTINGS

Reliable CRE detection needs three steps: an adequate blood culture, accurate carbapenem susceptibility testing, and confirmation of the mechanism. Each step is weak in many SSA laboratories, so CRE BSI is almost certainly under-detected [30].

7.1 Blood culture

Blood culture remains the reference standard for BSI, but sensitivity falls with low blood volumes in neonates and small children and with prior antibiotics, which are common before presentation in SSA. Many district hospitals have no blood culture service at all.

7.2 Susceptibility testing

Disc diffusion and automated systems are the usual first screens, but their performance varies with the resistance mechanism. Automated systems have reported KPC-producing *K. pneumoniae* as susceptible to imipenem or meropenem [38]. Ertapenem is the most sensitive screening agent for carbapenemase production. Breakpoints differ between CLSI and EUCAST and have changed over time, and laboratories using outdated breakpoints can miss CRE; one such gap allowed silent spread of KPC-producing *K. pneumoniae* in a facility for children and young adults [55].

7.3 Phenotypic carbapenemase tests

Table 3: Phenotypic carbapenemase tests characteristics.

Test	Principle	Strengths	Limitations
Modified Hodge test	Carbapenem inactivation enhances growth of a susceptible indicator strain	Cheap; widely used; formerly CLSI-recommended	Poor for NDM (false negatives) and weak with VIM, IMP and OXA types; false positives with AmpC/ESBL plus porin loss (Bonnin *et al*., 2012)
Carbapenem–EDTA combined disc or synergy tests	EDTA inhibits MBLs	Cheap; flags MBLs such as NDM	May miss low-level MBL producers; EDTA alone can inhibit growth (Walsh *et al*., 2005)

Carba NP and RapidecCarba NP	Colour change as carbapenem hydrolysis lowers pH	Result within about 2 h; high sensitivity and specificity for Enterobacterales	Weaker for OXA-48-like enzymes; does not identify class (Nordmann *et al*., 2012; Tijet*et al*., 2013)
Modified carbapenem inactivation method (mCIM) with eCIM	Carbapenem disc exposed to test organism, then used on indicator strain; EDTA variant separates MBLs	Low cost; CLSI-endorsed; distinguishes serine from metallo-carbapenemases	Overnight turnaround
Chromogenic screening agar	Selective medium for CRE	Useful for rectal screening	Cost; mainly research use (Arnold *et al*., 2011)

The modified Hodge test deserves particular caution in SSA because it performs poorly against NDM, the region's dominant carbapenemase. Where it is the only confirmatory test, a negative result does not exclude a carbapenemase.

7.4 Molecular and genomic methods

PCR for *bla*NDM, *bla*OXA-48-like, *bla*KPC, *bla*VIM and *bla*IMP gives definitive identification and guides drug choice, and whole-genome sequencing adds clone and plasmid data for outbreak investigation. A combination of phenotypic screening and genotypic confirmation is recommended. In SSA these tools are mostly limited to reference and research laboratories because of cost, equipment and expertise [30]. Genomic surveillance also finds CRE without any detectable carbapenemase gene, such as Nigerian and Kuwaiti isolates with carbapenem MICs above 32 μg/mL that carried efflux pump genes instead [19].

8 TREATMENT OF CRE BLOODSTREAM INFECTION IN CHILDREN

Treatment of paediatric CRE BSI rests largely on adult data and expert guidance, because paediatric trials are few [9,48]. In SSA, the carbapenemase mix, dominated by MBLs, and limited drug access narrow the options further.

8.1 General framework

Paediatric guidance suggests that antibiotic choice be driven mainly by susceptibility results, not simply by whether a carbapenemase is present [9]:

- Carbapenem MIC at or just above the susceptible breakpoint: extended-infusion meropenem may still be used; a 3-hour infusion can achieve target concentrations for MICs up to 8 μg/mL in healthy children.
- Clearly carbapenem-resistant isolates (meropenem MIC ≥4 μg/mL): a newer β-lactam/β-lactamase inhibitor active against the isolate is preferred where available.
- Combination partners: aminoglycosides are the preferred second agent given paediatric familiarity with dosing; fluoroquinolones can be used if susceptible; polymyxins (polymyxin B preferred for non-urinary infection) are reserved for when nothing else is active.

8.2 Matching the drug to the enzyme

The carbapenemase class determines which newer agents work, which is why molecular identification has direct clinical value:

- KPC: ceftazidime-avibactam, meropenem-vaborbactam and imipenem-relebactam are generally active.
- OXA-48-like: ceftazidime-avibactam is usually active; meropenem-vaborbactam and imipenem-relebactam are not reliable.
- MBLs (NDM, VIM, IMP): none of the licensed β-lactamase inhibitors inhibits MBLs. Options are ceftazidime-avibactam combined with aztreonam, which MBLs do not hydrolyse, or cefiderocol [48]. Aztreonam alone is unreliable because most MBL producers also carry ESBL, AmpC or OXA-48-like enzymes that hydrolyse it; avibactam protects aztreonam from these. This applies directly to the NDM plus OXA-181 co-producers common in Nigeria.

Nigerian CRE isolates show high resistance to ceftazidime-avibactam and ceftolozane-tazobactam, consistent with their high NDM prevalence [34]. This means the newer agent most often stocked is frequently inactive against the enzymes that matter most in the region.

8.3 Constraints in sub-Saharan Africa

Newer agents are often unregistered, unavailable or unaffordable, so clinicians fall back on colistin, aminoglycosides, tigecycline and fosfomycin. These agents have toxicity concerns, uncertain neonatal dosing and, for tigecycline, poor serum levels for BSI. Colistin use in neonates varies widely and its optimal dosing and combination remain unclear [41]. Treatment also depends on source control, such as removal of infected central lines, and on supportive critical care.

These constraints make prevention and stewardship the most realistic levers for reducing CRE mortality in children in SSA.

9 PREVENTION, STEWARDSHIP AND RESEARCH PRIORITIES

9.1 Infection prevention and control

Because most paediatric CRE BSIs in SSA arise from transmission within hospitals, IPC is the highest-yield intervention. Core measures include hand hygiene, aseptic central-line insertion and care bundles, safe injection practice, environmental cleaning with attention to sinks and drains, contact precautions and cohorting, and rectal screening of high-risk admissions where laboratory capacity allows [25]. Israel's national programme, which combined mandatory reporting, isolation and screening, cut CRE incidence by 79%, showing what coordinated action can achieve [44]. Neonatal CLABSI prevention bundles need adapting to paediatric realities such as small line sizes, parenteral nutrition and prematurity.

9.2 Antimicrobial stewardship

Carbapenem overuse, often driven by the absence of culture results, is the main selective pressure. Stewardship priorities include:

- Culture before antibiotics, with rapid reporting of Gram stain and susceptibility results.
- Local antibiograms to set empirical regimens, reviewed at 48–72 hours with de-escalation; NeoOBS found de-escalation was almost never done [41].
- Restricting carbapenems and reserve agents in line with the WHO AWaRe classification.
- Regulation of over-the-counter antibiotic sales and substandard medicines.

9.3 Research and surveillance gaps

The evidence reviewed here reveals consistent gaps:

- Paediatric-specific surveillance. Most Nigerian CRE data are from adults or mixed ages, and the South-East and North-East are under-represented [1].
- Molecular characterisation. Few paediatric isolates are genotyped or sequenced, so the carbapenemase mix, high-risk clones and plasmids driving paediatric BSI are poorly described.
- Adjusted outcome data. Studies that separate the effect of carbapenem resistance from host severity are few, and the one prospective SSA neonatal study that did so found no independent effect after adjustment.
- Affordable diagnostics. Validation of low-cost tests such as mCIM/eCIM and rapid lateral-flow carbapenemase assays in SSA laboratories is needed, as is retirement of the modified Hodge test where NDM predominates.
- Therapeutics. Paediatric and neonatal pharmacokinetic data, trials of empirical regimens such as NeoSep1, and access to MBL-active agents are needed.
- Colonisation and transmission studies linking neonatal gut carriage, the hospital environment and subsequent BSI.

10 CONCLUSION

CRE are now established causes of bloodstream infection among children in sub-Saharan Africa, concentrated in neonatal units and among the sickest, smallest infants. The regional carbapenemase profile, dominated by NDM and OXA-48-like enzymes with little KPC, differs from high-income settings and neutralises several of the newer β-lactam/β-lactamase inhibitors. Detection is hampered by weak laboratory capacity and by reliance on tests that miss NDM, so the true burden is underestimated. In Nigeria, CRE prevalence is rising and high-risk clones carrying *bla*NDM and *bla*OXA-181 are documented, but paediatric bloodstream data, especially from the South-East, remain scarce. Sustained paediatric surveillance with molecular typing, affordable carbapenemase testing, strengthened neonatal IPC, carbapenem stewardship and access to paediatric-appropriate MBL-active antibiotics are needed to protect the children most at risk.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

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Disclosure of conflict of interest

The authors declare no conflicts of interest.

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