ANTIMICROBIAL RESISTANCE IN THE WHO AFRICAN REGION:
a systematic literature review

World Health Organization
REGIONAL OFFICE FOR Africa

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FOREWORD

Antimicrobial resistance (AMR) remains an alarming public health threat worldwide. It causes high mortality and morbidity especially in low- and middle-income countries where access to diagnostics is limited and antimicrobial prescription and intake remain inadequately regulated. It is estimated that there is a continual and yearly increase and worsening of AMR cases. This undermines the effectiveness of the available treatment options and thus contributes to the persistence of microbial infections. Antimicrobial resistance occurs through different mechanisms, which include spontaneous (natural) genetic mutations and horizontal transfer of resistant genes through deoxyribonucleic acid (DNA). Antimicrobial resistant microorganisms are found in people, animals and the environment and can spread globally. Therefore, since it is a global public health problem involving several sectors, it also requires a global solution in the context of the One Health approach to achieve adequate control through the prevention, reduction, and mitigation of drug-resistant infections. WHO urges Member States as well as international, regional and national health institutions to regularly report on AMR status to serve as an evidence base for informing strategies and devising efficient preventive and control interventions. Regular surveillance of AMR can provide timely information on its emergence and spread in a given setting. This report presents the status of AMR in Africa by analysing the main types of resistance and the underlying genes where possible. The report also includes a summary on the status of drug resistance for TB, HIV and malaria.

ACKNOWLEDGEMENTS

We acknowledge that this review report was conducted following a convenient and thorough methodology; and therefore, presents key information on current AMR status in the WHO African Region from 2016 to 2020. However, we also acknowledge the possible data bias that could result from missing AMR information in articles published in languages other than French or English. All the authors have approved the review procedure, data analysis, reporting and submission of the analysis outcomes.

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ABBREVIATIONS AND ACRONYMS

AMR	antimicrobial resistance
ARV	antiretroviral (drugs)
AST	antimicrobial susceptibility testing
BSAC	British Society for Antimicrobial Chemotherapy
BSI	bacterial bloodstream infection
CA-SFM	Comité de l'antibiogramme de la société française de Microbiologie
CDC	Centers for Disease Control and Prevention
CLSI	Clinical and Laboratory Standards Institute
CoNS	coagulase-negative Staphylococci
CSF	cerebrospinal fluid
ctxB	cholera enterotoxin subunit B precursor
DRC	Democratic Republic of the Congo
DRM	drug resistance mutation
E	Ethambutol
ESBL	extended-spectrum beta-lactamases
EUCAST	European Committee on Antimicrobial Susceptibility Testing
GLASS	Global Antimicrobial Resistance Surveillance System
H	isoniazid
HIV	human immunodeficiency virus
IPC	infection prevention and control
MIC	minimal inhibitory concentration
MISA	methicillin-intermediate *Staphylococcus aureus*
MRSA	methicillin-resistant *Staphylococcus aureus*
MSSA	methicillin-susceptible *Staphylococcus aureus*
NA	Not applicable
NRTI	Nucleoside reverse transcriptase inhibitor
NNRTI	Non-nucleoside reverse transcriptase inhibitor
PCR	polymerase chain reaction
PDR	Pretreatment HIV drug resistance
R	rifampicin
RAM	resistance-associated mutation
spp.	species
tcpA	toxin coregulated pilin precursor

TDR	transmitted HIV drug resistance
UTI	urinary tract infection
WHO	World Health Organization
WHO-AFR	World Health Organization African Region
WHO-AFRO	World Health Organization Regional Office for Africa
Z	pyrazinamide
Zot	zonula occludens toxin

EXECUTIVE SUMMARY

Antimicrobial resistance (AMR) imposes a huge burden on patients and health care systems in low- and middle-income countries. In Africa, the overall burden of AMR is not well understood or documented due to inadequate data. Therefore, this report presents the findings of a review of recently published data (from 2016 to 2020) on AMR in the WHO African Region (WHO-AFR) to help understand the current AMR status in this part of the continent.

Research was conducted on articles and reports relevant to the topic from different databases, search tools and repositories such as PubMed, EMBASE, Scopus, Cochrane Database for Systematic Reviews, African Journals Online Library, Google scholar, CDC and WHO websites. The systematic selection of research articles followed different inclusion and exclusion criteria that had been set beforehand. A total of 167 articles were included in the final review analysis. Analysis of the selected articles mainly focused on the reported data on infectious agents and their associated resistance phenotypes and genotypes, where possible. For an extended analysis and a better presentation of AMR data in the WHO African Region, the reported and shared AMR data in the Global Antimicrobial Resistance Surveillance System (GLASS) was also considered, including a brief account of AMR in HIV, TB and malaria from the most recent publications. The percentage of resistant bacterial isolates was calculated from the total number of tested isolates for each of the reported bacterial spp.

The results show that the majority of the bacteria were isolated from blood specimens. Among gram-negative bacteria, *Klebsiella* spp. remain the most common bacteria, and *E. coli* isolates reported a high resistance percentage for recommended first- and second-line antibiotics: amoxicillin (24.5%); ampicillin (23.5%); trimethoprim/sulfamethoxazole (22.5%); amoxicillin/clavulanic acid (13.2%); chloramphenicol (12.3%). Resistance to ciprofloxacin was (8.2%) [Table 1]. Low resistance rates were reported for imipenem (0.1-3%) and meropenem (0.1-2.5%) in gram-negative bacteria. For gram-positive bacteria, *Streptococcus pneumoniae* show high resistance percentages against the key tested antibiotics: trimethoprim/sulfamethoxazole (64.3%); oxacillin (32.2%); penicillin (23.2%); tetracycline (28.3%); amoxicillin (20.6%); ampicillin (19.3%%); chloramphenicol (19.3%); amoxicillin/clavulanic acid (17.4%); ciprofloxacin (14.8%); gentamicin (13.5%); doxycycline (1.9%); and erythromycin (1.9%).

Mono-resistant and multidrug-resistant (MDR) cases of HIV, TB and malaria are also reported from the latest research findings in Africa.

This report presents the most recent in-depth review of the situation of AMR in relation to the most commonly prescribed antibiotics in the African Region. The review findings highlight the alarmingly persistent cases of AMR in the African Region, and the urgent need to implement the national action plans to combat AMR and improve surveillance programmes in each of the 47

Member States, as well as support IPC measures, raise stakeholder awareness and optimize antimicrobial stewardship, sharing and reporting of AMR data.

1. INTRODUCTION

1.1 Background

Antimicrobial resistance (AMR) is defined as the inherited or acquired ability of a microorganism to stop the antimicrobial drug from working against it to the extent that it cannot be used any longer. The available drugs used to treat microbial infections become less effective or ineffective and lead to the persistence and spread of the resistant organisms causing infections [1]. The bacteria overcome the effects of antimicrobial drugs (such as antibiotics) through five main biochemical mechanisms of resistance. These include enzymatic modification or destruction of the antibiotic; modification of the antibiotic target site; mimicking the antibiotic target with similar biochemical functions or overproduction of the antibiotic target; decreasing the antibiotic penetration; and elimination of the antibiotic from the cell by efflux pumps [2]. Bacteria may have multiple resistance mechanisms [3]. The main factors exacerbating the issue of AMR in Africa include the limited supply or access to antimicrobial drugs, while those that are available might be of poor quality or counterfeit. In addition, in low-resource settings such as Africa, antimicrobials including antibiotics can be sold over the counter or used in feeding animals as prophylaxis or growth promoters [4]. The issue of lack of regulation and quality control of drugs may be exacerbated by poor infection prevention and control (IPC) and water, sanitation and hygiene (WASH) interventions and can accelerate the spread of drug-resistant microorganisms.

Antibiotic susceptibility testing (AST) remains the standard diagnostic method for detecting bacterial resistance and guides clinicians in the appropriate and timely treatment of bacterial infections [5, 6]. AST results are crucial for surveillance studies to generate epidemiological data on bacterial pathogens and associated AMR. These data constitute the baseline information for national, regional and global strategies to contain the spread of AMR.

The disk diffusion test remains the recommended method for testing antibiotic susceptibility for most bacteria. This method is based on measuring and reporting the bacterial inhibition zone. The zone diameter establishes a measurement of the susceptibility of the bacterium to the antibiotic. The disc diffusion method may not be used for all organisms due to the inability of some bacteria to grow in solid media. Methods that determine the minimal inhibitory concentration (MIC) in fastidious or slow-growing bacteria are recommended [5]. The MIC is defined as the lowest concentration of the antibiotic that can inhibit or stop the growth of the bacteria [5]. The broth microdilution test and the Epsilometer test (E-test) are the most frequently used methods for MIC determination, and compulsory for some pathogens such as susceptibility testing of penicillin-resistant *Streptococcus pneumoniae* to guide antimicrobial therapy [7]. Next to conventional microbiological culture, molecular methods such as PCR (conventional PCR or real-time PCR) and sequencing (targeted sequencing or whole genome sequencing) are used in molecular characterization of AMR and determination of resistance markers [8-21].

There are guidelines on the standardized values for zone diameters (disc diffusion) and MIC breakpoints that are provided by different institutional committees such as the Clinical and Laboratory Standards Institute (CLSI) [22], the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [23], the French Society for Microbiology (CA-SFM) [24] and the British Society for Antimicrobial Chemotherapy [25].

Only a few reports and publications are available on the problem of AMR on the continent. Three main review articles have been published since 2001: two of them were conducted on the broad clinically relevant bacteria [26, 27], and one assessed the issue of AMR more specifically in children with sepsis not only in Africa but also covering all other resource-limited countries worldwide [28]. In addition, only nine countries of the African Region were able to report AMR data in the Global Antimicrobial Resistance Surveillance System (GLASS) over two recent years (2016-2018). There is a still inadequate coordination and implementation of policies to assess and monitor the situation of AMR in Africa despite the availability of GLASS. In these resource-limited settings, treatment is mostly based on presumptive clinical diagnosis with empirical choice of the antibiotic, but not on AST results. In 2020, the COVID-19 pandemic further contributed to the increased spread of AMR due to inappropriate use of antibiotics for case management of patients [29].

Most low-resource settings still experience the issue of inadequate infrastructure, lack of technical skills and essential supplies for the optimal diagnosis and treatment of AMR [30]. This leads to an increase of infectious diseases and associated AMR in low- and middle-income countries (LMICs). Detection of AMR in LMICs is insufficient even in some national reference laboratories and reflects lack of laboratory capacity to support diagnostic methods.

1.2 Rationale

AMR remains a significant threat to the treatment of bacterial infections globally and most importantly in low- and middle-income settings including Africa. The AMR threat adds to the existing higher burden of bacterial infections in such settings and low access to adequate diagnostics, specifically at intermediate and peripheral levels of the health system [1]. The establishment of microbiology laboratories in low-resource settings including Africa can improve patient management and provide the required surveillance data for developing local or regional treatment guidelines, and support the containment of AMR.

1.3 Scope and aim of this report

Understanding the recent status of AMR surveillance and trends of resistance in Africa could improve clinical practice by guiding the clinician's choice of the right antibiotic and informing decision-making for African Region Member States, WHO-AFRO, partners and stakeholders. To this end, a review of the currently available and published data on the aetiology of bacterial infections and their associated AMR patterns in the WHO African Region from 2016 to 2020 was conducted. The analysis focused on the AST methods currently in use, types of recent AMR patterns and regional distribution of resistance patterns. The report also includes a summary on the status of drug resistance for TB, HIV and malaria. This review report proposes recommendations, future options and interventions to contain AMR in the WHO African Region.

2. METHODOLOGY

2.1 Data sources and search strategy

Two freely accessible scientific web search engines, PubMed and Google scholar, were searched with the aim of capturing published research data on AMR. The search was extended to the entire African continent and later excluded articles from countries, which are not part of the WHO African Region. The following keywords related to the review topic were used: "Antimicrobial Resistance Africa", "Antimicrobial Susceptibility Africa", "Surveillance Africa", "Diagnostic Africa", and "Bacteria Diagnostic Africa". These five search keywords were entered in PubMed and Google scholar, respectively. All articles on AMR in the WHO African Region were then retrieved. The same search strategy was repeated for the second round of the search with the use of the same key words but with the name of each country of the African Region added next to it with each search.

2.2 Selection and rejection criteria

Retrieved articles were retained if they met and satisfied the following inclusion criteria: published between 2016 and 2020; published in English or French; reporting AMR research data in humans; conducted in countries of the WHO African Region; free accessibility of their abstracts and full texts; reporting data on AST; providing details on the total number of studied isolates; and were case reports or case series. Conversely, retrieved articles were rejected based on the following exclusion criteria: not providing information on the total number of studied isolates; conducted in other regions or countries than the WHO African Region; used on non-human subjects; conducted as randomized control trials of antibiotics, surveillance studies on antibiotic use/misuse, or as molecular investigations of AMR molecular markers; not having freely accessible abstracts or full text; or reviews of given types of AMR. In addition, reference lists of potential research articles retained at this stage were subsequently scrutinized for inclusion

criteria, and those meeting the criteria were added to the final list of potential research articles to be reviewed and included in this report.

2.3 Selection procedure

From the initially retrieved 48 003 articles, 7261 were excluded because they were either books or they did not have an abstract; 40 013 articles were excluded because they did not fit in our review topic or lacked free full text versions. A total of 342 articles were subsequently excluded because they were conducted on non-human subjects; as reviews of AMR or simply as molecular investigations of AMR markers. At the next stage, 240 articles were excluded because they were either published before 2016, showing a low quality assessment score or conducted from a country outside the WHO African Region. The total of 147 articles that were retained was also added to the other 20 that were identified from all their respective reference lists. This yielded a total of 167 articles that were analysed in this review. A complete description of all the steps followed to select the final articles that were included in this report is found on the flowchart presented here below.

2.4 Article quality assessment

The quality of each of the 167 selected articles was assessed based on the methodological quality and appropriateness for inclusion without limiting the consideration to their generated results. The criteria for quality assessment that were followed are the following:

(a) Is the research question clear and adequate to the study?

(b) Is the study design used appropriate to the set research question?

(c) Was the sampling method appropriate for the set research question and design?

(d) Were data collected and managed systematically?

(e) Were the collected data analysed appropriately?

2.5 Data extraction

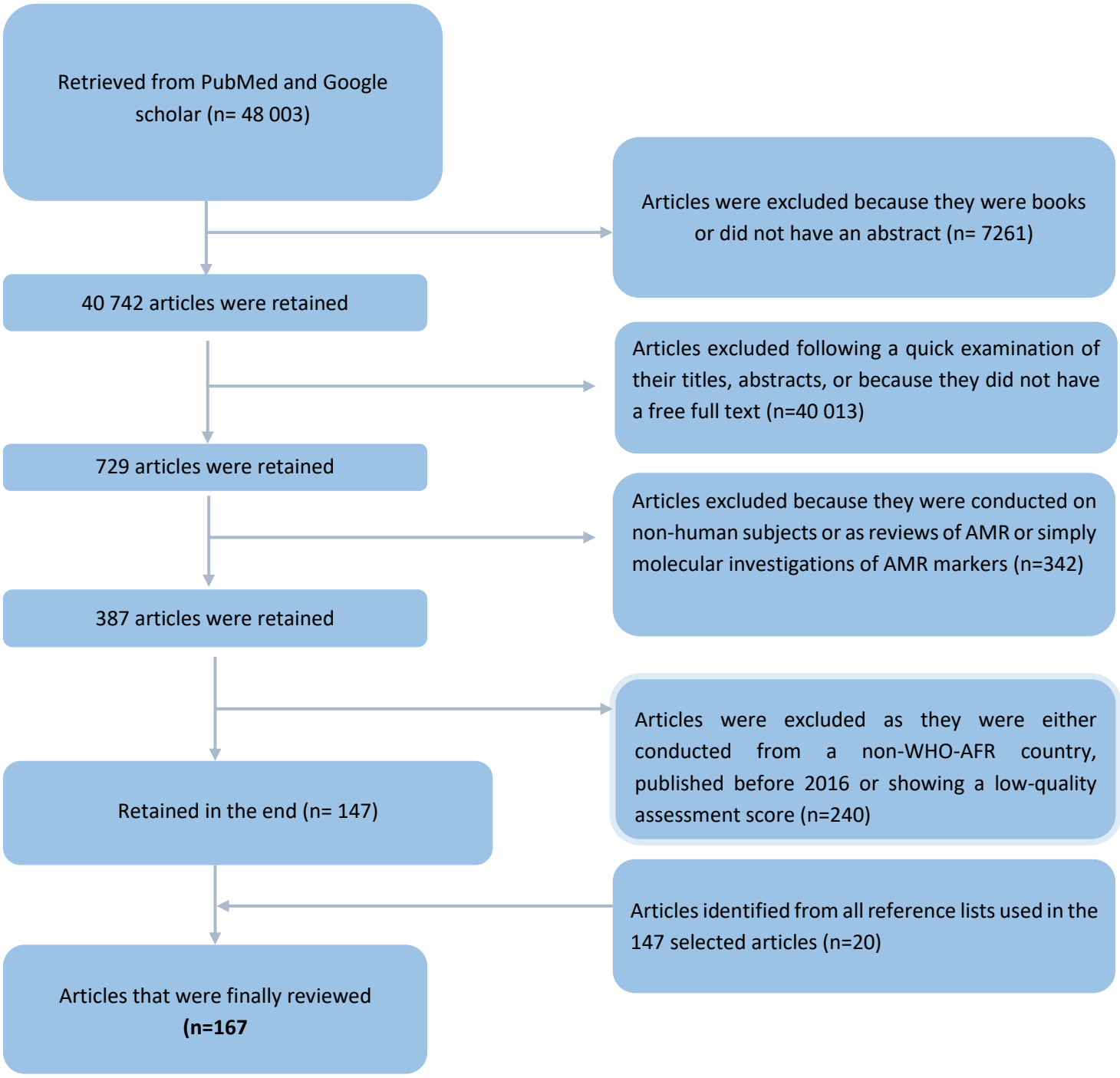
The extracted data from the 167reviewed articles were compiled in an Excel database (Excel 2016) that was designed for the purpose of this review report. The data that were extracted from articles are related to: the first author, publication year, title, DOI/PMID/Link, WHO-AFR country, study/data collection period, study objective, study design, study subjects, inpatient or outpatient, type of sample, age group, reported bacteria, infection/syndrome. Additionally, the extracted data included source of infection (health care- or community-acquired infection); investigation method (phenotypic or genotypic); bacterial identification method; AST method; tested antibiotics; and AST guidelines (Annex 1).

2.6 Data analysis

The total number of clinical bacterial isolates tested in each selected article was extracted and the overall number of isolates tested was calculated for susceptibility against the key antibiotics. From this step, the percentage of resistant bacterial isolates could then be deduced from the total number of tested isolates for each of the reported bacteria spp.

For an extended analysis and a better presentation of AMR data on the WHO African Region, reported and shared AMR data from the WHO African Region in GLASS were also considered. GLASS was launched in 2015 at the behest of the Sixty-eighth World Health Assembly in resolution WHA68.7, with the aim of supporting the global action plan on AMR (GAP-AMR), and specifically the second objective of the GAP-AMR, which is to strengthen knowledge through surveillance and research and to enhance existing activities [https://www.who.int/glass/en/] [31].

Figure 1: Illustration of the search and selection flow of articles



3. RESULTS

3.1 Reviewed articles and main data characteristics

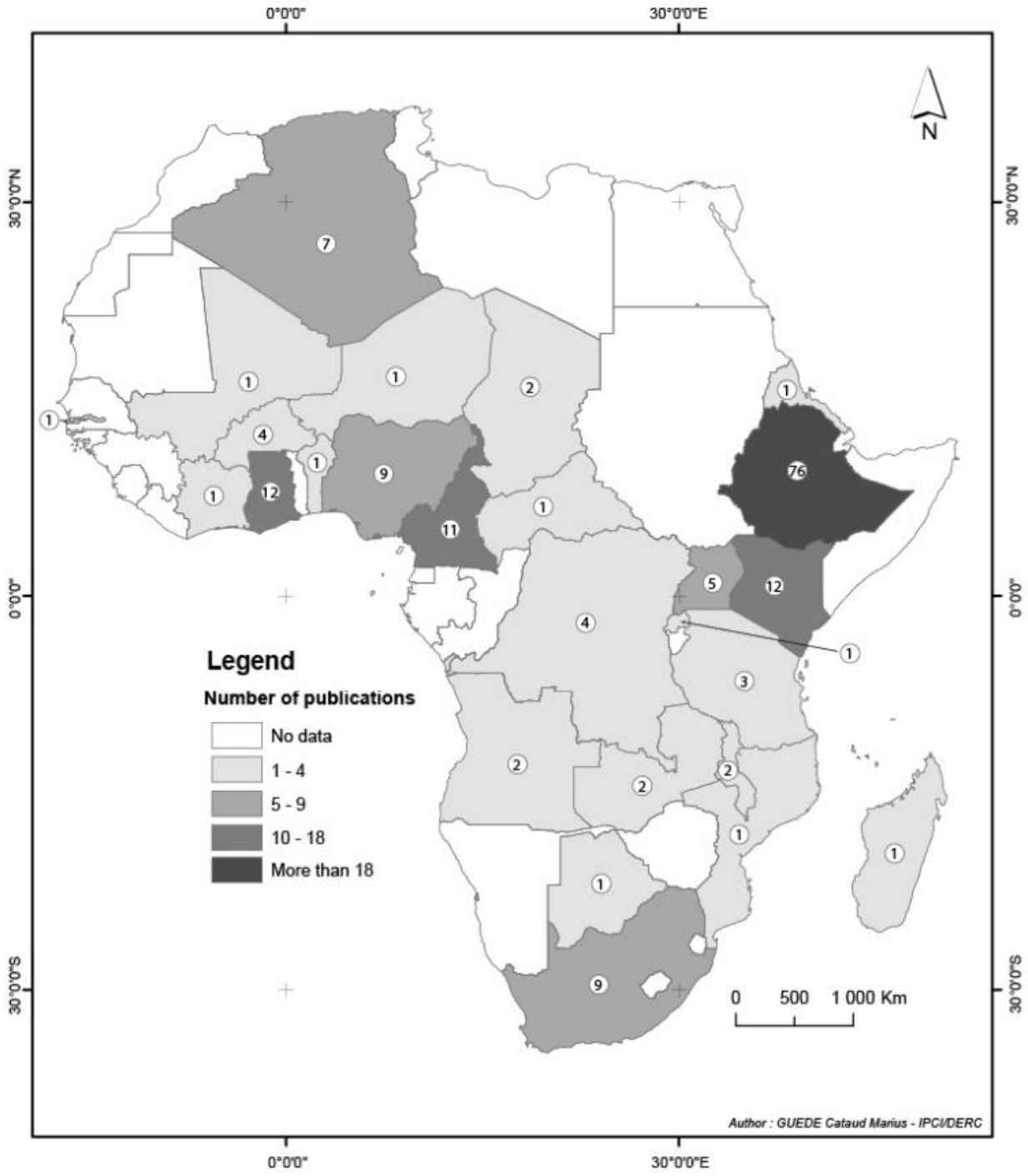
A total of 48 003 potential articles were reviewed from the two scientific databases, PubMed and Google scholar as described above, and the selection process yielded a total number of 167 articles [Annex 1] that met the inclusion criteria, and were included in the analysis [9, 12, 20, 32-215]. The majority of the final selected articles were published in 2019, (38, 22.6%), with most of them having a collection period for the reported isolates falling before 2016 (95, 56.5%). As shown in Figure 2, a high number of the reviewed articles were conducted in Ethiopia (76, 45.2%) with the rest of the countries represented by a low number of articles; for example, Mali, Niger, and Central African Republic, etc. are represented by 1 (0.6%) [Annex 2].

Considering the type of investigation (phenotypic or genotypic and phenotypic), more studies have used the phenotypic investigation method (123, 73.7%) which mostly relies on the standard microbiological culture, followed by a combination of both phenotypic and genotypic investigations (44, 26.3%) [Annex 2].

For the interpretation of the AST data, most of the studies used the CLSI guidelines (129, 76.8%), followed by those of EUCAST (17, 10.1%), whereas the CLSI and BSAC guidelines were the least used (2, 1.2%) or not mentioned in the rest of the articles. In contrast, for the AST methods, the majority of the reviewed studies used disc diffusion (114, 67.8%), and for bacterial identification, the majority of the reviewed studies used the common standard for microbiological culture (105, 62.5%).

The number of bacteria isolates reported in the reviewed articles varies from one medical condition (infection/syndrome) to another, and most of them are linked to BSI [Annex 3]. Thus, *Acinetobacter baumannii* was isolated in 65.9% of cases from samples of patients with BSI (65.9%). This is also the case for *Escherichia coli* (49.8%), *Group A Streptococcus* (75%), *Klebsiella pneumoniae* (67.2%), *Pseudomonas spp.* (38.5%), *Salmonella enterica* serovars Typhi (S. Typhi) (64%), non-typhoidal *Salmonella* serovars (50.4%), *Shigella spp.* (74.3%), *Staphylococcus aureus* (62.6%), and *Streptococcus* spp. (68.4%). The situation was different with *Proteus mirabilis*, which in 61% of cases was isolated from samples of patients with an upper urinary tract infection.

Figure 2: Distribution of articles included in the review per WHO-AFR country



3.2 Data analysis

Analysis of the data includes six main themes. Theme 1 presents a summary of the reported AMR data in GLASS from African countries from previous years, 2016 to 2018 [Annex 4]. The second and third themes present the mainly reported bacterial AMR patterns from the reviewed articles

among gram-negative and gram-positive bacteria, respectively. The fourth theme presents the AMR in *Vibrio cholerae* in Africa, 2016-2020; the fifth theme presents the main underlying genetic markers of the phenotypic AMR reported among the common gram-negative and gram-positive bacteria in the WHO African Region; and the last theme (sixth) presents data on AMR in HIV, TB and malaria in the WHO African Region.

Theme 1: AMR patterns (number of resistance cases (%)) from GLASS_WHO-AFR 2016-2018

The establishment of GLASS was requested by Member States upon the adoption of the WHO Global action plan on AMR in May 2015 (resolution WHA68.7). GLASS promotes a standardized approach to the collection, analysis and sharing of AMR, AMC and AMU data; a One Health model for AMR surveillance; and generation of data to inform AMR burden estimates. It is the first global system to incorporate official national data from surveillance of AMR in eight selected bacterial pathogens that cause common infections in humans, namely *Acinetobacter spp*.; *Escherichia coli*; *Klebsiella pneumoniae*; *Neisseria gonorrhoeae*; *Salmonella spp*.; *Shigella spp*.; *S. aureus* and *Streptococcus pneumoniae*. GLASS relies on continuous data sharing and global collaboration, harmonization and coordination among all partners involved in the implementation of AMR surveillance. Any new AMR data detected that may influence surveillance and control practices are communicating between GLASS networks. That includes resistance phenotypes not reported or very rare, new resistance genotypes associated with resistance mechanisms that can have a high impact on public health, high potential for propagation and health impact, and serious challenges in detecting and monitoring in the laboratory.

In the WHO African Region, the number of countries enlisted increased from seven in 2016 to 28 in 2020. During this period, WHO launched three data calls and the number of countries from the African Region that responded was nine in 2017 (report on 2016 AMR data), 14 in 2018 (2017 AMR data) and 15 in 2019 (2018 AMR data). They provided information on their national AMR surveillance systems and in addition, some reported on AMR rates: five countries in 2017; six in 2018; and seven in 2019.

The summary status of national surveillance systems showed that by 2019, thirty per cent of responding countries had established or were in the process of establishing a National Coordination Centre for AMR Surveillance, while 32% had designated National Reference Laboratories (NRLs). Almost all NRLs were participating in an External Quality Assessment (EQA) scheme and performing AST according to internationally recognized standards.

AMR isolates were mostly reported from the East, Southern and Western subregions of Africa. During this period, the number of surveillance sites increased from 35 to 93, while the number of patients with suspected infections moved from 4438 in 2017 to 26 628 in 2018 (2018 AMR

data). For the latter, 91% of AST results were available and the eight types of bacteria surveyed by GLASS were described from four infection sites: bloodstream (82%); urinary tract (10%); gastroenteric (6%) and genital (2%). *Staphylococcus aureus* and *Klebsiella pneumoniae* were mainly isolated from bloodstream infections; they accounted for 30% and 29%, respectively. *E. coli* was predominant in urinary tract infections (83%).

GLASS reports highlighted high resistance patterns in the WHO African Region; however, data are not yet representative of the national/regional level to be shared in this report. Nevertheless, they provide useful information that can be used for capacity building and advocacy (Annex 4).

Theme 2: AMR patterns among gram-negative bacteria in the WHO African Region, 2016-2020.

Among the commonly reported medical bacteria pathogens, 10 gram-negative bacteria species and serovars were selected from all other gram-negative bacteria reported in all the 167 reviewed articles, and their AMR data are presented in Table 1 below. They are *Acinetobacter baumannii*, *Escherichia coli*, *Haemophilus* spp., *Klebsiella spp*., *Neisseria spp*., *Proteus mirabilis*, *Pseudomonas spp*., *Salmonella* Typhi, *non-typhoidal Salmonella* serovars and *Shigella spp*. These gram-negative bacteria were tested against 28 different antibiotics: amikacin, amoxicillin/clavulanic acid, amoxicillin, ampicillin, azithromycin, cefotaxime, ceftazidime, ceftriaxone, cefuroxime, chloramphenicol, ciprofloxacin, trimethoprim/sulfamethoxazole, doxycycline, erythromycin, gentamicin, imipenem, levofloxacin, meropenem, nalidixic acid, nitrofurantoin, norfloxacin, ofloxacin, oxacillin, penicillin, piperacillin, piperacillin/tazobactam, tetracycline and tobramycin. Among all the 10 tested bacteria species, *Klebsiella spp.* remain the most tested bacteria with a high number of isolates and generally the most resistant. *E. coli* presents most of the reported high AMR percentages (%) for amoxicillin (24.5%), ampicillin (24%), amoxicillin/clavulanic acid (13.2%), chloramphenicol (12.5%), ciprofloxacin (8.2%) and trimethoprim/sulfamethoxazole (22.5%) [Table 1]. The highest overall phenotypic resistance for imipenem is reported in *E. coli*, whereas for meropenem, *E. coli* and *Haemophilus* spp. show an equal resistance proportion at 2.5% [Table 1].

Table 1: AMR patterns among gram-negative bacteria in the WHO African Region, 2016-2020

Antibiotic	*Acinetobacter baumannii* n (% resistance)	*Escherichia coli*n (% resistance)	*Haemophilus spp.* n (% resistance)	*Klebsiella spp. n* (% resistance)	*Neisseria spp. n* (% resistance)	*Proteus mirabilis n* (% resistance)	*Pseudomonas spp. n* (% resistance)	*Salmonella* Typhi n (% resistance)	Non-typhoidal *Salmonella serovars* n (% resistance)	*Shigella spp.* n (% resistance)
Amikacin	42 (1.9)	30 (2.5)	5 (1.4)	22 (1.3)	20 (0.7)	52 (0.6)	11 (0.8)	14 (0.7)	27 (0.2)	10 (04)
Amoxicillin/clavulanic acid	**NA**	**159 (13.2)**	**32 (9)**	**61 (3.6)**	**16 (0.6)**	**64 (0.7)**	**NA**	**16 (0.8)**	**0 (0)**	**12 (0.5)**
Amoxicillin	**NA**	**294 (24.5)**	**4 (1.1)**	**NA**	**26 (0.9)**	**184 (2)**	**NA**	**79 (3.7)**	**54 (0.4)**	**18 (08)**
Ampicillin	**NA**	**282 (23.5)**	**110 (30.8)**	**NA**	**12 (0.4)**	**104 (1.1)**	**NA**	**67 (3.2)**	**36 (0.3)**	**122 (5.2)**
Azithromycin	2 (0.1)	24 (2)	7 (2)	6 (0.3)	28 (1)	8 (0.1)	7 (0.5)	0 (0)	0 (0)	16 (0.7)
Cefotaxime	100 (4.5)	108 (9)	8 (2.2)	61 (3.5)	24 (0.9)	60 (0.7)	98 (7.4)	0 (0)	108 (0.8)	20 (0.9)
Ceftazidime	91 (4.1)	87 (7.2)	3 (0.8)	56 (3.2)	6 (0.2)	80 (0.9)	39 (2.9)	11 (0.5)	63 (0.5)	0 (0)
Ceftriaxone	84 (3.8)	123 (10.2)	30 (8.4)	57 (3.3)	14 (0.5)	54 (0.6)	40 (3)	0 (0)	171 (1.2)	6 (0.3)
Cefuroxime	85 (3.8)	120 (10)	11 (3.1)	61 (3.5)	16 (0.6)	80 (0.9)	6 (0.5)	9 (0.4)	27 (0.2)	14 (0.6)
Chloramphenicol	**NA**	**147 (12.3)**	**38 (10.6)**	**72 (4.2)**	**20 (0.7)**	**120 (1.3)**	**NA**	**53 (2.5)**	**630 (4.5)**	**44(1.9)**
Ciprofloxacin	**34 (1.5)**	**99 (8.2)**	**24 (6.7)**	**34 (2)**	**94 (3.4)**	**34 (0.4)**	**26 (2)**	**0 (0)**	**90 (0.6)**	**0 (0)**
Trimethoprim /sulfamethoxazole	**90 (4)**	**270 (22.5)**	**93 (16.1)**	**77 (4.5)**	**224 (8)**	**142 (1.6)**	**NA**	**62 (2.9)**	**630 (4.5)**	**186 (8)**
Doxycycline	9 (0.4)	192 (16)	8 (2.2)	77 (4.5)	18 (0.6)	10 (0.1)	4 (0.3)	9 (0.4)	63 (0.5)	8 (0.3)
Erythromycin	6 (0.3)	273 (22.7)	5 (1.4)	68 (3.9)	12 (0.4)	6 (0.1)	8 (0.6)	6 (0.3)	27 (0.2)	20 (0.9)
Gentamicin	71 (3.2)	117 (9.7)	69 (19.3)	51 (3)	76 (2.7)	46 (0.5)	39 (2.9)	12 (0.6)	198 (1.4)	30 (1.3)
Imipenem	**9 (0.4)**	**36 (3)**	**3 (0.8)**	**6 (0.3)**	**4 (0.1)**	**20 (0.2)**	**16 (1.2)**	**3 (0.1)**	**54 (0.4)**	**16 (0.7)**
Levofloxacin	7 (0.3)	87 (7.2)	6 (1.7)	25 (1.4)	10 (0.4)	104 (1.1)	35 (2.6)	10 (0.5)	63 (0.5)	12 (0.5)
Meropenem	**51 (2.3)**	**30 (2.5)**	**9 (2.5)**	**11 (0.7)**	**6 (0.2)**	**11 (0.1)**	**17 (1.3)**	**3 (0.1)**	**45 (0.3)**	**10 (0.4)**
Nalidixic acid	3 (0.1)	108 (10)	10 (2.8)	45 (2.6)	20 (0.7)	138 (1.5)	88 (6.7)	15 (0.7)	180 (1.3)	4 (0.2)
Nitrofurantoin	70 (3.1)	72 (6)	5 (1.4)	34 (2)	14 (0.5)	132 (1.5)	86 (6.5)	6 (0.3)	72 (0.5)	20 (0.9)
Norfloxacin	44 (2)	105 (8.7)	10 (2.8)	41 (2.4)	10 (0.4)	0 (0)	28 (2.1)	9 (0.4)	99 (0.7)	16 (0.7)
Ofloxacin	3 (0.1)	123 (10.2)	4 (1.1)	27 (1.6)	16 (0.6)	78 (0.9)	2 (0.2)	5 (0.2)	747 (5.3)	8 (0.3)
Oxacillin	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**
Penicillin	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**
Piperacillin	60 (2.7)	204 (17)	10 (2.8)	11 (0.6)	18 (0.6)	16 (0.2)	7 (0.5)	2 (0.1)	90 (0.6)	14 (0.6)
Piperacillin/tazobactam	43 (1.9)	93 (7.7)	8 (2.2)	6 (0.3)	8 (0.3)	6 (0.1)	24 (1.8)	6 (0.3)	45 (0.3)	12 (0.5)
Tetracycline	83 (3.7)	258 (21.5)	35 (9.8)	78 (4.5)	202 (7.2)	156 (1.7)	NA	53 (2.5)	423 (3)	130 (5.6)
Tobramycin	2 (0.1)	126 (10.5)	10 (2.8)	55 (3.2)	6 (0.2)	4 (0.04)	5 (0.4)	7 (0.3)	27 (0.2)	18 (0.8)

NA: Not applicable; since a natural resistance exists for this bacterial species towards the tested antibiotic type, while on the list of antibiotics, highlighted in bold are those recommended as first- or second-line antibiotics.

Theme 3: AMR patterns among gram-positive bacteria in the WHO African Region, 2016-2020

Conversely, for gram-positive bacteria (data presented in Table 2 below), the three main medically important gram-positive bacteria were assayed for antimicrobial susceptibility. These gram-positive bacteria are Group A *Streptococci*, *Staphylococcus aureus* and *Streptococcus pneumoniae*. They were tested against the following 26 different antibiotics: amikacin, amoxicillin, ampicillin, amoxicillin/clavulanic acid, cefotaxime, cefoxitin, ceftazidime, ceftriaxone, cefuroxime, chloramphenicol, ciprofloxacin, clindamycin, trimethoprim/sulfamethoxazole, doxycycline, erythromycin, gentamycin, imipenem, levofloxacin, nalidixic acid, nitrofurantoin, norfloxacin, ofloxacin, oxacillin, penicillin, tetracycline and vancomycin.

Streptococcus pneumoniae show high resistance percentages against the key tested antibiotics: Amoxicillin (20.6%); ampicillin (19.3%); amoxicillin/clavulanic acid (17.4%); chloramphenicol (19.3%); ciprofloxacin (14.8%); trimethoprim/sulfamethoxazole (64.3%); doxycycline (1.9%); erythromycin (1.9%); gentamicin (13.5%); oxacillin (32.2%); penicillin (23.2%); and tetracycline (28.3%).

Table 2: AMR patterns among gram-positive bacteria in the WHO African Region, 2016-2020

Antibiotic	*Group A streptococci* n (% resistance)	*Staphylococcus aureus* n (% resistance)	*Streptococcus pneumoniae* *n* (% resistance)
Amikacin	**NA**	1 300 (3)	**NA**
Amoxicillin	**25 (1.8)**	**8 800 (20)**	**1 600 (20.6)**
Ampicillin	**18 (1.3)**	**9 500 (21.6)**	**1 500 (19.3)**
Amoxicillin/clavulanic acid	**5 (0.4)**	**3 300 (7.5)**	**1 350 (17.4)**
Cefotaxime	2 (0.1)	3 800 (8.6)	650 (8.4)
Cefoxitin	3 (0.2)	2 000 (4.6)	150 (1.9)
Ceftazidime	8 (0.6)	6 000 (13.7)	250 (3.2)
Ceftriaxone	4 (0.3)	4 800 (10.9)	600 (7.7)
Cefuroxime	7 (0.5)	5 900 (13.4)	800 (10.3)
Chloramphenicol	**36 (2.6)**	**3 400 (7.7)**	**1 500 (19.3)**
Ciprofloxacin	**28 (2)**	**3 100 (7.1)**	**1 150 (14.8)**
Clindamycin	5 (0.4)	2 100 (4.8)	800 (10.3)
Trimethoprim/sulfamethoxazole	**43 (3.1)**	**7 468 (17)**	**5 000 (64.3)**
Doxycycline	**2 (0.1)**	**6 500 (14.8)**	**150 (1.9)**
Erythromycin	**20 (1.4)**	**4 300 (9.8)**	**1 050 (13.5)**
Gentamicin	**NA**	**2 800 (6.4)**	**NA**
Imipenem	5 (0.4)	1 800 (4.1)	550 (7.1)
Levofloxacin	7 (0.5)	1 500 (3.4)	350 (4.5)
Nalidixic acid	9 (0.6)	8 300 (18.9)	150 (1.9)
Nitrofurantoin	10 (0.7)	2 200 (5.0)	250 (3.2)
Norfloxacin	34 (2.4)	4 000 (9.1)	450 (5.8)
Ofloxacin	3 (0.2)	3 600 (8.2)	300 (3.9)
Oxacillin	**2 (0.1)**	**4 400 (10)**	**2 500 (32.2)**
Penicillin	**11 (0.8)**	**10 000 (22.8)**	**1 800 (23.2)**
Tetracycline	**35 (2.5)**	**5 400 (12.3)**	**2 200 (28.3)**
Vancomycin	2 (0.1)	1 200 (2.7)	600 (7.3)

NA: Not applicable, since a natural resistance exists for these bacterial species towards the tested antibiotic type, while on the list of antibiotics, highlighted in bold are the recommended first- or second-line antibiotics. Resistance to b-lactam in group A streptococci is reported in some studies; however, these isolates were not speciated and this review is therefore unable to specifically identify the Streptococcus pyogenes isolates within this group

Theme 4: AMR in Vibrio cholerae in the WHO African Region, 2016-2020

The serotyping of most of the *Vibrio cholerae* isolates have shown that the circulating *Vibrio cholerae* strains belong to the subtype O1 and Ogawa serotype [32, 86, 90, 216, 217].

The circulating *Vibrio cholerae* strains in Africa carry mostly reported resistance markers for the currently recommended antibiotics for treatment. The resistance rates for sulphamethoxazole-trimethropim and ampicillin ranged from 75% to 100%, while no resistance for ciprofloxacin was observed for any of the isolates.

Genotypic investigations reported resistance markers to ampicillin [90, 216, 217] and trimethoprim/sulfamethoxazole [32, 90, 216, 217]; these were the most commonly reported among *Vibrio cholerae* isolates.

The most phenotypic resistance and associated genetic markers of *Vibrio cholerae* isolates (% of all *Vibrio cholerae* isolates) are presented in Table 3 below.

Table 3: AMR in *Vibrio cholerae* in the WHO-African Region, 2016-2020

Phenotypic resistance	Genetic markers (% all *Vibrio cholerae* isolates)
Ampicillin	ctxB (93.5%)
Trimethoprim/Sulfamethoxazole	tcpA (77.5%)
Ciprofloxacin	zot (77.5%)

Genotypic investigations reported the following associated resistance genes: ZOT (77.5%) [32], tcpA (77.5%) [32] and ctxB (93.5%) [32, 217].

Theme 5: Genetic markers underlying phenotypic AMR in the WHO African Region

A compilation of the genomic data from the genotypic investigation-based studies shows the genetic markers that are frequently reported to be associated with the common AMR phenotypes among gram-negative and gram-positive bacteria in the WHO African Region. The AMR genes and mutations associated with extended-spectrum β-lactamase (ESBL), metallo-β-lactamases (MBL), carbapenemase, decreased ciprofloxacin susceptibility (DCS) and methicillin resistance, are mostly reported among *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Salmonella Typhi* and *Staphylococcus aureus*, respectively. For the ESBL genes, *blaCTX-M*, *blaTEM* and *blaSHV* are highly reported at 522 (60.3%), 203 (51%) and 604 (70 %), respectively [Annex 5]. The same genes are also detected in *Escherichia coli*, but at lower rates compared to *Klebsiella pneumoniae*. The *blaNDM* among other genes associated with metallo-beta-lactamase production remains the mostly widely reported and is found at higher

frequencies in *Klebsiella pneumoniae*. Furthermore, the *blaOXA*, *SCCmec* and *gyrA* mutation associated with carbapenemase, MRSA and DCS phenotypes are reported at 336 (49%), 116 (21.4%) and 487 (25%) respectively in *E. coli*, *S. areus* and *S. Typhi* [Annex 5].

Theme 6: AMR in HIV, TB and malaria

The circulating HIV strains in Africa include the nucleoside reverse transcriptase inhibitor- (NRTI) and non-nucleoside reverse transcriptase inhibitor- (NNRTI) resistant variants and they are frequently observed among ART-naive and experienced HIV-1-infected patients on the continent; the prevalence of pre-treatment drug resistance (PDR) to HIV, NRTIs and NNRTIs is high [218-252]. Different surveillance studies on the continent have also reported levels of NNRTI PDR in Cameroon, Namibia, Uganda and Zimbabwe. Various research reports from Africa show an increase of NNRTI and NRTI PDR associated with prior ARV exposure; this was also reported in Mozambique, Eswatini, South Africa, Uganda and Zimbabwe. The prevalence of NNRTI PDR of above 10% is observed in Africa and ranges from 8% in Cameroon to 15% in Uganda [WHO, HIV drug resistance report 2019]. The emergence of drug resistant variants of HIV-1 is associated with mutations within the HIV-1 pol genes that encode the molecular targets for major antiretroviral drugs (ARV). Resistance to lamivudine, tenofovir, efavirenz was reported at high rates in countries of the WHO African Region, specifically in Malawi [253]. The prevalence of HIV-associated drug resistance mutations is high in Central Africa, followed by West Africa, with the NNTI mutations high in East Africa followed by West, Central and Southern Africa (16.3%). The major nucleoside reverse transcriptase inhibitor mutations in all four African subregions were M18V and K65R gene mutations [254].

In Africa, the most frequently reported TB resistance cases are mono-resistance and multi-drug resistance (MDR-TB) [255]. In African countries in 2019, an estimated 2.6% (95% confidence interval [CI]: 1.6–3.7 %) of new cases and 11% (95% CI: 2.2–27%) of previously treated cases had MDR/RR-TB. TB mono-resistance is high for isoniazid, followed by rifampicin, and is mostly reported from Zimbabwe and Eswatini; whereas high rates of MDR are reported from Côte d'Ivoire, Ethiopia, Lesotho, Namibia, Zambia and Zimbabwe.

The associated resistance gene mutations that were reported are found in *katG*, *rpoB* (n=3591), *rrs*, *inhA*, *pncA* and *embB*; and the commonest lineage families circulating in Africa are T, LAM, Beijing, Cameroon, CAS and H. Mono-resistance to pyrazinamide, bedaquiline and clofazimine is found and associated with mutations in *pncA*, *atpE*, *Rv1979c*, *Rv0678* and *pepQ* genes respectively [256-267]. MDR-TB, characterized by resistance to isoniazid and rifampicin, is also reported and associated with mutations in the gene loci *rpoB*, *katG*, and *inhA* [256, 265].

Resistance to antimalarial drugs has also been reported on the African continent with clinical and parasitological failure above 30% for chloroquine (CQ) and less than 3% for artemisinin-based combination therapy (ACT) and their associated resistant genes and gene mutations: chloroquine resistance associated with *Pfcrt* 76Thr primary mediator and *pfmdr1* 86Tyr and 1246Ty mutations; piperaquine resistance associated with *pfcrt* mutations; quinine associated with mutations in *pfmdr1*, *pfmdr6*, *pfcrt*, *pfmrp1*, and *pfnhe1*; mefloquine resistance associated with the increased *pfmdr1* copy number; dihydroartemisinin (DHA), artemether and artesunate all associated with *K13PD* mutations; atovaquone associated with mutations in cytochrome b particularly *268Ser*, *268Cys* and *268Asn*; pyrimethamine associated with *pfdhfr* mutations (*108Asn, 51Ile, 59Arg*, and *164Leu*); proguanil associated with *pfdhfr* mutations (*108Asn, 51Ile, 59Arg*, and *164Leu*); sulfadoxine associated with *pfdhps* mutations (primarily *437Gly, 540Glu, 581Gly*); and sulfadoxine-pyrimethamine resistance [268-282]. The most recent antimalarial drug resistance in Africa remains artemisinin resistance that was recently reported in Rwanda and for the first time in Africa [283].

4. Discussion

4.1 Data interpretation and discussion

The findings described in this review report are mainly AMR data that have been extracted and analysed from a total of 167 articles published between 2016 and 2020. The articles are outcomes of microbiology research that were conducted in Africa. Available data that have been shared in GLASS from 2016 to 2018 from a limited number of WHO-AFRO countries were also considered. In addition, a brief account of *Vibrio cholerae* in the WHO African Region was provided, based on what has been reported from the reviewed articles. Furthermore, the analysis was extended to other important infections on the African continent such as HIV, TB and malaria, with more emphasis on recent publications on their phenotypic and genotypic resistance.

Only a few countries from the African Region have shared their AMR data through GLASS, and this obviously contributes the most to the frequently encountered issue of AMR data paucity in Africa. For the 167 reviewed articles that constituted this review, it was observed that different panels of antibiotics, AST methods and different AST interpretation guidelines were used. Thus, standardization of the microbiological identification and AST methods, and sharing of AMR data are required to enable regional and international organizations such as WHO to closely monitor the extent and evolution of the AMR problem in Africa.

These AMR cases constitute major and ongoing public health threats; they are also highlighted in the WHO list of critical-priority AMR bacteria for which new research, discovery, and

development of new antibiotics are highly needed [284]. Therefore, timely and continuous surveillance of bacterial and TB infections, reporting and sharing of AMR data are needed in Africa to guide the required new approaches for control and treatment of bacterial infections.

In this review, the susceptibility results from selected articles were evaluated with caution, given the inconsistencies in the choice of antibiotic combinations in the various articles. For instance, in some cases, amoxicillin was tested and reported *for Acinetobacter*, and ampicillin and amoxicillin for *Klebsiella* spp., although these bacteria have acquired a natural resistance to the tested antibiotics. In the same trend of natural resistance forms, oxacillin and penicillin were also tested in gram-negative bacteria, although they are known to remain inactive to these bacteria. *Citrobacter* remains an opportunistic bacterium and not a true medically important bacterium in humans [22, 285, 286]. In all these cases, the compiled, corresponding extracted data were recorded as not applicable "NA" in Tables 1 and 2 of the results.

Based on the review report, among gram-negative bacteria, resistance in *E. coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Neisseria spp*., non-typhoidal *Salmonella* serovars and *Vibrio cholerae* remains significant in Africa. ESBLs and carbapenems resistance are reported at low but alarming rates in Africa.

The results of this review mirror those from previous reviews conducted on AMR in Africa and published in 2014 [27] and 2017 [26]. For instance, resistance of the key gram-negative bacteria such as *Enterobacteriaceae* to the commonly recommended first- and second-line antibiotics is reported in the results of this review as in the two previous review studies. In addition, for gram-positive bacteria, resistance of *Staphylococcus aureus* to oxacillin and resistance rates to penicillin in *Streptococcus pneumoniae* observed in the results of this review were previously reported [26, 27].

This underscores the persistence of the AMR problem in the WHO African Region and that choice of antimicrobial therapy based on WHO Access, Watch and Reserve (AWaRe) classification Access and Watch may be is limited, and could constitute a huge burden and result in high mortality in Africa.

The present findings also confirm the presence of some important genetic markers for the key resistance forms such as ESBL and carbapenem production among pathogens causing BSI, STI, enteric fever and invasive salmonellosis in Africa.

It is already known that carbapenem resistance is mediated by transferable carbapenemase-encoding genes. These genes are already known from different research projects conducted in Europe, Asia and South America, whereas the African setting remains less explored and

documented. Gram-negative bacteria, mainly *Enterobacteriaceae*, become resistant to carbapenems through three main mechanisms: enzyme production, efflux pumps and porin mutations. Three important groups of enzymes that are responsible for carbapenem resistance are: *KPC* (*Klebsiella pneumoniae* carbapenemase) (Ambler class A); MBLs (Metallo-ß-Lactamases) (Ambler class B) and OXA-48-like (Ambler class D); and *blaIMP*, *blaVIM-1*, *blaSPM-l*, *blaNDM-1*, *blaOXA-23*, *blaOXA-24*, *blaOXA-58* and *blaKPC* resistance determinant genes reported from Africa.

In addition to the burden of resistance to front-line antibiotics (first- and second-line), ESBL production and carbapenems, *Vibrio cholerae O1* serotype are also reported in this review. Cholera is responsible for around 4.3 million new cases and causes 21 000 to 143 000 deaths every year. Alterations in CTX phages and the pathogenicity islands contribute to the virulence of *V. cholerae* and are responsible for frequently reported cholera epidemics [287]. In most of the cases, *Vibrio cholerae* is associated with severe acute watery diarrhoea which remains the main distinctive symptom of cholera [288]. The *V. cholerae* serogroup O1 is the major cause of cholera outbreaks not only in Africa but also globally. The same serogroup was imported from Bangladesh, India, Iran and Iraq during the seventh pandemic that took place in the 1970s [289]. The evolved new variant of *Vibrio cholera* which is also more virulent was found to be associated with the CTX prophage rearrangements. This resistant *Vibrio Cholerae* strain is globally disseminated and constitutes a huge burden in low-resource settings such as Africa [290]. This mirrors the results of this review where most of the *V. cholerae* isolates reported in Africa belong to the *V. cholerae* O1 serogroup. This review also highlighted the carriage of two (*ctxB* and *tcpA*) out of three known biotype-specific genes (*ctxB*, *rstR*, *tcpA*) and one out of 13 known putative virulence genes (*ctxA*, *ctxB*, *zot*, *ace*, *tcpA*, *hlyA*, *stn*, *chxA*, *rtxA*, *ompU*, *toxR*, *mshA*, *TTSS*) of *V. cholerae* O1 [291]. Although there are still gap in timely reporting of data, Africa remains the main setting where cholera outbreaks and epidemics occur.

AMR data from Africa also indicate an increase of HIV drug resistance. In many African countries, tenofovir-containing regimens constitute the recommended first-line antiretroviral therapy (ART) and utilization of second-line treatment in these countries is still limited; a good example is South Africa. However, a considerable proportion of HIV drug resistance was reported in people living with HIV receiving tenofovir-containing first-line ART. The findings of this review highlight resistance to NNRTIs. Therefore, to meet the global target to end AIDS by 2030, NNRTIs should be replaced as first-line ART treatments in endemic settings such as Africa. In the same vein, dolutegravir is currently included in first-line regimens to treat HIV. As a matter of fact, dolutegravir (DTG) in combination with an NRTI backbone is recommended as the preferred first-line regimen for people living with HIV and initiating ART, whereas DTG in combination with an

optimized NRTI backbone may be recommended as a preferred second-line regimen for people living with HIV for whom non-DTG-based regimens are failing.

For TB, the first-line treatment tablets include isoniazid, rifampicin, pyrazinamide and ethambutol. For all retreatment cases (relapse, failure, and defaulter) a second line of treatment is administered: two months of R/H/Z/E/streptomycin, followed by one month of R/H/Z/E, and finally five months of R/H/E (eight months total treatment) [292]. However, in patients with confirmed rifampicin-susceptible and isoniazid-resistant tuberculosis, treatment with rifampicin, ethambutol, pyrazinamide and levofloxacin is recommended for a duration of six months. The burden of AMR in tuberculosis in Africa is growing and is largely driven by the considerable spread of MDR and extensively drug-resistant (XDR) mycobacterium tuberculosis strains. MDR-TB, which is defined as resistance to isoniazid and rifampicin, is frequently reported from African countries where HIV/AIDS remains endemic. This constitutes a major barrier to the WHO target of ending TB by 2035, since Africa remains the main source of new cases of TB. Therefore, urgent efforts and adoption of new tools for surveillance are required to confirm and report the true burden of AMR in tuberculosis in Africa.

The widespread use of antimalarial drugs has contributed significantly to the failure of the existing antimalarial drugs on the market, and this has hampered the achievement of the targets for eradication of malaria worldwide. Resistance to antimalarial drugs has been frequently reported since the 1950s and malaria has subsequently developed different mechanisms of resistance to successively developed drugs.

Malaria infection is now commonly treated with a combination of two drugs; artemisinin and piperaquine. However, resistance to antifolates, which are used to prevent malaria in some settings, remains widespread. Moreover, resistance to artemisinin-based combination therapies, the currently used standard treatment for malaria in Africa, has recently emerged. Resistance to artemisinin was reported from Rwanda for the first time in Africa [283]. This set a devastating scenario on the African continent where, in 2018, over 90% of the more than 400 000 deaths recorded from malaria were reported. Mutations in the *Plasmodium falciparum* multidrug-resistant gene (*pfmdr1*) was reported to alter the susceptibility of the parasite to artemisinin-based combination therapy [293].

The results of this review emphasize and recall the urgent need to improve surveillance programmes in each and every country of the WHO African Region to support antimicrobial stewardship.

4.2 Data limitations

The main limitations of this review include the exclusion of articles and reports published in languages other than English and French. For instance, there are several articles that are published in Spanish and Portuguese. Therefore, there could be articles from Spanish-speaking African countries (Equatorial Guinea) and Portuguese-speaking African countries (Angola, Cabo Verde, Guinea-Bissau, Mozambique and São Tomé and Principe) that were missed. Second, this review cannot guarantee the full representativeness of AST data since it only focused on articles with free access to their full content. In addition, this review reported AMR data only for medically important pathogens that are mostly reported in African laboratory settings. Furthermore, most African countries have poorly functioning laboratory, AMR surveillance and reporting systems. Therefore, their data were not accessible and were not included in this report.

There were very few reports from South Africa, which has a better functioning health and national AMR surveillance system than neighbouring countries. These data were not accessible for the search conducted for this review, and therefore larger AMR trends might have been missed. A further limitation relates to combining AMR results from different patient groups across different countries to compare the data. This approach might have levelled out peaks of resistance in different settings.

5. CONCLUSION AND RECOMMENDATIONS

5.1 Conclusion

This report presents an in-depth review of the most recent situation of AMR to the commonly prescribed antibiotics on the African continent. These AMR cases constitute a major and ongoing public health threat, and they are highlighted on the WHO list of critical-priority AMR bacteria for which new research, discovery, and development of new antibiotics are highly needed. In addition, resistance to first-line treatment regimens, MDR cases for HIV, TB and malaria are reported in Africa. The findings of this review will fill the gaps in AMR data for Africa; will help decision-makers and health care workers to develop more efficient preventive strategies as well as adequate policies for antibiotic stewardship and surveillance in line with the global action plan for AMR. More timely and effective surveillance studies and programmes for bacterial infections are required to deal with the current AMR threats presented in this report for the WHO African Region. This will result in a considerable positive impact on patients and reduce health care costs on the continent.

5.2 Recommendations

First, from the data extraction and analysis, it was observed that different panels of antibiotics, different AST methods were used without adhering to international recognised AST interpretation guidelines or standards. Thus, standardization of microbiological identification and AST methods is needed in diagnostic and research laboratories in the WHO African Region.

Second, considering the regularly reported lack of AMR data from Africa, accurate and sustainable surveillance for the emergence of AMR and sharing of data from Africa in the GLASS system should constitute high priorities. This will enable regional and international organizations such as WHO and other stakeholders to monitor the extent and evolution of the AMR problem on the continent. Finally, the different WHO consolidated lists of essential medicines should be successfully implemented or adapted based on the local AMR status.

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ANNEXES

Annex 1: Final list of selected articles and associated data

Link: ..\..\..\Annex 1 Final list of selected articles and associated data.xlsx

Annex 2: Data characteristics

Characteristic	Frequency (%)
Publication year	
2016	25 (14.8)
2017	39 (23.2)
2018	42 (25)
2019	38 (22.6)
2020	23 (13.7)
End data collection period	
Before 2016	84 (50)
Between 2016-2018	65 (38.7)
Between 2019-2020	12 (7.1)
Not mentioned	10 (5.9)
African country	
Algeria	7 (4.2)
Angola	2 (1.2)
Benin	1 (0.5)
Botswana	1 (0.6)
Burkina Faso	4 (2.4)
Cameroun	11 (6.5)
CAR	1 (0.6)
Chad	2 (1.2)
Eritrea	1 (0.6)
Ethiopia	76 (45.2)
Gambia	1 (0.6)
Ghana	12 (7.1)
Ivory cost	1 (0.6)
Kenya	12 (7.1)
Madagascar	1 (0.6)
Malawi	2 (1.2)
Mali	1 (0.6)
Mozambique	1 (0.6)
Nigeria	9 (5.4)
Rwanda	1 (0.6)
South Africa	5 (2.9)
Tanzania	3 (1.8)
The DRC	4 (2.4)
Uganda	5 (2.9)
Zambia	2 (1.2)
In more than one African country	4 (2.4)

Characteristic	Frequency (%)
Study design	
Case control	1 (0.6)
Longitudinal	1 (0.6)
Cross-sectional	87 (51.7)
Observational	3 (1.8)
Prospective	12 (7.1)
Retrospective	9 (5.4)
Surveillance	4 (2.4)
Not mentioned	71 (42.3)
Source of Data	
Inpatient	10 (5.9)
outpatient	8 (4.7)
Both	26 (15.5)
NA	3 (1.7)
Not mentioned	146 (86.9)
Investigation method	
Phenotypic	123 (73.7)
Phenotypic & Genotypic	44 (26.3)
Source of infection	
Hospital acquired	5 (2.9)
Community acquired	4 (2.4)
Both	3 (1.8)
NA	5 (2.9)
Not mentioned	171 (10.1)
AST guidelines	
BSAC	2 (1.2)
CA-SFM	7 (4.2)
CA-SFM & EUCAST	2 (1.2)
CLSI	137 (81.5)
CLSI & BSAC	1 (0.6)
CLSI & EUCAST	8 (4.7)
EUCAST	19 (11.3)
Not mentioned	12 (7.1)
AST Methods	
Broth microdilution	2 (1.2)
Disc diffusion	115 (68.5)
Disc diffusion & broth microdilution	4 (2.4)
Disc diffusion & E-test	12 (7.1)
Disc diffusion & MIC	23 (13.7)

Characteristic	Frequency (%)
Disc diffusion & VITEK	1 (0.6)
Disc diffusion, D-test & VITEK	1 (0.6)
Disc diffusion, E-test & MIC	2 (1.06)
Disc diffusion, broth microdilution & MIC	1 (0.6)
E-test	4 (2.1)
NA	2 (1.06)
Not mentioned	5 (2.6)
PHX system	1 (0.6)
VITEK	13 (7.7)
VITEK & E-test	1 (0.6)
VITEK & MALDI-ToF	1 (0.6)
VITEK, broth microdilution & E-test	1 (0.6)
Bacterial identification methods	
BACT/ALERT	4 (2.4)
BACT/ALERT & API	1 (0.6)
BACTEC	4 (2.4)
BACTEC & API	3 (1.8)
BACTEC & MALDI-ToF	1 (0.6)
BACTEC, API & VITEK	1 (0.6)
BACTEC, BACT/ALERT & API	2 (1.2)
Conventional BC	1 (0.6)
NA	1 (0.6)
Not mentioned	4 (2.4)
Standard microbiological culture & API	20 (11.9)
Standard microbiological culture & MALDI-ToF	11 (6.5)
Standard microbiological culture	105 (62.5)
Standard microbiological culture & BACTEC	1 (0.6)
Standard microbiological culture & CAMP Test	6 (3.5)
Standard microbiological culture & Hodge test	1 (0.6)
Standard microbiological culture & Vibrio cholera TM Difco BD	1 (0.6)
Standard microbiological culture & VITEK	10 (5.9)
Standard microbiological culture, API & MALDI-ToF	4 (2.4)
Standard microbiological culture, API & VITEK	1 (0.6)
Standard microbiological culture, CAMP test, modified Hodge Test & CIM	1 (0.6)
VITEK	5 (2.9)
CAR: Central African Republic; DRC: Democratic Republic of the Congo; NA: not applicable	

Annex 3: Total number (%) of reported bacteria isolates per disease or infection in Africa, 2016-2020

Bacteria isolate	BSI n (%)	Ear infection n (%)	Enteric fever n (%)	Gastroenteritis n (%)	Meningitis n (%)	Invasive Salmonellosis n (%)	Ocular infection n (%)	Skin infection n (%)	UTI n (%)	Wound infection n (%)	Total
Acinetobacter baumannii	1472 (65.9)	NA	NA	NA	NA	NA	NA	NA	NA	744 (33.3)	**2216**
Escherichia coli	599 (49.8)	NA	NA	393 (32.5)	NA	NA	NA	NA	201 (17)	NA	**1193**
Group A Streptococcus	1052 (75)	NA	NA	NA	NA	NA	NA	NA	NA	350 (25)	**1402**
Klebsiella spp.	17397 (67.2)	NA	NA	9 (0.03)	NA	NA	NA	NA	NA	8482 (32.7)	**25888**
Proteus mirabilis	3531 (39)	NA	NA	NA	NA	NA	NA	NA	5540 (61)	NA	**9071**
Pseudomonas spp.	505 (38.5)	167 (12.6)	NA	NA	NA	NA	NA	NA	450 (34)	191 (14.4)	**1313**
Salmonella Typhi	4062 (64)	NA	732 (11.6)	801 (12.6)	NA	734 (11.6)	NA	NA	NA	NA	**6329**
Non-typhoidal *Salmonella serovars*	7037 (50.4)	NA	NA	NA	NA	6930 (49.6)	NA	NA	NA	NA	**13967**
Shigella spp.	1735 (74.3)	NA	NA	600 (25.7)	NA	NA	NA	NA	NA	NA	**2335**
Staphylococcus aureus	27534 (62.6)	NA	NA	NA	NA	NA	198 (0.5)	98 (0.2)	NA	16096 (36.6)	**43913**
Streptococcus spp.	5315 (68.4)	615 (7.9)	NA	NA	NA	NA	737 (9.5)	625 (8)	NA	481 (62)	**7773**

Gastroenteritis combines data for both gastroenteritis and Diarrhea; NA means that there is no reported isolate for the considered bacteria for that specific disease or infection; BSI: Bacterial bloodstream infection; STI: Sexually Transmitted Infection and UTI: Urinary Tract Infection.

Annex 4: Summary AMR per country, region and type of sample in Africa, GLASS report, 2016-2018

Bacteria isolate	Country	African Region	N. bacteria isolates	Type of sample			
				Blood n (%)	Genital n (%)	Stool n (%)	Urine n (%)
Acinetobacter	Ethiopia, Malawi, Mali, Nigeria, South Africa, Zambia	East, Southern & Western Africa	27674	27674 (100)	0 (0)	0	0 (0)
Escherichia coli	Ethiopia, Madagascar, Malawi, Mali, Nigeria, South Africa, Uganda & Zambia	East, southern & Western Africa	82627	48417 (58.6)	0 (0)	0 (0)	34210 (41.4)
Klebsiella pneumoniae	Madagascar, Malawi, Zambia, Nigeria, Uganda, Ethiopia, Mali, Mozambique, Nigeria & South Africa	East, southern & Western Africa	83389	73389 (88)	0 (0)	0 (0)	10000 (12)
Neisseria gonorrhoeae	Madagascar, Malawi, Uganda, South Africa	East & Southern Africa	11893	0 (0)	11893 (100)	0 (0)	0 (0)
Salmonella spp.	Malawi, Mali, Nigeria, South Africa, Uganda & Zambia	East, southern & Western Africa	16447	7418 (45.1)	0 (0)	9029 (54.9)	0 (0)
Shigella spp.	Madagascar, Malawi, South Africa & Uganda	East & Southern Africa	5575	0 (0)	0 (0)	5575 (100)	0 (0)
Staphylococcus aureus	Madagascar, Malawi, Mali, Mozambique, Nigeria, South Africa & Uganda	East, southern & Western Africa	10700	10700 (100)	0 (0)	0 (0)	0 (0)
Streptococcus pneumoniae	Malawi, Mali &South Africa	Southern & Western Africa	10700	10700 (100)	0 (0)	0 (0)	0 (0)

Annex 5: Percentage AMR genetic markers among gram-negative and gram-positive bacterial isolates in Africa, 2016-2020.

Bacteria	ESBL			Metallo-β-lactamase					Carbapenemase	MRSA	DCS	
	blaCTX-M n(%)	*blaTEM* n(%)	*blaSHV* n(%)	*blaNDM n(%)*	*blaSPM n (%)*	*oprD n(%)*	*blaIMP n(%)*	*PSE n(%)*	*blaOXA n(%)*	*SCCmec* n(%)	*gyrA* mutation n(%)	*gyrB* mutation n(%)
Klebsiella pneumoniae	**522(60.3)**	203(51%)	604(70)	1003(90%)					242(43.2)			
Escherichia coli	**343(28.8)**	191(43%)	200(30%)						336(49)			
Staphylococcus aureus										116 (21.4)		
Salmonella Typhi											487(25)	176(7.8)
Pseudomonas aeruginosa					305(70)	53(10)	26(5)	14(2.5)				