


Antimicrobial Resistance Rates and Surveillance in Sub-Saharan Africa: Where Are We Now?

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Introduction: Although antimicrobials have traditionally been used to treat infections and improve health outcomes, resistance to commonly used antimicrobials has posed a major challenge. An estimated 700,000 deaths occur globally every year as a result of infections caused by antimicrobial-resistant pathogens. Antimicrobial resistance (AMR) also contributes directly to the decline in the global economy. In 2019, sub-Saharan Africa (SSA) had the highest mortality rate (23.5 deaths per 100,000) attributable to AMR compared to other regions.

Methods: We searched PubMed for articles relevant to AMR in pathogens in the WHO-GLASS list and in other infections of local importance in SSA. In this review, we focused on AMR rates and surveillance of AMR for these priority pathogens and some of the most encountered pathogens of public health significance. In addition, we reviewed the implementation of national action plans to mitigate against AMR in countries in SSA.

Results and Discussion: The SSA region is disproportionately affected by AMR, in part owing to the prevailing high levels of poverty, which result in a high burden of infectious diseases, poor regulation of antimicrobial use, and a lack of alternatives to ineffective antimicrobials. The global action plan as a strategy for prevention and combating AMR has been adopted by most countries, but fewer countries are able to fully implement country-specific action plans, and several challenges exist in many settings.

Conclusion: A concerted One Health approach will be required to ramp up implementation of action plans in the region. In addition to AMR surveillance, effective implementation of infection prevention and control, water, sanitation, and hygiene, and antimicrobial stewardship programs will be key cost-effective strategies in helping to tackle AMR.

Keywords: antimicrobial resistance, surveillance, sub-Saharan Africa, GAP, NAP

Background

Antimicrobial resistance (AMR) is a huge challenge to public health and directly impacts economic growth globally, with developing countries in Africa bearing the biggest burden of the negative effects of AMR.^{1,2} AMR is the ability of microorganisms to persist or grow in the presence of drugs designed to inhibit or kill them. This results in therapeutic failure, which negatively impacts the global control and management of infectious diseases. Infections caused by antimicrobial-resistant pathogens are reported to result in approximately 700,000 deaths globally every year.³ Furthermore, if no intervention strategies are initiated, it is estimated that by 2050, mortalities attributed to AMR will have increased to 10 million annually,⁴ with Africa and South Asia bearing the highest burden of deaths.⁵

Impact of Antimicrobial Resistance

The impact of AMR can be classified as either clinical or economic.⁶ The clinical effects of AMR include severe infections, increased morbidity, treatment failure, and mortality.⁷ In 2019, an estimated 4.95 million deaths were associated with AMR globally, with 1.27 million deaths being attributed to AMR.⁸ Lower respiratory and other chest infections, bloodstream and intra-abdominal infections accounted for 78.8% of mortalities attributed to antimicrobial-resistant infections. Compared to other Global Burden of Disease study regions, sub-Saharan Africa (SSA) and South

Asia had the highest mortalities (23.5 deaths per 100,000 and 21.5 deaths per 100,000, respectively) attributable to AMR. Globally, Western SSA had the highest death rate attributable to AMR, 27.3 deaths per 100,000, followed by Eastern, Central, and Southern SSA (Table 1).⁸ The high death rate attributable to AMR in SSA is a plausible effect of ineffective water, sanitation, and hygiene (WASH) infrastructure,^{9,10} inefficient infection prevention and control, poor regulation of antimicrobial use, and constrained healthcare systems. In neonatal sepsis, 31% of mortalities (690,000) reported were plausibly attributed to antimicrobial-resistant infections.¹¹

The economic effects of AMR comprise increased length of hospitalization, higher healthcare costs,^{7,12} and decreased labor supply and labor efficiency.¹³ The global economic cost associated with AMR is estimated to be US\$ 100 trillion by 2050 if the current trend persists.¹⁴ Currently, the economic cost associated with AMR in Europe is estimated to be more than €2.0 million, while in the USA the cost is approximately \$55 billion.¹⁵ According to projections by RAND Europe, the economic loss due to AMR would be the highest in the SSA region if no intervention were implemented.¹⁶

Role of Antimicrobial Use in Increasing Rates of AMR

AMR essentially occurs as the result of the acquisition, expression, and transfer of resistance genes in pathogens. Pathogens acquire resistance genes through natural selection when exposed to antimicrobial pressure.^{16,17} Indeed, the rapid emergence of antimicrobial-resistant pathogens is often accelerated by the inappropriate use and overuse of antimicrobial agents, especially antibiotics, in humans, animals, and agriculture/the environment.^{18,19} While antimicrobials are often used to improve treatment outcomes, inappropriate and/or unnecessary consumption of antimicrobials by humans is a huge contributor to the emergence of AMR. Inappropriate usage/consumption of antimicrobials in humans occurs through inappropriate prescription,²⁰ needlessly lengthy courses of treatment,²¹ self-medication,^{22–25} incomplete use of prescribed antimicrobials, and irregular use of reserve antimicrobials.

A study published in 2021 reported that there was a 46% increase in the global consumption of antimicrobials between 2000 and 2018.²⁶ The study found that the consumption rate increased from 9.8 (9.2–10.5) daily defined doses (DDD) to 14.3 (13.2–15.6) DDD per 1000 population per day. According to the World Health Organization (WHO) report on surveillance of antimicrobial consumption, in 65 countries, consumption ranged from 4.4 to 64.4 DDD per 1000 population per day.²⁷ In the four SSA countries assessed, consumption ranged from 4.4 DDD in Burundi to 27.29 DDD per 1000 population per day in Tanzania.

Owing to the global increase in human population, demand for food, both plant and animal products, has increased. Nearly three-quarters of all antimicrobials sold globally are used in food-producing animals.²⁸ In food-producing animals, antimicrobials are mainly used for the prevention and treatment of disease.^{19,29,30} Although the use of antimicrobials is important in ensuring the health of the animals, prolonged use for non-therapeutic purposes (eg prophylaxis, growth promotion), and often at sub-therapeutic levels, contributes to the emergence and persistence of AMR.²⁹

The use of antimicrobials in animals contributes to AMR in both animals and humans. Study reports have shown that between 2015 and 2019, 3558–4279 tons of antimicrobials were used in animal production in 13–27 African countries.³¹

Table 1 Death Rates Involving Infection, Associated with and Attributable to AMR, in SSA in 2019

| SSA Region | Deaths Involving Infection | Deaths Associated with Resistance | Deaths Attributable to Resistance | Deaths Rate per 100,000 Attributable to Resistance | Ref |
|--------------|---------------------------------|-----------------------------------|-----------------------------------|--|-----|
| Western SSA | 1,850,000 (1,510,000–2,270,000) | 524,000 (412,000–663,000) | 125,000 (95,400–161,000) | 27.3 (20.9–35.3) | [8] |
| Southern SSA | 334,000 (276,000–399,000) | 62,400 (48,400–79,800) | 15,300 (11,300–20,400) | 19.4 (14.3–25.9) | |
| Eastern SSA | 1,310,000 (1,080,000–1,610,000) | 366,000 (290,000–464,000) | 88,200 (67,000–116,000) | 21.4 (16.3–28.1) | |
| Central SSA | 418,000 (335,000–520,000) | 113,000 (86,600–144,000) | 27,200 (19,600–36,400) | 20.7 (14.9–27.7) | |

Abbreviation: SSA, sub-Saharan Africa.

Globally, the largest AMR hotspots in animal health are China and India. However, Brazil and Kenya have also been identified as important hotspots for the emergence of AMR attributed to use of antimicrobials in animals.²⁹

It has been shown that the reduction of inappropriate antimicrobial use directly contributes to the decrease in the development of AMR; however, this alone would not be adequate to deal with the global AMR challenge.³² Consequently, there is a need to control the high rate of emergence and spread of antimicrobial-resistant strains and genes in the environment, animals, and human population (the One Health approach).

Methodology

In this review, “sub-Saharan Africa” refers to the countries that constitute the WHO- Africa region. The SSA region was then divided into four sub-regions (Western, Eastern, Central, and Southern). Relevant English literature (original articles and reviews) from the four sub-regions was retrieved from PubMed and Google Scholar and considered for review. The literature search was based on several search terms: antimicrobial resistance, multi-drug resistance, sub-Saharan Africa, surveillance, global action plan, national action plan, and One Health approach. The pathogens discussed were selected on the basis of being priority pathogens for surveillance and reporting to the WHO Global Antimicrobial Resistance and Use Surveillance System (GLASS),^{33,34} with *Vibrio cholerae* being included as an important neglected tropical disease and with emerging multidrug-resistant strains from the region. The inclusion criteria also included articles on the selected pathogens from SSA countries, articles reporting on antibiotic resistance rates and genes, and articles published between the years 2000 and 2022. These criteria were inclusive of both monomicrobial and polymicrobial studies. The abstracts of all articles that met the above criteria were reviewed. Where insufficient detail was provided, the entire article was reviewed before determining whether to include it or not. Exclusion criteria were articles on non-WHO-GLASS pathogens, articles from beyond the SSA region, conference abstracts, and intervention trials. Duplicate references and publications reporting the same data in different journals were excluded.

Results and Discussion

Antimicrobial Resistance Rates in Sub-Saharan Africa

AMR is a challenge in both developed and developing countries. However, AMR prevalence varies considerably geographically in different continents, regions, and countries.³⁵ In SSA, different pathogens were found to have varying rates of resistance to different antimicrobial agents and these may be different from region to region. This review focused on AMR among key enteric infectious diseases of public health significance in the SSA region.

Diarrheagenic *Escherichia coli*

Diarrheagenic *Escherichia coli*, especially enteropathogenic *E. coli* (EPEC) and enterotoxigenic *E. coli* (ETEC), accounts for 14.26 million (5.63–30.90 million) and 222.64 million (144.95–322.85 million) episodes each year, respectively. According to the 2016 Global Burden of Disease (GBD) report, cumulatively these two pathotypes result in 63,523 deaths among all ages annually, throughout the world.³⁶ Other important *E. coli* pathotypes have been implicated, namely: enteroaggregative *E. coli* (EAEC), Shiga toxin-producing *E. coli* (STEC), enteroinvasive *E. coli* (EIEC), and diffusely adhering *E. coli* (DAEC), which are important in specific regions globally.³⁷ In SSA, the precise burden associated with diarrheagenic *E. coli* is not known; however, prevalence rates ranging from 14.7% to 82% have been reported in Nigeria,³⁷ Gabon,³⁸ Burkina Faso,³⁹ Kenya,⁴⁰ South Africa,⁴¹ and Tanzania.⁴² Children under the age of five have the highest risk of infection in the region. Transmission is via the fecal route, either directly through person-to-person contact or indirectly through contaminated food and water. Primarily, the diagnosis of diarrheagenic *E. coli* in patients and populations is through physical examination, signs and symptoms, and laboratory diagnosis – which is not routinely performed in primary care facilities owing to inadequate infrastructure. Confirmatory tests for diarrheagenic *E. coli* pathotypes are carried out in tertiary and research laboratories, where molecular methods, both culture-based and culture-independent assays, are utilized.

The standard treatment for diarrheagenic *E. coli* is oral rehydration, and antimicrobials are only recommended in severe cases. Over the years, antimicrobial-resistant diarrheagenic *E. coli* has emerged and varying resistance rates have

been reported (Table 2). Resistance genes harbored in a variety of mobile genetic elements have been implicated: *bla*TEM, *bla*SHV, *bla*CTX-M-15, *bla*OXA-2, *bla*AmpC, *bla*OXA-181, *bla*NDM, *catA*, *tetA*, *sulI*, II & III, *dfpA*, *aac*(6') *lb*, *aadA1*, *qnrS1*, and *rmtA*.^{41,43–49} Of concern are carbapenemase-encoding genes, which have been observed among diarrheagenic *E. coli* isolates in several countries in the region. For instance, in Ghana⁴⁷ and Burkina Faso,⁴⁶ ST410 diarrheagenic *E. coli* isolates were reported to have the *bla*OXA-181 gene (a variant of the class D *bla*OXA-48), which was contained in an IncX3 plasmid. Another diarrheagenic *E. coli* isolate in Ghana, of the sequence type 940, was also demonstrated to have *bla*OXA-181 but in an IncFIC (FII) plasmid. In addition, it harbored the *qnrS1* gene, which confers resistance to fluoroquinolones in an IS26 transposon.⁴⁷ An ST410 with the *bla*NDM-1 gene contained in an IncHI1, as well as Tn125 transposon, and an *ISSm-1*-like insertion sequence belonging to the novel *IS110* family has also been reported, further raising concerns regarding the effectiveness of carbapenems in treatment.⁴⁵

Currently, no licensed vaccine is available for diarrheagenic *E. coli*, but several candidates are in different stages of development.⁵¹ Control measures are needed to prevent diarrheagenic *E. coli* in the short term, such as improved WASH infrastructure, exclusive breastfeeding, optimal nutrition, and the creation of community awareness.

Cholera

Cholera, caused by the bacterium *Vibrio cholerae*, is a diarrheal disease that causes devastating epidemics as well as sporadic cases in many settings in SSA that still have challenges with overcrowding, poor WASH infrastructure, and displaced populations. According to the WHO, 1.3–4 million cholera infections occur globally and out of these 21,000–143,000 result in death. In SSA, cholera is still endemic and is responsible for 141,918 infections per year (95% CI 141,538–146,505).⁵² The bacterium *V. cholerae* is composed of 206 recognized serogroups,⁵³ two of which (ie serogroups O1 and O139) cause epidemics. These serogroups are further divided into two distinct serotypes, namely, Classical and El Tor. The *V. cholerae* Ogawa biotype has been shown to be the most prevalent in the region, while epidemics are mainly caused by Wave 3 atypical O1 El Tor strain, which has been reported to be resistant to multiple antimicrobials,^{54,55} as shown in Table 3.

In the past decade, *V. cholerae* isolates have become resistant to penicillins, aminoglycosides and sulfonamides, quinolones, tetracycline, macrolides, and phenicols,^{55–59} and more recently several studies have reported strains showing reduced susceptibility to fluoroquinolones and third generation cephalosporins.^{54,57,58,60} This resistance has been associated with the mutation of housekeeping genes such as *gyrA* (Ser83Ile) and *parC* (Ser85Leu),^{56,60} the presence of mobile genetic elements such as integron class 2,⁵⁶ and the presence of integrative conjugative elements (ICEs), mainly SXT/R391 (Figure 1). However, clinical and environmental non-O1/O139 *V. cholerae* have been reported to have low-level resistance

Table 2 Antibiotic Resistance Rates of Clinical Diarrheagenic *E. coli* (DEC) in SSA

| Country | Isolates | Antibiotic Resistance Rates (%) of Clinical DEC Isolates | | | | | | | | | | | | Ref |
|--------------|----------|--|------|------|------|------|------|------|------|------|------|------|-----|------|
| | | TET | COT | CHL | CAZ | CTX | CIP | NAL | CRO | AMP | AMC | CN | IMI | |
| Nigeria | 165 | ND | 78.2 | ND | 22.4 | 12.1 | 5.5 | ND | ND | ND | 40 | 4.2 | ND | [37] |
| South Africa | 120 | 91 | 96 | 94 | ND | ND | 45 | ND | ND | 98 | ND | ND | 36 | [44] |
| South Africa | 324 | 84 | 82 | 10 | 38 | 45 | ND | 42 | ND | 80.9 | ND | ND | ND | [41] |
| Tanzania | 687 | ND | 82 | 20.5 | ND | ND | 0 | ND | ND | 80.9 | 14.4 | ND | ND | [42] |
| Kenya | 136 | 82.8 | 61.4 | 62.1 | ND | ND | 28.3 | 11 | 12.4 | 83.3 | 26.2 | 47.6 | ND | [40] |
| Ghana | 21 | ND | 100 | ND | 100 | 100 | 100 | ND | ND | ND | ND | 81 | 0 | [43] |
| Ghana | 37 | ND | 80.5 | ND | 16.1 | 19.3 | ND | ND | ND | ND | ND | 0 | 0 | [47] |
| Ethiopia | 73 | ND | 67.1 | ND | ND | 6.9 | 2.7 | 27.4 | ND | ND | 64.4 | ND | ND | [50] |

Abbreviations: TET, tetracycline; COT, cotrimoxazole; CHL, chloramphenicol; CAZ, ceftazidime; CTX, cefotaxime; CIP, ciprofloxacin; NAL, nalidixic acid; CRO, ceftriaxone; AMP, ampicillin; AMC, amoxicillin/clavulanic acid; CN, gentamicin; IMI, imipenem; ND, not done.

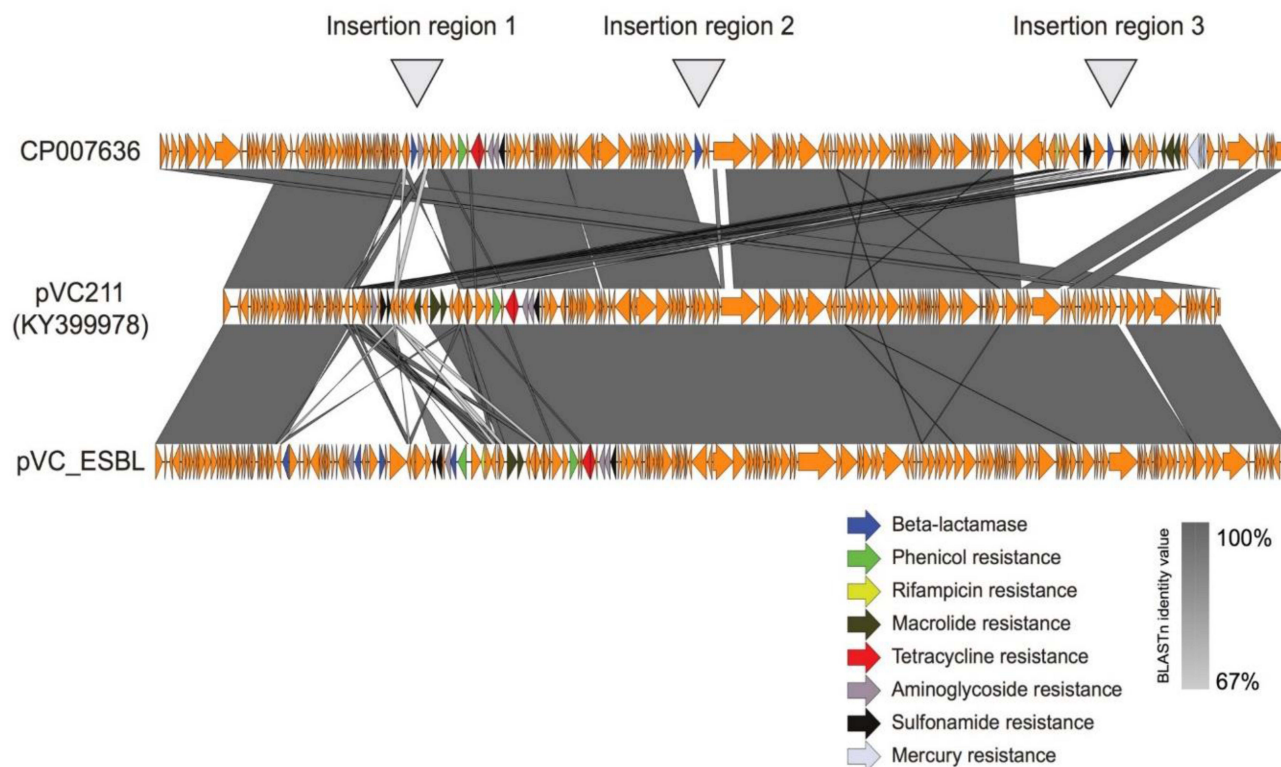
Table 3 Antibiotic Resistance Rates of Clinical *Vibrio cholerae* in SSA

| Country | Serogroup | Antibiotic Resistance Rates (%) of <i>V. cholerae</i> | | | | | | | | Ref |
|------------|------------------|---|-----|-----|------|-----|------|----|-----|------|
| | | DO | AZM | CIP | NA | SXT | AMP | CN | TET | |
| Uganda | O1 Inaba | ND | ND | <10 | >50 | >55 | 100 | 0 | >50 | [61] |
| Nigeria | O1 Ogawa | ND | ND | 0 | ND | 50 | ND | ND | 75 | [62] |
| Ghana | O1 Ogawa | 2.5 | ND | 0 | ND | 95 | 90 | ND | 0 | [58] |
| Kenya | O1 Inaba & Ogawa | 1.0 | ND | 0 | 83.2 | ND | 89.1 | 0 | 97 | [63] |
| Mozambique | O1 Ogawa | 56 | 13 | 0 | 100 | 75 | 100 | ND | 50 | [64] |

Abbreviations: DO, doxycycline; AZM, azithromycin; CIP, ciprofloxacin; NA, nalidixic acid; SXT, sulfamethoxazole–trimethoprim; AMP, ampicillin; CN, gentamicin; TET, tetracycline; ND, not done.

to commonly used antimicrobials.⁶⁰ In Kenya, the extended-spectrum β -lactamase (ESBL)-producing *V. cholerae* isolates have been found to carry a 168,803-bp putative conjugative plasmid belonging to *IncA/C* that we designated as pVC_ESBL. The pVC_ESBL plasmid shares extensive sequence identity and synteny with related plasmids (Figure 2), and the incorporation of the class 1 integron and the insertion of the *bla*_{CTX-M-15} on the plasmid backbone.

Oral rehydration remains the mainstay of management of cholera cases, while antimicrobial use is reserved for the treatment of severe illness. Currently, three WHO pre-qualified oral cholera vaccines (OCVs) – Dukoral®, Shanchol™, and Euvichol® – are administered through mass vaccinations, especially in cholera-endemic areas for the purpose of reducing transmission in endemic settings. In addition to vaccines, improvement of the WASH infrastructure will aid in the control of cholera in SSA.

**Figure 1** Resistance elements inserted into the novel pVC_ESBL plasmid in Kenyan cholera strains.

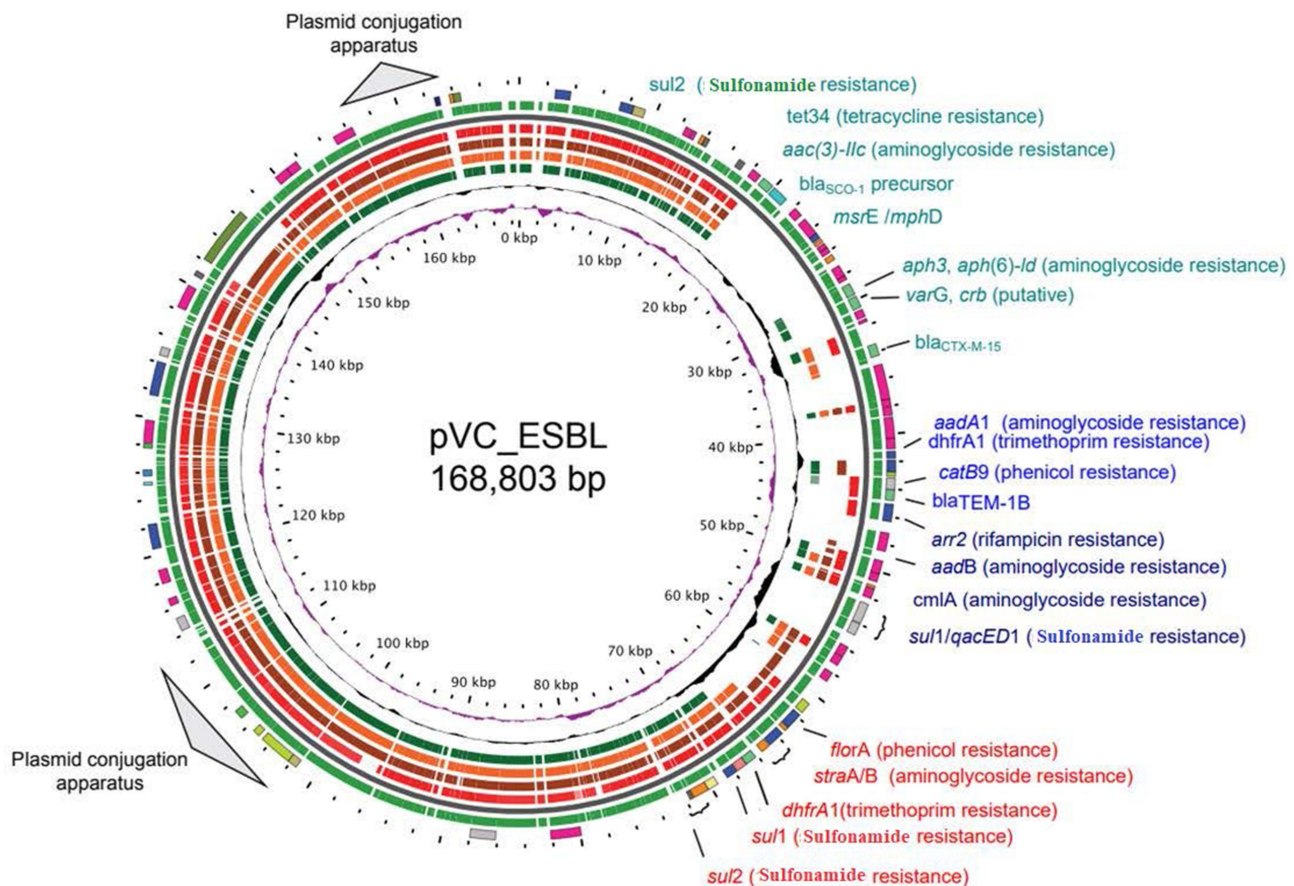


Figure 2 There are three main regions on the pVC_ESBL: SXT R319 carrying the *floR-dhfrA1-strA-StrB-sul2* genes, class I integron carrying *aadB-arr2-bla_{TEM1B}-cmlA-bla_{CTX-M-15}-arr2-aadA1* cassettes and with *sul1* and a truncated *qacEΔ1* gene at the 3' conserved end, and resistance genes inserted into the plasmid backbone encoding resistance to *bla_{CTX-M-15}*, *aac(3)-IIc* that confer resistance to streptomycin, kanamycin, and tobramycin, and a putative gene for tunicamycin resistance.

Typhoid Fever

Typhoid fever is caused by *Salmonella enterica* serotype Typhi (*S. Typhi*). Globally, 10.9 million (9.3–12.6 million) cases of typhoid fever occur every year, resulting in nearly 117,000 deaths.⁶⁵ In SSA, approximately 1.5 million cases are reported annually and 19,900 deaths, accounting for approximately 17% of global deaths.⁶⁵ In the 1980s in most SSA countries, *S. Typhi* isolates were fully susceptible to firstline antibiotics, but in the past two decades, multidrug-resistant (defined as resistance to ampicillin, trimethoprim–sulfamethoxazole, and chloramphenicol) *S. Typhi* has emerged and spread throughout the region.^{66–68} Because of this resistance, treatment options were revised to include azithromycin, fluoroquinolones, and third-generation cephalosporins. Subsequently, *S. Typhi* isolates with reduced susceptibility to these antimicrobials have now been reported in Kenya,^{68,69} South Africa,⁷⁰ and Congo.⁷¹ In a study undertaken in Ibadan, Nigeria, 4.0% of febrile patients with bacteremia were found to be positive for *S. Typhi*, while 1% had invasive non-typhoidal *Salmonella* (iNTS) infections.⁷² All of the *Salmonella* isolates except one showed multidrugresistance (resistance to at least three antimicrobial classes), with ciprofloxacin non-susceptibility observed in 70.3% and 57% of *S. Typhi* and iNTS, respectively. Recent data from Kenya show that *S. Typhi* H58 subgroups circulating in the study setting all had high rates (>70%) of multidrug resistance (MDR) and clearly showed that multidrug-resistant strains predominate and have a high carriage rate in the asymptomatic population.⁷³

Previously, *S. Typhi* populations were classified into 85 haplotypes (haploid genotypes), but currently, they are categorized into four clusters, 16 clades, and 49 subclades.⁷⁴ Subclade 4.3.1 (previously haplotype 58) is the predominant MDR genotype in SSA,⁷⁵ with a prevalence ranging from 60.4% to 97%,^{73,76–78} which has been associated with not only

acute cases but also carriers.⁷³ The resistance in 4.3.1 genotype has been attributed to the presence of translocated regions containing plasmids such as IncIII and IncN (subtype PST3),^{66,69,73,77,78} and the presence of chromosomal mutations in the quinolone resistance-determining regions (QRDRs) of genes *parC*, *gyrA*, *gyrB*, and *gyrS*.^{73,78}

One of the key factors that has contributed greatly to the AMR of *S. Typhi* in SSA is the challenges encountered in diagnosis. First, treatment is often prescribed based on symptoms; this is due to the unavailability of microbiology laboratories to perform culture, which is the gold standard but requires invasive sampling, adequate infrastructure, and skilled staff. Often, typhoid symptoms are compounded by or confused with other febrile illnesses such as malaria, owing to their similarity. Secondly, clinicians rely on the Widal test, which is accessible and cheap, and does not require sophisticated technical knowledge to use. However, the Widal test has been proven to be unreliable as it cross-reacts with other *Salmonella* serotypes and other enteric bacteria. The test is open to widespread abuse and misinterpretation, titers are often guessed using a rapid slide agglutination without serial dilution/tubes, timing of the test is inaccurate, and serum quantities are not measured (there is often no measuring device), among other challenges.⁷⁹ The introduction of rapid and easy-to-use diagnostic tools for typhoid fever surveillance, potentially including environmental surveillance, and the improvement of existing methods have been recommended⁸⁰ as some of the best approaches to facilitate the identification of high-risk areas. Such rapid and easy-to-use tools need to be affordable, applicable to the illnesses, easy to perform anywhere, and safe and easy to store in rural areas, among other key desirable factors.

Antibiotic treatment is still the mainstay of typhoid management. The recommended antimicrobials are fluoroquinolones, third-generation cephalosporins, and azithromycin. Vaccination prophylaxis is key in the control and prevention of typhoid, especially in endemic areas. Three typhoid vaccines are currently recommended by the WHO: 1) typhoid conjugate vaccine (TCV), 2) unconjugated polysaccharide vaccine (Vi-PS), and 3) oral live-attenuated Ty21a vaccine. Table 4 shows the antibiotic resistance rates of *S. Typhi* from clinical samples as previously reported in various countries in SSA. Based on these studies, the AMR rates of *S. Typhi* vary in different countries and regions.

Invasive Non-Typhoidal Salmonellosis

iNTS accounts for 534,600 (409,000–705,000) cases and 77,470 (46,360–122,800) deaths annually worldwide; out of these, 421,600 (316,000–574,100) cases (26.2% attributed to HIV infection) and 66,520 deaths occur in SSA.⁸⁷ The highest incidence is observed among children aged 0–5 years, followed by the 15–19 and 35–49-year-old age groups. The major predisposing factors for iNTS infection in children are malnutrition, malaria parasitemia, and underdeveloped immunity, while in adults, HIV infection is the primary factor.^{88–91} Other significant host factors are anemia and sickle cell.^{92,93} In urban areas where iNTS is endemic, malnutrition plays a key role in adult infection, especially where exposure to malaria is minimal.⁸⁹ In SSA, the incidence of iNTS disease in children ranges from 166 to 568/100,000

Table 4 Antibiotic Resistance Rates of Clinical *Salmonella enterica* Serotype Typhi Isolates in SSA

| Country | Antibiotic Resistance Rates (%) of Clinical <i>S. Typhi</i> Isolates | | | | | | | | | | Ref |
|----------|--|------|------|------|-----|------|------|-----|------|------|------|
| | Isolates | TET | COT | CHL | CAZ | CTX | CIP | NAL | CRO | AMP | |
| Kenya | 144 | 73 | 70 | 72 | ND | 6 | 6 | 7 | 4 | 72 | [69] |
| Uganda | 18 | 83 | ND | 83 | ND | ND | 0 | 5.6 | 0 | 83 | [81] |
| Ethiopia | 6 | 83.3 | 50 | 83.3 | 0 | 0 | 16.7 | 50 | 16.7 | ND | [82] |
| Ethiopia | 6 | ND | 66.7 | 16.7 | ND | 100 | 16.7 | 100 | 0 | 83.3 | [83] |
| DRC | 470 | ND | ND | 54.9 | ND | ND | 24.5 | ND | ND | 70 | [84] |
| Nigeria | 440 | 100 | 100 | 100 | ND | 27.3 | 27.3 | ND | ND | 100 | [85] |
| Zimbabwe | 41 | >45 | ND | >90 | ND | ND | 22 | <5 | 0 | >90 | [86] |

Abbreviations: TET, tetracycline; COT, cotrimoxazole; CHL, chloramphenicol; CAZ, ceftazidime; CTX, cefotaxime; CIP, ciprofloxacin; NAL, nalidixic acid; CRO, ceftriaxone; AMP, ampicillin; ND, not done.

cases of person-years of observation (pyo).⁹⁴ In most parts of SSA, iNTS presents as non-specific febrile illness, which poses a major challenge in diagnosis as it is difficult to distinguish from other febrile illnesses endemic in these settings, such as malaria. In addition, most NTS infections present as invasive disease, especially among children less than 5 years of age and those with underlying immunosuppressive conditions.⁹⁵ Of all the NTS serotypes, *S. Typhimurium* and *S. Enteritidis* contribute the highest proportion of invasive disease. In Kenya, for instance, of all iNTS isolates, 33.6% were *S. Typhimurium* while 22.8% were *S. Enteritidis*.⁹⁶ A review published in 2017⁹³ found that since 1966, NTS has been a major cause of bacteremia in 33 out of 54 African countries, accounting for up to 39% of community-acquired bloodstream infections in the region and resulting in an average case fatality rate of 19%. Increasing rates of MDR in iNTS are of great concern, and the situation is even more acute in SSA settings where alternative options for effective treatment are being rapidly eroded. High levels of multidrug-resistant iNTS have been reported in Kenya,^{97–99} and in other parts of SSA, including DRC,^{100,101} Ghana,¹⁰² and Uganda,¹⁰³ posing a major challenge to treatment and management options for severe disease.

Invasive strains of multidrug-resistant NTS circulating in SSA are predominantly *S. Typhimurium* ST313 and *S. Enteritidis* ST11, although *S. Dublin* ST10 has only been associated with resistance in West Africa.^{96,104} These strains harbor the notorious Tn21 transposon on an *incF* plasmid (p*SLT*-BT), which contains a plethora of resistance genes. In addition, resistance to third generation cephalosporins has been attributed to the presence of ESBL-encoding genes such as *bla*CTX-M, while non-susceptibility to fluoroquinolones has been associated with mutation of the *gyrA* gene.¹⁰⁴ Multidrug-resistant *S. Typhimurium* ST313 has now been reported from several countries in SSA, including Kenya,¹⁰⁵ Malawi,⁶⁷ Central African Republic, Senegal, Burkina Faso,¹⁰⁶ DRC,¹⁰⁷ Nigeria,¹⁰⁸ Ghana,¹⁰² South Africa, and Mozambique,^{79,109} where iNTS is endemic and produces septicemia in the absence of gastroenteritis.

In another study of the genetic characteristics and transmission patterns associated with multidrug-resistant iNTS serovars across SSA,¹⁰⁴ multiple multidrug-resistant iNTS serovar sequence types were identified as circulating in several countries that were sampled. High carriage rates observed in endemic sites in Kenya of MDR ST313¹¹⁰ are likely to provide a reservoir for community spread of infection to vulnerable populations, adding new challenges in the control and prevention of iNTS disease.

Efforts to increase access to diagnostic services are required to improve patient outcomes and also to estimate disease burden. There are currently no rapid diagnostic tests available for the detection of iNTS, and the development of such tests would greatly facilitate the study and management of iNTS disease in SSA. The development of novel diagnostic tools is challenging owing to the diversity of NTS serotypes, but the use of locally targeted lipopolysaccharide antigen is likely to be useful.^{79,111}

Third generation cephalosporins (ceftriaxone) and fluoroquinolones (ciprofloxacin) are the mainstay of iNTS treatment. Non-fluoroquinolone-susceptible cases are usually treated with azithromycin. Currently, no vaccine is available for the long-term prevention and control of iNTS, but several vaccine candidates are under development. Sustained disease

Table 5 Antimicrobial Resistance Rates of Clinical *Salmonella enterica* Serotype Typhimurium Isolates in SSA

| Country | Antimicrobial Resistance Rates (%) of Clinical <i>S. Typhimurium</i> Isolates | | | | | | | | | | | Ref |
|------------|---|-------|-------|-------|-----|-----|------|------|-----|-------|------|-------|
| | Isolates | TET | COT | CHL | CAZ | CTX | CIP | NAL | CRO | AMP | AZM | |
| Gambia | 19 | 10–20 | 20–30 | 10–20 | ND | ND | 0 | ND | 0 | 20–30 | ND | [112] |
| Congo | 345 | ND | 95.1 | 87.6 | ND | ND | 13.3 | ND | 3.8 | 92.5 | 36.2 | [101] |
| Mali | 178 | ND | 92.1 | 91.0 | ND | ND | ND | ND | 0 | 93.8 | ND | [113] |
| Mozambique | 460 | 16.4 | 63.9 | 43.3 | ND | ND | 0 | 16.7 | 0 | 71.4 | ND | [114] |
| Malawi | 294 | ND | ND | ND | ND | ND | 0.2 | ND | 0.3 | ND | ND | [115] |
| Kenya | 45 | 20 | 100 | 80 | ND | 0 | <5 | 20 | ND | 100 | ND | [116] |

Abbreviations: TET, tetracycline; COT, cotrimoxazole; CHL, chloramphenicol; CAZ, ceftazidime; CTX, cefotaxime; CIP, ciprofloxacin; NAL, nalidixic acid; CRO, ceftriaxone; AMP, ampicillin; AZM, azithromycin; ND, not done.

Table 6 Antimicrobial Resistance Rates of Clinical *Salmonella enterica* Serotype Enteritidis Isolates in SSA

| Country | Antimicrobial Resistance Rates (%) of Clinical <i>S. Enteritidis</i> Isolates | | | | | | | | | | | Ref |
|------------|---|------|-------|-------|-----|-----|-----|------|------|-------|-----|-------|
| | Isolates | TET | COT | CHL | CAZ | CTX | CIP | NAL | CRO | AMP | AZM | |
| Gambia | 49 | 80 | 70–80 | 80–90 | ND | ND | 0 | 0 | 100 | 80–90 | ND | [112] |
| Congo | 316 | ND | 84.2 | 84.2 | ND | ND | 2.2 | ND | 0 | 86.1 | 0 | [101] |
| Mali | 55 | ND | 56.4 | 40 | ND | ND | ND | ND | 18.2 | 92.7 | ND | [113] |
| Mozambique | 133 | 64.3 | 66.7 | 69.1 | ND | ND | 0 | 25.2 | 0 | 69.1 | ND | [114] |
| Malawi | 73 | ND | ND | ND | ND | ND | 0.5 | ND | 0.2 | ND | ND | [115] |

Abbreviations: TET, tetracycline; COT, cotrimoxazole; CHL, chloramphenicol; CAZ, ceftazidime; CTX, cefotaxime; CIP, ciprofloxacin; NAL, nalidixic acid; CRO, ceftriaxone; AMP, ampicillin; AZM, azithromycin; ND, not done.

surveillance of multidrug-resistant iNTS organisms is necessary, and there is a need to speed up iNTS vaccines. Tables 5 and 6 show the antibiotic resistance rates of *S. Typhimurium* and *S. Enteritidis*, respectively, as reported in various studies conducted in SSA.

Multidrug-Resistant *Klebsiella pneumoniae*-Associated Infections

Klebsiella pneumoniae is the third leading causative agent for healthcare-associated infections, after *E. coli* and *S. aureus*.^{117,118} It is an opportunistic pathogen which causes infections on otherwise sterile sites, for example septicemia, bacteremia, and infections of the respiratory tract, urinary tract, and central nervous system. Of concern are outbreaks in neonatal units, where the infection rates are 3–20-fold higher than rates in high-income countries.¹¹⁸ More than 50% of healthcare-associated infections associated with *K. pneumoniae* are reportedly ESBL producers,¹¹⁹ and hence the WHO has recognized ESBL and carbapenem-resistant *K. pneumoniae* as public health priorities.¹²⁰ In SSA, precise burden estimates for resistant *K. pneumoniae* are lacking and the available data are generated in referral/research/university hospitals, the context of which does not represent the broad range of healthcare settings.¹¹⁸ These data, however, indicate that the rates are increasing.

In SSA, high-risk populations are newborns and patients admitted to intensive care units (ICUs), especially those with underlying comorbidities.^{121,122} The main driving factors for resistant *K. pneumoniae* are poor hand hygiene among healthcare workers, contaminated medical equipment, and poor waste management practices in hospitals.^{123,124} These drivers are associated with inadequate supply of equipment, poor infrastructure relating to infection control, and understaffed healthcare settings, which result in overcrowded wards and high patient load.

Based on the seven-gene multilocus sequence typing, *K. pneumoniae* is classified into various sequence types (STs). ST15, ST17, and ST70 have been associated with ESBL strains, and have been reported in Eastern Africa and Southern Africa.^{125–127} ST152, ST340 (Clonal Group 258), and ST307 have been associated with carbapenem resistance and have only been reported in Southern Africa.^{128–130} These resistant strains have been shown to harbor multiple resistance genes encoded on the chromosome or on plasmids; namely, *bla* SHV, *bla* LEN, *bla* OKP, *bla* CTX-M, *bla* OXA, *bla* TEM, *bla* KPC, *bla* NDM, *bla* KPC, and *bla* VIM.^{128–130}

To control and prevent hospital-associated resistant *K. pneumoniae*, effective infection control measures will have to be undertaken to ensure hand hygiene, proper use of personal protective equipment, injection safety, and proper disinfection of hospital surfaces and sterilization of medical equipment. Education and training of healthcare workers is crucial, with an aim to create awareness on effective infection control and its impact on nosocomial infections, and antibiotic stewardship. In addition, the implementation of local and national surveillance systems is required in the region to give precise burden estimates.

Carbapenem-Resistant *Acinetobacter baumannii*

Acinetobacter species are Gram-negative bacteria commonly pervasive in the environment (soil and water).^{131,132} Of all the 60 known *Acinetobacter* species, *Acinetobacter baumannii* complex, which consists of *Acinetobacter pittii*,

Acinetobacter nosocomialis, and *Acinetobacter baumannii* (*A. baumannii*), is the most clinically relevant.^{132,133} *Acinetobacter baumannii* accounts for the majority (approximately 90%) of clinical infections, followed by *A. pittii* and *A. nosocomialis*.¹³⁴ *Acinetobacter baumannii* is an opportunistic bacterial pathogen mainly associated with hospital-acquired infection,¹³⁵ however, community-acquired infections are increasing.¹³⁶ It is a Gram-negative, catalase-positive, oxidase-negative, non-fermenting coccobacillus that is aerobic, pleomorphic, and non-motile. It has a high incidence among immunocompromised individuals, particularly those who have experienced a prolonged (>90-day) hospital stay.^{135,136} Other risks that exacerbate these infections include prolonged exposure to antibiotics, mechanical ventilation, and central venous catheter use.¹³¹ *Acinetobacter baumannii* is often implicated in bloodstream, urinary tract, pneumonia, skin and soft tissue infections, and meningitis.^{138,139}

Owing to its AMR,¹⁴⁰ *A. baumannii* is one of the ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *A. baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp.) that pose a huge global health challenge because of their MDR.¹³⁹ Carbapenem-resistant *Acinetobacter baumannii* (CRAB) is currently ranked first on the WHO list of critical pathogens urgently in need of new antibiotic development.¹⁴¹ The global prevalence of *A. baumannii*, its widespread antibiotic resistance, and most recently, the unforeseen emergence and spread of clinical isolates resistant to colistin, the last resort in current antimicrobial therapy, all necessitate its inclusion in national surveillance systems and national action plans.^{141,142} According to the WHO-GLASS report 2021,³⁴ *A. baumannii* and *E. coli* were the most frequently reported pathogens globally in the AMR surveillance systems. A review published in 2021 that looked into data on *A. baumannii* from the 29 countries in the low-income country (LIC) group showed that there are very few reports coming out of this group of countries.¹⁴¹ Out of the 29 countries, only 16 countries reported the detection of *A. baumannii* within their territories at least once in the last 21 years. Accordingly, 11 out of the 29 have no *A. baumannii* reports at all in the three searched databases. The country with the highest number of reports was Ethiopia, with 10 reports. Interestingly, high rates of carbapenem resistance have been reported in other studies of comparable countries in terms of economic development (reaching 100% in some instances).¹⁴¹ The modest numbers of *A. baumannii* reported in LICs could therefore just be a reflection of the low numbers of isolates investigated in many of these studies. Accordingly, it could be very difficult to obtain a good estimate of the prevalence of carbapenem resistance detected in the LICs.¹⁴¹

Carbapenems have been the preferred antibiotics for the treatment and management of multidrug-resistant *A. baumannii*; however, previous use has led to the emergence of and increase in carbapenem-resistant *A. baumannii*.¹⁴³ *Acinetobacter baumannii* has a high propensity for intrinsic resistance to different antibiotics and the ability to acquire different antibiotic resistance genes. The choice of carbapenem as a marker for MDR is based on its correlation with broad-range coresistance to different antibiotics.¹⁴⁴ Carbapenem resistance in *A. baumannii* is predominantly mediated by carbapenem-hydrolyzing Ambler class D β -lactamases (CHDLs), especially the oxacillinase (OXA) type, and Ambler class B metallo- β -lactamases (MBLs).¹⁴⁵ Studies in SSA have detected CHDL genes, including *blaOXA-23-like*, *blaOXA-24-like*, *blaOXA-58-like*, *blaOXA-143-like*, and *blaOXA-235-like*, among others, and MBL genes (*blaIMP*, *blaVIM*, and *blaNDM*) in carbapenem-resistant *A. baumannii*.^{145–150}

In 2019, *A. baumannii* infections were the fifth most common cause of deaths attributable to antimicrobial-resistant bacteria globally, with 57,700 mortalities attributable to carbapenem-resistant *A. baumannii*.¹⁵¹ The global percentage of resistance to carbapenems of *A. baumannii* varies geographically in different continents, regions, and countries.¹⁵² Several recent studies in SSA have reported varying levels of carbapenem resistance in *A. baumannii* (Table 7). A 2018 study reported that in East Africa, *A. baumannii* had the highest prevalence (23%) of carbapenem resistance compared to other multidrug-resistant bacteria.¹⁴⁸

There are currently no vaccines available against *A. baumannii*; however, several studies have investigated the efficacy of different vaccine candidates through preclinical trials. This highlights the need for vaccine research as one of the measures for managing *A. baumannii* infections.¹⁵²

Staphylococcus aureus

Staphylococcus aureus infections have long been a public health concern, and particularly those associated with methicillin-resistant *Staphylococcus aureus* (MRSA), which continues to threaten modern healthcare. An MRSA study

Table 7 Antimicrobial Resistance Rates of Clinical *Acinetobacter baumannii* in SSA

| | | Antimicrobial Resistance Rates (%) of <i>A. baumannii</i> | | | | | | | | Ref |
|--------------|-----|---|------|------|------|------|------|------|------|-------|
| | | MEM | IPM | LVX | CAZ | FEP | CIP | CN | SXT | |
| Ghana | 24 | 8.3 | 8.3 | 25 | 20.8 | 16.7 | 50 | 50 | 66.7 | [145] |
| Ghana | 87 | 59.8 | ND | 67.8 | 75.9 | ND | 64.4 | 72.4 | 70.1 | [149] |
| Nigeria | 34 | 91.2 | 82.4 | 97.1 | 94 | 97.1 | 97.1 | 97.1 | 100 | [146] |
| South Africa | 141 | 87 | 89 | ND | 90 | 81 | 67 | 74 | 69 | [153] |
| Ethiopia | 102 | 60.7 | ND | ND | 100 | 93.3 | 74.4 | ND | 68.2 | [154] |
| Uganda | 19 | 100 | 100 | ND | 90 | 63 | 63 | 79 | ND | [155] |
| Kenya | 27 | 88.9 | ND | 66.7 | ND | 100 | ND | ND | ND | [147] |

Abbreviations: MEM, meropenem; IPM, imipenem; LVX, levofloxacin; CAZ, ceftazidime; FEP, cefepime; CIP, ciprofloxacin; CN, gentamicin; SXT, trimethoprim/sulfamethoxazole (co-trimoxazole); ND, not done.

conducted in the European Union, published in 2019, estimates an annual number of disability-adjusted life-years (DALYs) at 148,727 (131,757–166,361) per 1,000,000 population, infections at 112,782 (103,186–122,006), and attributable deaths at 6810 (6096–7559).¹⁵⁶ While surveillance systems are in place in developed countries, they are lacking in developing countries, including those in the SSA region, and most data are from single-center studies. Nevertheless, community and healthcare-associated MRSA has been reported in most countries, including Kenya, Uganda, Nigeria, South Africa, Ghana, Mozambique, Ethiopia, and Tanzania, where the MRSA prevalence ranges from 1.25% to 53.4%.^{157–164} The most common risk factors associated with MRSA infection are HIV infection, prior antibiotic use, ICU admission, prior or prolonged hospitalization, indwelling catheters, invasive procedures, open wounds and burns, residency at long-term care facilities, mechanical ventilation, renal failure, and MRSA colonization history.^{165,166} Laboratory diagnosis is by culture, serology, and molecular assays. Often, laboratory equipment is available in tertiary facilities, but not in primary healthcare facilities.

The choice of treatment for *S. aureus* infections is dependent upon susceptibility, site, and origin of infection, ie community or hospital-acquired. Various antimicrobials are recommended, for either monotherapy or combined therapy, including methicillin, oxacillin, erythromycin, tetracycline, clindamycin, rifampicin, vancomycin, linezolid, teicoplanin, trimethoprim/sulfamethoxazole, daptomycin, quinupristin/dalfopristin, amikacin, ciprofloxacin, chloramphenicol, mupirocin

Table 8 Antimicrobial Resistance Rates of *Staphylococcus aureus* in SSA

| Country | Isolates | Antimicrobial Resistance Rates (%) of <i>S. aureus</i> | | | | | | | | | | Ref |
|--------------|----------|--|------|-----|------|------|------|------|------|-----|-----|-------|
| | | MRSA | DA | VA | PEN | SXT | TET | CIP | ERY | CHL | CN | |
| Kenya | 944 | 27.8 | 0 | 4.9 | 91.9 | 56.9 | 33.2 | ND | ND | ND | ND | [157] |
| Uganda | 41 | 38 | 0 | ND | ND | 43 | 56 | 24 | 32 | 24 | 17 | [158] |
| Ghana | 308 | 3 | 5 | ND | 97 | 4 | 42 | ND | 6 | ND | 3 | [159] |
| Nigeria | 217 | 2.4 | ND | ND | 97.2 | 84.3 | 13.8 | ND | ND | ND | N | [160] |
| South Africa | 2709 | 46 | <30 | 0 | ND | <50 | <40 | <30 | <40 | ND | <50 | [161] |
| Ethiopia | 80 | 1.25 | 28.8 | 0 | 88.8 | 5 | 52.5 | 1.25 | 18.8 | 5 | 15 | [162] |
| Mozambique | 84 | 8 | ND | ND | 89 | 36 | 59 | ND | ND | ND | ND | [163] |
| Malawi | 783 | NA | ND | ND | ND | 24 | ND | 19 | 53 | 34 | 23 | [172] |

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; DA, clindamycin; VA, vancomycin; PEN, penicillin; SXT, trimethoprim/sulfamethoxazole (co-trimoxazole); TET, tetracycline; CIP, ciprofloxacin; ERY, erythromycin; CHL, chloramphenicol; CN, gentamicin; ND, not done; NA, not available.

phosphomycin, fusidic acid, and tigecycline. Resistance to these antimicrobials has emerged (Table 8), and the most common resistance phenotype among clinical *S. aureus* is erythromycin, tetracycline, and co-trimoxazole. This has been attributed to the presence of several genes; *aac(6')-Ie-aph(2'')-Ia*, *aph(3')-IIIa*, *ant(4')-Ia*, *aph3*, and *aacA-aphD*, conferring resistance to aminoglycosides; *tetK/M* genes against tetracycline; *dfpG/dfpA* genes against trimethoprim; *ermA*, *ermC*, or *msrA* genes against clindamycin; and *gyrA* and *grrA* genes against fluoroquinolones.^{158,167,168} A majority of MRSA isolates have been shown to innately harbor *mecA* and *blaZ* genes, which encode for a range of penicillinases. Moreover, the most prevalent genotypes have been demonstrated to be ST5, ST8, ST15, ST88, ST152, ST241, and ST239.^{162,169–171}

With the rise of AMR, research and development for vaccines has grown considerably; however, most vaccine candidates have failed to pass phase III clinical trials and, therefore, no vaccine is currently licensed. In the short term, proper implementation of infection control and prevention measures will be key in reducing and tackling *S. aureus* infections, and especially those caused by MRSA.

Pseudomonas aeruginosa

Pseudomonas aeruginosa is a Gram-negative bacterium commonly found in water and soil.¹⁷³ It is an opportunistic pathogen commonly associated with hospital-acquired infections, particularly bloodstream infections, urinary tract infections, and pneumonia, resulting in considerable morbidity and mortality. The risk factors often associated with *P. aeruginosa* infections include prior hospitalization, ICU stay, and previous use of antibiotics.¹⁷⁴

Pseudomonas aeruginosa has an intrinsic ability to develop resistance to frequently used antibiotics, which often leads to treatment failure. Of concern is its resistance to beta-lactams,¹⁷⁵ especially carbapenems, as they are often used for empiric treatment of last resort.¹⁷⁶ The WHO has listed carbapenem-resistant *P. aeruginosa* as one of the three critical global priority pathogens that require development of new antibiotics.¹⁴⁴ It is estimated that in 2019, antimicrobial-resistant *P. aeruginosa* accounted for 84,600 mortalities, with carbapenem-resistant *P. aeruginosa* accounting for 38,100 deaths globally.¹⁵¹ The prevalence of carbapenem-resistant *P. aeruginosa* ranges from 6% to 34.8%, as reported in various studies conducted in Uganda, Ghana, South Africa, Zambia, Nigeria, and Ethiopia.^{176–181}

Although *P. aeruginosa* has an intrinsic resistance to several antibiotics, it can develop resistance through the acquisition of resistance genes.^{182,183} Various carbapenemase-encoding genes have been observed: *blaIMP*, *blaSPM*, *blaVIM*, *blaNDM*, *blaOXA-23*, *blaOXA-48*, *blaSIM*, *blaAIM*, *blaBIC-1*, *blaNMC-A*, and *blaOXA-58*. The co-occurrence of class I and class II integrons has also been reported, which possess a variety of resistance genes, such as *ant(4')-Iib*, *dfpA*, *aadAB*, *qnrVC1*, *gyrA*, and *parC*.^{147,177,179,181,182,184–187}

One Health Approach to Tackle AMR

The One Health approach is an important concept that recognizes the inseparable links between human, animal, and environmental health.¹⁸⁸ Although AMR surveillance studies have mainly focused on humans and animals, the environment is a critical aspect in the control of AMR. Residues of antibiotics used in humans and animals often end up in the environment,^{189,190} especially water sources, leading to the persistence of antibiotic residues and resistance genes in the environment. Consequently, hospital waste, farm, industrial, human waste, and waste water treatment plants become reservoirs and dissemination pathways of AMR.¹⁸⁹ Therefore, as part of the control measures applied to combat AMR, it would be imperative to identify the environmental reservoirs and dissemination pathways of AMR, and undertake continuous AMR surveillance in the environment¹⁹¹ and improvement of WASH infrastructure. The importance of the One Health approach is clearly demonstrated in the global action plan (GAP) on AMR.

Implementation of the Global Action Plan and National Action Plans in Sub-Saharan Africa

The GAP to combat AMR was adopted in 2015 by 194 member states of the WHO through decisions made at the 68th session of the World Health Assembly, by the Food and Agriculture Organization (FAO) Governing Conference, and by delegates at the World Assembly of World Organisation for Animal Health, formerly the Office International des Epizooties (OIE). This followed reports of alarming rates of resistance to healthcare and community-acquired infections

as well as reports of resistance in agriculture, livestock, and fisheries. Considering the transboundary challenges of AMR, world leaders attending the United Nations General Assembly in 2016 recognized the need for collaboration in tackling AMR.²⁷ Based on the framework of the GAP, countries were urged to develop national action plans (NAPs) to tackle AMR by 2017.¹⁹² The aim of the GAP is to ensure the successful treatment and prevention of infectious diseases with effective, safe medicines that are quality assured, used in a responsible way, and accessible to all who need them.⁵ The GAP lays out important activities based on five objectives to be undertaken through a continuous multisectoral approach, aimed at minimizing the impact of AMR globally.

The five objectives are: 1) to improve awareness and understanding of AMR; 2) to strengthen knowledge through surveillance and research; 3) to reduce the incidence of infection; 4) to optimize the use of antimicrobial agents; and 5) to ensure sustainable investment in countering AMR.^{5,27} To underscore the importance of the One Health (human health, animal health, and agriculture) approach in combating AMR, a tripartite collaboration that involves the WHO, FAO, and OIE was initiated. The role of the tripartite collaboration is to encourage progress in the development, costing, and harmonization of NAPs, while monitoring and evaluating the progress made by the member states.

Globally, two-thirds of the 194 WHO member states are reported to have developed NAPs.¹⁹² The overall performance of SSA countries in the implementation of NAPs has been reported to be inadequate. Between 2016 and 2017, only 14 countries in the WHO Africa region reported having developed NAPs, while nine could monitor antimicrobial consumption and use.²⁷ A more recent study found that 11 (25%) out of 44 SSA countries had NAPs on AMR, with 32% and 2% performing routine AMR surveillance on clinical and veterinary pathogens, respectively.¹⁹³ Fifty-nine percent of the countries reported having a dedicated laboratory that serves as the National Reference Laboratory for AMR. By February 2022, a library of existing, publicly available NAPs on AMR compiled by the WHO (<https://www.who.int/teams/surveillance-prevention-control-AMR/national-action-plan-monitoring-evaluation/library-of-national-action-plans>) included 15 SSA countries with fully developed NAPs: Burkina Faso, Eritrea, Eswatini, Ethiopia, Ghana, Kenya, Liberia, Malawi, Mauritius, Nigeria, Sierra Leone, South Africa, Tanzania, Zambia, and Zimbabwe.

The Eastern SSA region has been reported to have the highest number of countries implementing NAPs, followed by Southern, Western, and Central SSA. A high number of East African countries was found to be undertaking AMR surveillance in human and animal pathogens.^{193,194} Southern African countries were found to have the highest rate of developing antimicrobial stewardship guidelines and antimicrobial legislation. Although most SSA countries have developed or are in the process of developing NAPs on AMR, Guinea and Angola were reported to be missing NAPs on AMR.

Some of the countries with the best implementation of NAPs in SSA are Tanzania, Ethiopia, Kenya, South Africa, Zambia, and Ghana. In Kenya, for example, owing to the multisectoral nature of AMR and the need for a concerted effort across sectors, the NAP was developed through a multisectoral One Health approach and endorsed jointly by the cabinet secretaries responsible for human health, animal health, and crop production. However, elsewhere, Mozambique was found to have inadequate implementation of NAPs, especially in collaboration with different sectors.¹⁹⁴ According to the findings of a study by Iwu and Patrick, the performance of SSA countries in the different thematic areas of the GAP was 38±12% in awareness creation and training, 18±13% in surveillance, 33±13% in prevention and control infections, 28±23% in optimal use of antimicrobial agents, and 59±12% in multisector and One Health collaboration.¹⁹⁴ In several SSA countries, including Kenya, the Fleming Fund¹⁹⁵ has greatly facilitated the implementation of the NAPs, especially raising awareness, ensuring an expanded antimicrobial stewardship framework to optimize antimicrobial use, increase AMR and antimicrobial use surveillance, monitoring, and data sharing, and the implementation of infection control and prevention strategies.

Challenges in Implementation of NAPs in Sub-Saharan Africa

Although some progress has been in the implementation of NAPs in SSA, several challenges still hinder effective implementation. Whilst most of the SSA countries have developed NAPs, their full implementation is the greatest challenge. Some of the challenges that hinder the implementation of NAPs are: 1) a lack of political commitment, 2) inadequate funding, 3) poor coordination and collaboration between the different sectors, 4) inadequate surveillance

data, 5) poor infrastructure and health systems, 6) staffing shortages, and 7) a lack of monitoring and quality assurance systems.^{196,197}

Political commitment is a key factor in the successful implementation of NAPs on AMR.¹⁹⁸ Consequently, the absence of political will often translates into poor or lacking resource allocation for the implementation of NAPs, and inadequate regulatory policies and enforcement. The lack of commitment by policymakers or political leaders could be attributed to the lack of awareness and appreciation of the impact of AMR on the quality of human life. Inadequate funding/resource allocation in SSA is attributable to limited resources, and a lack of awareness and/or commitment by the private and public sectors. The implementation of NAPs is a resource-intensive activity; therefore, a lack of continuous funding results in a paucity of surveillance data, staffing inadequacy, and poor infection prevention and control. The scarcity of financial resources in most SSA countries means that funding of NAPs is not prioritized, since government spending on health is low. In 2001, African governments through the Abuja declaration committed to spending 15% of government budgets on public health. However, between 2002 and 2014, the percentage of government spending on health decreased in approximately half of SSA countries.¹⁹⁹ It is important to note that a WHO report estimated that between 20% and 40% of health budgets are wasted through inefficiencies and corruption.²⁰⁰

Effective implementation of NAPs requires multisectoral collaboration and coordination between human health, animal health, and environmental/food sectors. The multisectoral collaboration ought to involve governments, healthcare workers, researchers, academicians, veterinarians, farmers, and the private sector.¹⁹⁴ However, owing to the absence of coordinating agencies, coordination among the different sectors is problematic. One of the challenges identified in the implementation of NAPs in Mozambique was the poor collaboration between the different sectors.¹⁹⁴

Data on disease epidemiology, AMR, antibiotic consumption, environmental exposure pathways, access to healthcare, morbidity, hospital readmission rates, length of stay in hospital, and mortality rates are critical in informing policy and actions to be undertaken at the country level. However, because of the huge costs associated with research and other data collection, there is a scarcity of data in SSA. Consequently, the absence of these data creates a challenge in the successful implementation of NAPs, since it is difficult to assess whether progress is being made.

Poor WASH infrastructure and healthcare systems are also a challenge in the implementation of NAPs in SSA since they contribute to the spread of antimicrobial-resistant pathogens and poor diagnosis. Proper diagnostic or microbiological laboratory services are critical in ensuring the proper use of antimicrobials; however, poor diagnostic services remain a huge problem in SSA.

Inadequate competent human resources have also been identified as a major challenge in healthcare provision in Africa.^{194,197,201} Lack of personnel has also been identified as a barrier to antimicrobial stewardship programs.²⁰² The inadequacy of staff working on AMR limits the implementation of NAPs at the country level.

Improvement of Implementation of NAPs Towards Control and Prevention of AMR

To actualize the objectives of the GAPS, there needs to be an improvement in the implementation of NAPs at the country level. While several SSA countries have developed NAPs, these plans have not yet been fully implemented. In an implementation handbook published in 2022,²⁰³ the WHO has outlined six steps that would ensure the sustainable implementation of NAPs on AMR: 1) strengthening governance, 2) prioritizing activities for implementation, 3) costing the NAPs' operational plan, 4) resource mobilization, 5) implementing prioritized activities, and 6) monitoring and evaluation.

To ensure the effective implementation of NAPs, SSA countries need to prioritize the funding of these plans. There is a need to factor in the funding of these plans as part of the health sector. Governments also need to engage the private sector in the mobilization of resources. It is also imperative to have a coordination team that is comprised of expert groups and members from different sectors. The coordination team would be critical in identifying areas of priority at the national level, harmonizing the activities of different NAPs, mobilizing resources, and engaging policymakers. The coordination team would also be imperative for SSA countries in monitoring antimicrobial use and in the continuous surveillance of AMR prevalence and patterns. However, to achieve this, SSA countries need to ensure that there is a capacitated human resource dedicated to the implementation of NAPs. Scientists and academicians also need to undertake research that focuses not only on resistance levels but also on the impact of AMR on the socio-economic

aspects of human life. Collaboration among SSA countries would be critical, especially in the areas of coordinated training, legal frameworks, and data-sharing platforms.

Conclusion

AMR continues to be a major challenge in the effective control and management of infectious pathogens. This review has highlighted the AMR rates in different WHO-GLASS and locally important enteric pathogenic bacteria, and the successes and challenges in the implementation of NAPs in sub-Saharan Africa. Countries including Tanzania, Ghana, and South Africa were found to have better implementation of NAPs as a result of the multisectoral collaboration in those countries. Based on the available data, it is important to note that death rates attributable to AMR are highest in SSA, yet the paucity of data in SSA on AMR prevalence and antimicrobial use is a huge impediment to the effective control and management of infectious diseases. The few available data indicate an increase in reports of AMR rates and resistance genes, which could be resulting in treatment failure and increasing mortalities. Therefore, there is a need for SSA countries to ensure continuous data generation, which will be key in informing strategies to be implemented at the country level as different countries have varying resistance levels. It is also imperative that the One Health approach is implemented in the surveillance and control of AMR. In addition to surveillance, effective implementation of infection, prevention and control, hand hygiene, and antimicrobial stewardship programs will be key cost-effective strategies in tackling AMR.

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