



The importance of “one health approach” to the AMR study and surveillance in Angola and other African countries

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ABSTRACT

The dissemination of multidrug-resistant (MDR) bacterial isolates in low- and middle-income countries, including several African countries, is a major concern. The poor sanitary conditions of rural and urban families observed in certain regions may favor the transmission of bacterial infections between animals and humans, including those promoted by strains resistant to practically all available antibiotics. In Angola, in particular, the presence of these strains in human hospitals has already been described. Nevertheless, the information on antimicrobial resistance (AMR) prevalence in Angola is still scarce, especially regarding veterinary isolates.

This review aimed to synthesize data on antimicrobial resistance in African countries, with a special focus on Angola, from a One Health perspective. The main goals were to identify research gaps that may require further analysis, and to draw attention to the importance of the conscious use of antimicrobials and the establishment of preventive strategies, aiming to guarantee the safeguarding of public health. To understand these issues, the available literature on AMR in Africa was reviewed. We searched PubMed for articles pertinent to AMR in relevant pathogens in Angola and other African countries. In this review, we focused on AMR rates and surveillance capacity.

The principal findings were that, in Africa, especially in sub-Saharan countries, AMR incidence is high due to the lack of legislation on antibiotics, to the close interaction of humans with animals and the environment, and to poverty. The information about current resistance patterns of common pathogenic bacteria is sparse, and the number of quality studies is limited in Angola and in some other Sub-Saharan African countries. Also, studies on the “One Health Approach” focusing on the environment, animals, and humans, are scarce in Africa. The surveillance capacity is minimal, and only a low number of AMR surveillance programs and national health programs are implemented. Most international and cooperative surveillance programs, when implemented, are not properly followed, concluded, nor reported. In Angola, the national health plan does not include AMR control, and there is a consistent omission of data submitted to international surveillance programs. By identifying One Health strengths of each country, AMR can be controlled with a multisectoral approach and governmental commitment.

1. Overview of antimicrobial resistance problem in Africa

Antimicrobial resistance (AMR) (in the herein article, the term antimicrobial is used with a narrower meaning: bacterial resistance) is a global problem, being at present one of the greatest threats faced by

humanity [1]. According to the World Health Organization (WHO), AMR is responsible for higher mortalities and morbidity in low- and middle-income (LMI) countries, due to the increased burden of bacterial infections, poor diagnostic resources, and less access to quality antibiotics [2].

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There are several social and economic drivers responsible for high levels of antibiotic resistance in developing countries, including some African countries. The social factors related to the increase in AMR are settled in community education and way of life. The community presents limited knowledge on antibiotics and antibiotic resistance transmission; antibiotics are frequently used as growth promoters in livestock, poultry, and aquatic animals, and often added directly to dairy products to extend shelf-life; habitats are shared between households, livestock, and poultry, and there are poor hygiene habits; surface waters are shared by humans and animals; and there is also a problem of overcrowding in urban areas. The existence of counterfeit antibiotics and the over-the-counter sales of these drugs is a problem shared by the population, health entities, and the government. The population buys and sells these products; health professionals do not warn about the dangers of using counterfeit antibiotics and selling antibiotics without a prescription; and the government does not impose laws or restrictions on these practices. The government must provide the means for health professionals to have the necessary training on this topic so that they can pass information to the population [3–5].

There are several drivers in the government's role related to AMR increase. The lack of regulations and permissive antibiotic trade; lack of food safety measures, regulations, and control; unmonitored food supply chain; poverty and related economic and political drivers; poor sanitation structures; and particularly the lack of commitment to the population and to the need to halt AMR, probably due to the fact that the government itself is not aware of the AMR hurdle and its implications [3–5].

The problem of AMR in LMI countries is less acknowledged, partly due to limited diagnostic capacities, and to the lack of real-time data recording and surveillance and inadequate legislation in sub-Saharan Africa [6]. In fact, a survey conducted across 14 sub-Saharan African nations revealed that just 1.3% of the 50,000 medical laboratories perform bacteriology testing [7]. In the African continent, which, according to the World Bank 2021/22 (<https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups>), comprises 23 LMI countries out of a total of 134, 43% of the countries do not have available data on AMR prevalence, but the most recent findings confirmed AMR resistance to conventionally used antibiotics [8]. Sub-Saharan Africa and South Asia remained the two main regions with elevated AMR-related death rates in 2019 [9]. Nevertheless, there are some reports available on clinical isolates resistant to antimicrobials commonly used in sub-Saharan Africa [10]. In Angola, a country with around 34 million inhabitants and an emerging economy, the occurrence of community- and healthcare-associated multidrug-resistant (MDR) bacteria has been described [1]. As such, it is of major importance to develop more studies aiming to assess the prevalence, emergence, and dissemination of both Gram-positive and Gram-negative resistant bacteria in several settings in Angola and in other African countries. These objectives are in accordance with the One Health initiative which encourages interdisciplinary collaboration between the human, animal, and environmental sectors, aiming to promote healthcare, longevity, and quality of life [11,12].

The global development and dissemination of resistant strains in clinical settings is well documented, as well as their spread into the environment, being influenced by water quality, air quality, urbanization, and sanitation practices [2,3]. Yet, the use of antibiotics is described as the key factor for the selection of resistant bacteria [13]. Still, it is estimated that the use of antibiotics will increase by 67% in 2030 [14]. This fact is worrisome, since antimicrobial ineffectiveness makes clinical management and infection prevention an extremely difficult challenge, prompting the dissemination of bacterial infections associated with increased economic and social costs and increased morbidity and mortality rates [2,15]. The rise of treatment failures due to the inefficacy of first choice antibiotics towards MDR infections, often incites clinicians to resort to other options, often more expensive and/or presenting a higher toxic potential, such as using antibiotics usually

avoided due to their side effects [16].

1.1. Antimicrobial abusive use in livestock

In animal production, antibiotics are mainly applied for the treatment and prevention of diseases; yet, although not being allowed in European countries and some others, in LMI countries they can be used for non-therapeutic purposes, increasing the chance of AMR bacteria development [17,18].

In Africa, 15% of countries are authorized to use antimicrobials as animal growth promoters, as antimicrobials use remains unregulated in these countries [17]. The repeated use of low doses of antimicrobials in animal production for promoting growth, improving feeding proficiency, and for prophylaxis, results in substantial selection pressure towards the emergence of AMR [19]. In fact, the repeated exposure of bacteria to sub-lethal amounts of these compounds favors the selection and maintenance of resistance determinants, significantly contributing to antimicrobial resistance dissemination among animals and their by-products [19]. AMR is a consequence of the extensive use of antibacterial agents in veterinary settings, as 73% of all antimicrobials sold worldwide are administered in animal production [20], but also in agricultural settings and human medicine. So, humans can acquire AMR strains through person-to-person transmission, usually by direct contact [21], animal-to-person transmission, and environmental exposure [22] (Fig. 1).

Antibiotics present in water used for irrigation can be absorbed by crop tissues (particularly roots); however, their uptake by crops is usually low [23]. Overall, antibiotic uptake is restricted, highly selective, and plant- and antibiotic-specific [23]. There is a significant amount of research on antibiotics uptake by plants, but less on the dissemination of antimicrobial resistant genes and antimicrobial resistant bacteria into crop tissues [23,24]. Nonetheless, there is evidence that both antimicrobial resistant genes and antimicrobial resistant bacteria can accumulate on plant surfaces following manure treatments, and for that reason, it has been proposed that crops and soils should be fallowed prior to harvest [24]. In fact, specific crops and crop rotation can have an impact on the types of resistance genes discovered in soils [25].

Unprocessed crop manure may include AMR bacteria that can contaminate food and water, potentially increasing foodborne and waterborne exposures [25]. Therefore, contaminated soil and surface waters pose a health risk to communities that use soils for domestic agriculture and surface water for personal consumption, livestock, and crop irrigation, contributing to AMR transmission cycle [25].

The responsible use of antimicrobials in veterinary medicine is essential to guarantee animals' overall well-being, prevent the spread of infectious diseases on farms [18], and avoid zoonotic infections [19]. To intensify animal production, antibiotics can be administered to farm animals not only for the treatment of infectious diseases, but also for metaphylaxis, in which the identification of disease symptoms in one animal prompts antibiotic administration to all animals in close contact to control the spread of the disease [26]; and for prophylaxis, in which sub-therapeutic doses are administered to animals before the detection of clinical signs of disease, to prevent the occurrence of infections [16,26]. As it is likely that the development of AMR is also influenced by the use of antibiotics in healthy animals [19], the use of these compounds to treat sick animals only after the disease has been diagnosed is an imperative measure to promote animal welfare [27]. Therefore, the incidence of AMR is higher in developing countries, where humans interact closely with animals and the environment, and the burden of antimicrobial-resistant bacteria in farm animals and their potential transmission through the food chain is underestimated in poor resource environments [28].

1.2. Counterfeit medicines and over-the-counter sales of antibiotics

One of the reasons for the high frequency of AMR and MDR strains in

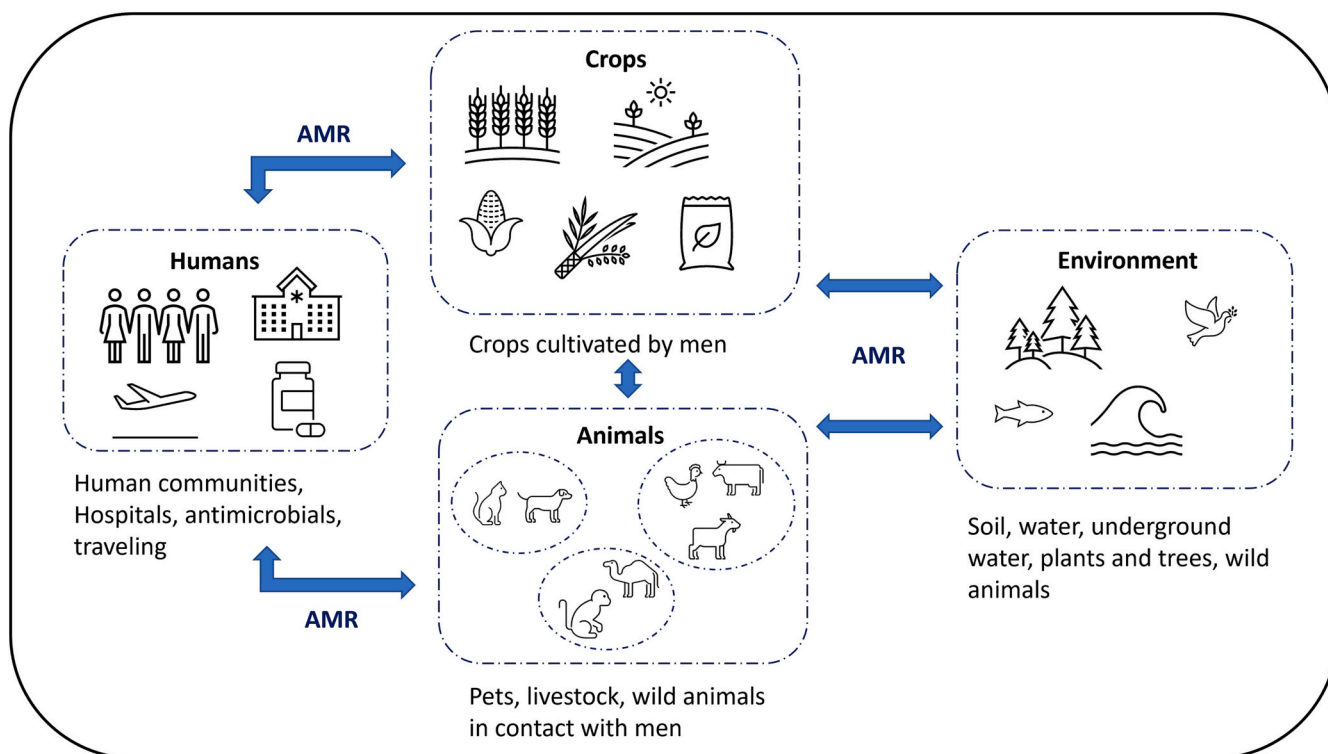


Fig. 1. Antimicrobial resistance flow between Humans, Animals, Crops, and the Environment.

Africa is related to the community setting, where antibiotic abuse may be linked to physician's prescribing behavior, diagnostic uncertainty, patient behavior (not completing antibiotic therapy or self-prescribing), and the level of public awareness on antibiotic use [29].

In developing African countries, the provision of several unauthorized health services to communities, such as medical consultations, diagnostic services, and the prescription and distribution of medicines, can lead to the misuse and abuse of antimicrobials. This can, in turn, contribute to the increase in the selection pressure leading to antibiotic resistance [30].

Also, counterfeit medicines and over-the-counter sales of antibiotics can be additional problems. Counterfeit medicines are a huge problem that can compromise the fight against AMR. Counterfeit antibiotics are a substandard type of medicine, that may contain incorrect ingredients or sub-therapeutic doses of the correct ones, leading to antibiotic resistance, treatment failure, and subsequent increased morbidity and mortality [31,32]. Counterfeit antibiotics presence in the global pharmaceutical market is a serious health threat that spares no borders or countries, being of special relevance in developing countries and, to a lesser extent, in developed ones [32].

Likewise, the sale of antibiotics without a prescription is also worrisome, despite being legally prohibited in most developed countries [33]. In developing countries, there is an urgent need to apply sales restrictions and to promote the training and qualification of pharmacists. These measures could potentially lead to a decrease in the selection pressure prompted by antibiotic abuse and consequently in antibiotic resistance [34].

Although data related to the extent and patterns of antibiotic use in food-producing animals in LMI countries is limited, it is known that, in these countries, antibiotics are being used by farmers without veterinarians' supervision due to over-the-counter availability [35], a practice that plays a key role in antibiotic resistance dissemination.

The widespread availability of substandard medicines is a major contributor to AMR, and the continued use of such products promotes the growth of resistant bacteria, which cannot be removed even with last-resort antibiotics [36]. Recently, antimalarial medications

comprising quinine, sulphadoxine/pyrimethamine, chloroquine, and mefloquine were obtained from informal pharmacies in Congo, Burundi, and Angola. It was shown that one product had a low active pharmaceutical ingredient quality, one had an active pharmaceutical ingredient substitution, and 13 samples originated "out of specification" results [37]. In Togo, 8% of the samples tested, including antibiotics and medicine for non-communicable diseases, did not comply with pharmacopeial specifications, and none was falsified [38]. In South Africa, a study reported that 55.4% of the samples tested, including amoxicillin, single or in combination with clavulanic acid, and paracetamol alone or in combination with other drugs, were able to fulfill all pharmacopeial requirements, but most of them failed some quality testing [39].

However, it is important to refer that, according to WHO (<https://www.afro.who.int/countries/angola/news/angola-invests-strengthening-pharmacovigilance>), "To guarantee access to quality medicines and improve drug assistance to the population, in 2023 Angola has carried out a series of initiatives that include the creation and approval of policies that guide pharmacovigilance, strengthening the supervision of sale and consumption of medicines, as well as the implementation of a system for single and reliable purchases of medicines, with the support of strategic partners, including the WHO".

1.3. Surveillance systems

Antimicrobials have the dual advantage of being relatively inexpensive and having highly consistent effects on animal and human bacterial diseases [40]. So, they are essential for the treatment of infections and for the maintenance of overall health [41]. Mapping antimicrobial supply chains is one of the measures that can help overcome the problem of antimicrobial resistance, avoiding counterfeit antibiotics, and over-the-counter sales of antibiotics [42]. Surveillance systems are the basis for a better understanding of the epidemiology of antibiotic resistance and the key for combating this problem that threatens public health. Surveillance data can serve to improve public health at the local level, evidence-based health policies, and responses to health emergencies [17,43].

Surveillance must encompass beyond the magnitude of antibiotic consumption, also focusing on the types, rates, and extent of antibiotic-resistant bacteria and the mechanistic basis of antibiotic resistance [5]. As such, global actions must be established to increase and strengthen international cooperation and support capacity building, especially in LMI countries [35]. Europe and the United States have the best surveillance reporting, while sub-Saharan Africa and South and Southeast Asia have the least developed surveillance coverage [43]. In LMI countries, the challenges to establish such surveillance networks are enormous, due to poor laboratory infrastructures, absence of risk communication, lack of trained and qualified personnel, and a higher incidence of counterfeit antibiotics [44].

According to the Global Health Security (GHS) index scores for Angola [45] (<https://www.ghsindex.org/wp-content/uploads/2021/12/Angola.pdf>), a national AMR plan for the surveillance, detection, and reporting of priority AMR pathogens is not available in this country. On the website of Angola's National Institute for Health Research, there are no mentions of the capability to test for any of the priority AMR pathogens. The government does not conduct environmental detection or surveillance activities (e.g., soil or waterways) for antimicrobial residues or AMR organisms. There is national legislation and regulations requiring prescriptions for antibiotic use for humans (with evidence of gaps in enforcement), but not for animals. There are no surveillance systems for zoonotic diseases or pathogens available, and there are neither biosecurity nor biosafety systems implemented. Regarding dual-use research and the culture of responsible science, there is an absence of research on especially dangerous pathogens, toxins, pathogens with pandemic potential, and/or other dual-use research.

Angola presents poor laboratory system strength and quality and laboratory supply chains (e.g., there is no national laboratory that serves as an accredited reference facility, like the International Organization for Standardization [ISO] 15,189:2003). There is also a poor or absence of access to surveillance data. However, the government has made a commitment via public statements, legislation, and/or a cooperative agreement to share surveillance data with other countries in the region during a public health emergency. Also, there is an absence of case-based investigations [45].

Regarding the epidemiology workforce, the country has an applied epidemiology training program available, and the government supports citizens internships in other countries to participate in applied epidemiology training programs. However, there is no specific animal health field epidemiology training program available, and there is no public evidence that the country has at least 1 trained field epidemiologist per 200,000 people. Finally, Angola has implemented a risk communication plan, but the emergency preparedness and response planning present many debilities [45]. In 2015, the WHO implemented The Global Antimicrobial Resistance and Use Surveillance System (GLASS), aiming to improve AMR surveillance and controlling measures, by gathering and analyzing data from epidemiological, clinical, and population-studies [5]. At the present, GLASS englobes 127 countries, including several African countries, such as Angola, that joined the program in 2020 [46]. Since then, it seems that Angola has not submitted any data to GLASS [47].

In 2018, the African Centers for Disease Control and Prevention (Africa CDC) developed a framework for monitoring antimicrobial resistance in this continent [5]. International organizations, such as WHO, Food and Agriculture Organization (FAO), and World Organization for Animal Health (WOAH), have invested heavily in defending public health of risks associated with the use of antibiotics [48]. South Africa, for example, has developed a national antimicrobial resistance strategy network, to establish strategies to reduce the burden of antimicrobial resistance [49]. Still, it is difficult to estimate the exact prevalence of antimicrobial resistance in the African continent due to the low number of antimicrobial resistance surveillance programs [50].

Reports from the WHO's joint external evaluation program were

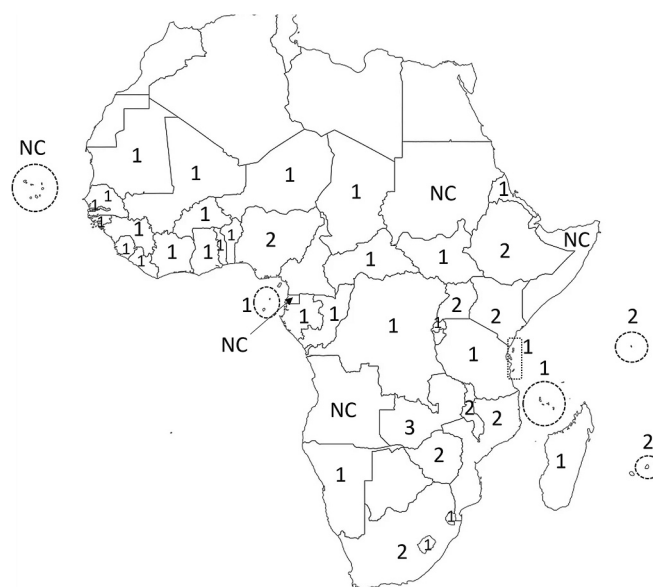
performed aiming at evaluating countries' capacities for preventing, identifying, and responding to public health risks, such as AMR [6]. According to a study that analyzed these cooperative and voluntary reports in sub-Saharan countries, East Africa had the highest percentage of countries with AMR national action plans and human and animal AMR surveillance programs, whereas Southern Africa reported the highest training programs and antimicrobial management. However, most sub-Saharan African countries did not have implemented national action plans and showed low mean AMR preparedness (Fig. 2), suggesting that AMR has not been a priority [6].

The study showed that Angola, Cape Verde, Equatorial Guinea, and Somalia did not complete the joint external evaluation report, and most countries demonstrated no capacity. Nigeria, Ethiopia, Kenya, Uganda, Mozambique, Malawi, Zimbabwe, South Africa, Mauritius, and the Seychelles had a joint external evaluation score of limited capacity or developed capacity, and Zambia was the only country with a demonstrated capacity or sustainable capacity to prevent, identify, and respond to public health risks (Fig. 2) [6].

In short, in most African countries, with some exceptions, surveillance systems such as the WHO's joint external evaluation program, and some national health plans, have a high probability of not being implemented, of not being properly followed up, or of not being reported or completed. Such surveillance systems would be most important for the detection of emerging antibiotic-resistant bacteria and antibiotic resistance genes, and would contribute to the early detection of outbreaks, allowing for the early and timely establishment of corrective actions [28].

2. Antimicrobial resistance in Angola

Angola is a LMI country and the sixth largest economy in sub-Saharan Africa. It is a country vulnerable to outbreaks, like yellow fever, malaria, cholera and Zika, that overload the health services compromising the life and health of the population. Also, communicable diseases including tuberculosis, meningococcal disease, and Methicillin-Resistant *Staphylococcus aureus* (MRSA), account for more than 50% of deaths [51].



Angola is among the 30 countries with the highest incidence of tuberculosis, MDR tuberculosis, and tuberculosis associated with HIV worldwide [52]. A study on *Mycobacterium tuberculosis* clinical isolates from Luanda revealed that 24.7% of the 89 clinical isolates were resistant to one or more antimicrobial drugs and 4.5% were MDR. This study highlighted the high rate and emergence dynamics of MDR tuberculosis in Luanda [53]. Likewise, another study found a high prevalence rate of MDR tuberculosis among retreatment cases (71.1%) and new cases (8.0%) in a rural setting [54].

Angola, together with Congo and Liberia, has never completed a drug-resistance survey so far. Despite this, there was recently a first attempt to promote an electronic medical record system in two health facilities of Luanda in the context of the tuberculosis national program in Angola [55].

Most of the available studies on AMR in Angola focus on human isolates or antimicrobials applied to human medicine. A project aiming to monitor the occurrence of MDR bacteria used in the treatment of human infections allowed to detect MDR *Escherichia coli* in urine samples from humans in the Huambo province, and also ampicillin-resistant *Enterococcus faecium* in samples obtained from humans, animals, and the environment in the Benguela province, [56,57]. Conceição et al. [58] isolated MRSA strains from children treated at the emergency room and outpatients from a pediatric hospital in Luanda and described an overall MRSA prevalence of 12.7%. Also, fluoroquinolone-resistant *Alcaligenes faecalis* was isolated from human patients with chronic suppurative otitis media with ear discharge [59]. This bacterium is commonly found in birds, and most probably the use of bird feces by humans as a traditional remedy to prevent ear secretions may explain this unexpected outcome. It is reported for the first time the antimicrobial resistance patterns and population structure of ten *Salmonella enterica* serotype Typhi from human patients with typhoid fever in Luanda [60]. The authors found resistant strains, emphasizing the need for continuous monitoring of this pathogen which incidence in Angola is high.

To the best of our knowledge, only one study in Angola comprised samples from humans, animals, and the environment [57]. The study included several samples from healthy humans, from animals, water from animal drinkers, and a cistern supplying the drinkers of a wild park, from farm production animals and their environment, from rivers serving inhabitants of Lobito and Catumbela cities, from treated and untreated human drinking waters, from residual waters from two points of a Benguela wastewater treatment station, and from urban/hospital sewer lines in Benguela, Damba-Maria, and Catumbela cities. Results showed that the occurrence of MDR ampicillin resistant *Ent. faecium* outside of a hospital context suggests β -lactam selective pressure, as reported in other sub-Saharan countries [10]. This is worrying, as this class of antimicrobials, which includes compounds such as penicillins and cephalosporins, is critical for the treatment of several serious infections, and antibiotics such as glycopeptides are not readily available in Angola or other sub-Saharan countries [57]. Monitoring AMR outside clinical contexts is essential to support the establishment of empirical therapy guidelines in this country, especially considering the favorable conditions for bacterial transmission and infection, and the uncontrolled use of antimicrobials [10,57].

Based on the premise that there is a relationship between the storage of antimicrobials and their misuse, a study in Angola concluded that interventions in the community that reinforce the appropriate use of antibiotics must be carried out with a focus on women, since they are the ones who store, and manage antibiotics [61]. In Angola, the close contact of farm animals with humans and the interaction between ecological systems are risk factors for AMR transmission [62]. Companion animals may also represent potential sources of antimicrobial resistance dissemination to humans, due to the extensive use of antimicrobial agents in veterinary medicine. In this country, the number of companion animals, especially dogs, is rising; however, to the authors' best knowledge, no studies have been carried out on the antimicrobial resistance profiles of commensal or pathogenic bacteria from pets in this

country. However, a study regarding stray dogs living in rural areas found a high prevalence of CTX-M-15-producing (group of extended-spectrum β -lactamase (ESBL)) and fluoroquinolone-resistant *E. coli* colonizing the animals' gastrointestinal tract. These results indicate that stray dogs are important reservoirs and transmitters of AMR, even if never being treated with antibiotics [1]. Recently, a study reported for the first time *Bartonella henselae* infections in stray cats and hemotropic mycoplasmas in cats and dogs in Angola, potentially posing a threat to other animals and humans as transmitters of pathogens [63]. Therefore, studies on pets and animals living near communities would be of major importance since they would allow gathering data aiming to improve guidelines for antimicrobial treatment of companion animals, to reduce the selective pressure caused by the incorrect empirical prescription of antibiotics [56], and to enforce measures that restrict the transmission of AMR pathogens from companion, stray, and wild animals to humans.

Despite reports on AMR cases in Angola are still scarce, there is a will to change this and ameliorate health conditions in this country. According to the global health observatory, to improve the health status of its population, Angola has established several major health sector partnerships, including with Cuban cooperation, the World Bank, the European Union, the Global Fund, and United Nations agencies. In addition, partnerships with non-governmental organizations, civil and regional associations were also celebrated. The support of the European Union, World Bank, and Global Fund has been decisive for the establishment of the 2013–2017 national development plan and of the 2012–2025 national health development plan, which are the main tools for implementing public policies in the country [51].

In November 2019, the WHO conducted a joint external evaluation of the core capabilities of international health regulations for Angola and stated that the country was developing a national action plan for AMR, but only the Ministry of Health was involved, excluding other public and private groups [64]. The "WHO Country Cooperation Strategy 2015-2019: Angola" report makes minimal mention of AMR [65], and the more recent 2019–2020 WHO's country self-assessment survey on AMR contains no information on Angola [66]. Unfortunately, Angola does not have a national action plan on AMR, according to WHO [67], and there are no mentions of AMR in the national health development plan 2012–2025 [68]. Therefore, it is urgent to develop and implement AMR surveillance in Angola to control the spreading of the AMR transmission cycle and decrease the mortality associated to diseases caused by bacterial species resistant to conventional antimicrobials.

3. Antimicrobial resistance data in African countries

Despite of only a small repertoire of low-quality antimicrobials being available in African countries, which are often sold over-the-counter without a prescription or proper diagnostic guidance [69], recent studies show that antimicrobial consumption in sub-Saharan Africa is high and that morbidity and mortality rates related to bacterial resistance are the highest in the world [70]. Nevertheless, available information about current resistance patterns of common pathogenic bacteria in sub-Saharan Africa, where surveillance capacity is minimal and the relative burden of infectious disease is high, is still scarce [71].

In Africa, resistance to commonly available antibiotics has already been observed in *M. tuberculosis*, *S. aureus*, *Salmonella* spp., *E. coli*, and *Pseudomonas aeruginosa* [10,72]. In another study performed in sub-Saharan Africa, 90% of Gram-negative bacteria were found to be resistant to chloramphenicol, an antibiotic commonly used in these countries, with resistance to third-generation cephalosporins, such as ceftriaxone, being less common [10].

A systematic review of AMR in patients with bacteremia in Africa between 2008 and 2019 focused on publications from PubMed and Google Scholar, including a total of 27 papers [73]. After analyzing data presented in these studies, the authors claimed that only 23% (11/47) of the WHO African region's member states had reports on AMR in bacteremia. The pooled resistance rates indicate a concerning degree of

MRSA and ESBL-producing *E. coli*. For *E. coli*, the pooled resistance profiles included resistance towards cefotaxime (42%) and imipenem (4%), and for *S. aureus* towards cloxacillin (34%), and oxacillin (12%). Consistent with this study, in South Africa bacteremia cases that occurred from 2007 to 2011 at a Tertiary Children's Hospital were associated with MRSA [74]. Moreover, *K. pneumoniae* ESBL producers were detected in hospitalized patients [75], and carbapenemase producing *Enterobacteriaceae* were found in blood cultures [76].

The prevalence of Hospital-acquired ESBL-producing Enterobacteriaceae is increasing worldwide. A study on the prevalence of these bacteria in community and hospital settings in East, Central, and Southern African countries was carried out, reviewing articles from inception to 2019 [77]. Authors observed a significant incidence of ESBL-producing Enterobacteriaceae, the majority of which related with the CTX-M enzyme, with considerable variance among countries. *E. coli* and *Klebsiella pneumoniae* were the dominant clinical isolates. The highest ESBL-producing Enterobacteriaceae prevalence was found in Congo (92%), the lowest in Zimbabwe (14%), and the prevalence was higher in hospital settings than in community settings.

Another systematic review analyzed the clonal diversity of MRSA in Africa described from 2014 to 2020, based on results from six electronic databases [78]. Only 30% of African countries provided sufficient genotyping data. There was an increase in the distribution of ST1, ST22, and ST152, but a decrease of ST239/241 MRSA clones. Interestingly, ST88-IV [2B] was widely spread over the continent, especially in three Portuguese-speaking countries: Angola, Cape Verde, and São Tomé and Príncipe [78]. A study in Tanzania on the prevalence of MRSA showed that these strains have been increasing in Tanzania, with studies describing an increase of MRSA associated clinical infections from 0.4% in 1999 to 23.3% in 2010 [79].

The Sub-Saharan African region has a high tuberculosis incidence. An article examined studies in Sub-Saharan Africa from 2010 to 2020 that reported mixed tuberculosis infection and heteroresistance [80]. Several databases were examined, but only 18 papers matched the inclusion criteria. The frequency of mixed strain infection was between 3% and 21%, while drug resistance ranged from 0.06% to 19%, highlighting the importance of monitoring these conditions for proper tuberculosis treatment.

In Ethiopia, a systematic review was carried out to determine antimicrobial resistance between 2009 and 2019, based on studies available at the PubMed/Medline database [81]. Among Gram-positive bacteria, the vancomycin resistance ranged from 8% (*Enterococcus* species) to 20% (*S. aureus*), with *E. coli*, *K. pneumoniae*, and *P. aeruginosa* being the most common Gram-negative pathogens resistant to conventionally used antimicrobials.

As previously mentioned, animals are important vectors for antimicrobial resistance transmission, posing a serious threat to food security and safety [49]. High levels of multidrug-resistant bacteria isolated from production animals and their by-products have been documented in several African countries. A study performed in Egypt [82] showed that milk and dairy products may carry a potential risk for the dissemination of multi-resistant and toxigenic *S. aureus*, which may be associated with neglected hygienic practices during the production and storage stages.

A report from Ghana described that animal isolates may present higher resistance levels when compared to human isolates. These findings can be associated with the fact that farmers can easily access antibiotics through veterinarians and veterinary chemical stores [83]. It has also been observed that only 63% of farmers complete the recommended dosage of antibiotics and therapeutic scheme prescribed for animals [18]. Also in Ghana, resistant bacteria, including critical pathogens such as *E. coli* (62.2%), *Klebsiella* spp. (60.4%), and *Pseudomonas* spp. (52.1%), were isolated from human, animal, food, and environmental samples, with high rates of resistance towards ampicillin, cefadroxil, cefotiam, cloxacillin, cotrimoxazole, erythromycin, penicillin, and trimethoprim [84].

In Nigeria, a study on *E. coli* from poultry farms revealed that 88% of

the isolates were resistant to ciprofloxacin [85]. In addition, there was an excessive bacterial load of *E. coli* isolated from abattoirs and aquaculture effluents in this country, related to a high multiple AMR index [86].

In a review on *Campylobacter* prevalence in Sub-Saharan Africa, including resistant strains, the authors concluded that *Campylobacter jejuni* and *C. coli* were the predominant species isolated from animals in Nigeria, South Africa, and Tanzania, with cattle and chickens being identified as the most important hosts and possible transmission sources for humans; furthermore, the authors pointed out that most *Campylobacter* isolates were resistant to erythromycin (44%), ampicillin (39%), tetracycline (33%), nalidixic acid (31%), and ciprofloxacin (30%) [87]. In another systematic review, covering 791 studies [88], the authors also concluded that *Campylobacter* spp., mainly *C. jejuni* and *C. coli*, were highly prevalent in West Africa (Nigeria, Ghana, Burkina Faso, Côte d'Ivoire, Benin, Niger and The Gambia), being more frequently isolated from food-producing animals (34%) than from hospitalized patients (10%); in contrast, this study revealed that the rate of MDR human isolates was much higher (91%) than the percentage of MDR isolates obtained from food-producing animals (59%). Interestingly, although ciprofloxacin is not approved for use in veterinary medicine [85], the rate of resistance to this antibiotic was higher in animal isolates than in those from humans [88].

Enterococcus spp. and *Salmonella* spp. MDR strains have been isolated from meat samples in Tunisia, with *Ent. faecalis* being the most prevalent species (41%) and showing a high resistance profile towards erythromycin and tetracycline [89].

In a study performed on broiler chickens in Algeria, the authors found that 51% and 27% of the avian *Salmonella* were resistant to ciprofloxacin and cefotaxime, respectively [90].

In South Africa, more than 70% of the antibiotics used for livestock production are available without a prescription [91] leading to AMR dissemination. In fact, *E. coli* containing the mobilized colistin resistance gene *mcr-1* has been detected in this country, not only in cattle but also in hospitalized and ambulatory patients. Colistin is a last-resort antibiotic for the treatment of infections promoted by carbapenem-resistant bacteria [92]. Also in South Africa, *Salmonella* serovars from humans and meat samples presented a MDR profile to commonly used antibiotics such as gentamicin and ciprofloxacin [93]. In this country, *Enterococcus* spp. isolates resistant to ampicillin, penicillin G, and vancomycin, some of which were positive for the genes *vanA* and *vanB*, were obtained from groundwater samples in rural communities [94], while Shiga toxin-producing *E. coli* O157 with a MDR profile was detected in dairy cattle feces [95]. Healthy domestic ruminants, particularly cattle, and sheep, are considered natural reservoirs of Shiga toxin-producing *E. coli*, a pathotype responsible for clinical disease in humans, characterized by diarrhea, hemorrhagic colitis, or hemolytic uremic syndrome [95].

A study in Kenya found that *E. coli* isolates ($n = 123$) from fecal samples of camels exhibited high levels of resistance towards penicillin and second, third, and fourth generations cephalosporins [96]. The presence in camels of MDR *E. coli* with ESBL- and non-ESBL-encoding genes is worrying, especially considering that animal husbandry practice is one of the primary drivers of AMR in arid and semi-arid areas of Africa, and may jeopardize the pastoral community health.

Some studies on wildlife were also carried out, as these animals can be a source and reservoir of zoonotic pathogens. A study conducted by Wiethoff et al. assessed the prevalence of antimicrobial resistant species in wild Gabonese pangolins sold in Gabon ($n = 89$) from 2021 to 2022 [97]. Most resistant isolates were identified as *Pseudomonas* ($n = 170$), followed by *Stenotrophomonas* ($n = 113$), and *Achromobacter* ($n = 37$). Also, pangolins were found to be colonized with human-related ESBL-producing *K. pneumoniae* and *E. coli*. These isolates clustered with human isolates from Nigeria and Gabon, pointing to a transmission between pangolins and humans or a common source of infection.

In South Africa, antibiotic-resistant bacteria have been detected in the feces and raw meat of wild animals. Resistance to ampicillin and

streptomycin was most prevalent in *E. coli* obtained from both types of samples, and *S. aureus* isolated from game meat showed high resistance to penicillin [98].

Another work focused on MDR enterohaemorrhagic *E. coli* serogroups present in the feces of hunted wildlife in Nigeria, including cane rats (*Thryonomys swinderianus*), royal antelope (*Neotragus pygmaeus*), African giant rats (*Cricetomys gambianus*) and waterbucks (*Kobus ellipsiprymnus*) [99]. Authors found that 83% of the samples were positive for *E. coli*, and that all isolates obtained were MDR. Also, 6% of the isolates corresponded to enterohaemorrhagic *E. coli* and possessed virulence-associated genes. This study showed the importance of wildlife surveillance to control the AMR transmission cycle and the spread of zoonotic diseases.

Moreover, wastewater treatment plants and soil are also sources of AMR bacteria. A study carried out in the Eastern Cape Province, South Africa, revealed that wastewater treatment plants can be a source of resistant *E. coli* [100].

A systematic study based on 17 publications from 2000 to 2021 crossing 27 African nations was performed, comprising a total of 3438 isolates from drinking water ($n = 6$), rivers ($n = 5$), wastewater ($n = 4$), and wastewater/river ($n = 1$). Authors concluded that there was an estimated high prevalence of *E. coli* (72%), and most isolates were resistant to penicillin (93%), followed by erythromycin (92%), and ampicillin (69%) [101].

A study on the genomic surveillance of AMR *E. coli* isolated from fecal sludge and sewage in Uganda was conducted by Gomi et al. [102]. The genomic analysis of *E. coli* isolates ($n = 181$) demonstrated the predominance of certain clones in both fecal sludge and sewage, as well as the worldwide high-risk clones ST1193 and ST131. AMR determinants such as *bla*_{CTX-M-15} resistance gene and *gyrA* and *parC* mutations played key roles in AMR gene transmission.

A study in South Africa evaluated the human exposure to *Campylobacter* and associated AMR genes through ingestion in two South African rivers [103]. South Africa relies on its freshwater systems, including rivers, for recreation, irrigation, and domestic purposes. The study found that rivers may be a source of *Campylobacter* and AMR genes, which can be transmitted to humans via oral route during recreation activities, and potentially to other interfaces such as animals and plants.

Another study in South Africa characterized *Citrobacter* spp. (*C. braakii*, *C. murlinae*, and *C. portucalensis*) from surface water [104]. Data indicated that these species were multidrug resistant bacteria with intrinsic ESBL genes. Furthermore, all four genomes of ESBL-producing *Citrobacter* species had the *bla*_{CMY} resistance gene, posing a transmission risk to the environment and possibly to other interfaces.

In Burkina Faso, sewage water used for urban agriculture was also identified as one of the main sources of resistant pathogens spread among animals and humans [105].

Different studies on the presence of pathogens in water and street food sold were carried out in Maputo, Mozambique. One study concluded that water had high fecal contamination, including high MDR (40%) Enterobacteriaceae, representing a threat to health [106]. Another study also found a high prevalence of *Klebsiella* spp. and *Aeromonas* spp. resistant to β -lactam antibiotics in water [107]. When comparing the pathogenic potential of *E. coli* in water and ready-to-eat street food, a study also conducted in Maputo revealed that 31% of the isolates were MDR, with *E. coli* isolates from water presenting higher resistant rates in comparison with food isolates. The authors also found that 73% of the MDR isolates contained virulence genes [108]. These studies highlight the extreme importance of strengthening waterborne disease control measures towards food and water sold in the streets of Mozambique.

The presence of AMR bacteria in crops is a known reality in Africa. *E. coli* was found in all 25 composite lettuce samples analyzed in a study from 2022 performed in five major produce farms in Ghana [109]. Authors found that 82% of all bacterial isolates were MDR, and 48% were ESBL-producing, of which 8% carried the *bla*_{TEM} resistance gene.

Therefore, there is an urgent need to support farmers in implementing safety measures towards AMR control, as irrigation sources are frequently contaminated with human and animal waste.

In Nigeria, samples from agricultural farms that use untreated water for irrigation, including soil, manure, and irrigation water samples, and vegetables from open markets were analyzed regarding the presence of resistant bacteria [110]. ESBL *E. coli* strains from agricultural farms were isolated from soil (68%), manure (84%), irrigation water (28%), and vegetables (24%), and in 37% of the vegetables from open markets. Moreover, 86% of the isolates were MDR. Also, in South Africa, fresh vegetables bought from street vendors, trolley vendors, farmers' market stalls, and supermarket chain stores had a high prevalence of ESBL/AmpC-producing Enterobacteriaceae (*E. coli*, *Enterobacter cloacae*, *Enterobacter asburiae*, and *K. pneumoniae*, among the dominant species), and 96% of the 77 isolates selected for characterization were MDR [111].

4. One health

To date, data on AMR from a One Health perspective in Africa is limited [112]. Some relevant papers on One Health in Africa will be now discussed; most are systematic reviews focusing on studies in Africa, and two of them were carried out in two African countries, Cameroon, and Zambia.

In a recent systematic review on AMR from a One Health perspective performed in Cameroon, a total of 66 of 97 publications found on PubMed, Google Scholar, and African Journals Online databases were in compliance with the PRISMA guidelines and met the qualifying requirements [113]. These studies identified AMR bacteria in samples from humans (68%), animals (14%), and the environment (8%). Overall, bacteria from 19 different species were resistant to all antibiotic classes. MDR rates in bacteria from human origin were significant, including in *E. coli* (47%), *K. pneumoniae* (51%), and *Staphylococcus* spp. (45%). *Salmonella* spp. was reported in 6 of the animal studies with an MDR rate of 46%, whereas *Staphylococcus* spp. was reported in 8 of the environment studies with an MDR rate of 67%. This review demonstrates high resistance to antibiotics routinely administered to humans, animals, and the environment in Cameroon.

In a study from Zambia, 716 publications available in PubMed, Cochrane Libraries, the Medical Journal of Zambia, and African Journals from conception to 2021, were assessed and analyzed using the PRISMA criteria [114]. Only 25 papers met the eligibility requirements for a systematic review, indicating that AMR is understudied in this country, with AMR data being unavailable for six of Zambia's ten provinces. Authors referred that those 21 isolates from humans, animals, and the environment, evaluated against 13 antibiotic classes, were MDR. Across humans, animals, and the environment, the most prevalent organisms tested were *S. aureus*, with a wide range of resistance patterns. *E. coli* exhibited high resistance to cephalosporins (24–100%) and fluoroquinolones (20–100%). Authors concluded that increased standardization of antimicrobial susceptibility testing in Zambia would allow tracking of AMR over time.

The purpose of a review by Escher et al. was to uncover molecular studies on AMR in One Health settings in Africa, and to assess the prevalence of AMR genes in humans, animals, and the environment [112]. Due to the small number of studies that included environmental samples, this meta-analysis solely contained data from humans and animals. The inclusion criteria were met by 18 studies from a total of 10,464 papers on AMR in Africa available in the PubMed, Web of Science, and Scopus databases, published from 2000 to 2020, performed in ten different countries: Algeria, Botswana, Egypt, Ethiopia, Ghana, Nigeria, South Africa, Tunisia, Uganda, and Zambia. The papers focused on *E. coli*, *Salmonella* spp., *Campylobacter* spp. and *Staphylococcus* spp. The findings of this review revealed no significant prevalence of AMR genes in animal samples, including samples from cattle, pigs, and poultry, in comparison with human samples. As a result, the authors

concluded that cattle production in Africa is not a significant driver for AMR emergence. However, the small sample sizes may have contributed to some contradictory outputs, and it was not possible to assess the AMR spreading routes.

A review on the genomics and resistance epidemiology of gram-negative bacteria in Africa used data from research papers published between 2015 and 2019. The authors analyzed results from 30 species from samples obtained in 31 countries and 24 genera from samples from 41 countries [115]. *E. coli*, *K. pneumoniae*, *S. enterica*, *Acinetobacter baumannii*, *P. aeruginosa*, *Enterobacter* spp., *Neisseria meningitidis/gonorrhoeae*, *Vibrio cholerae*, *C. jejuni*, and other potential pathogens were identified as prevalent AMR gene carriers in Africa. Most pathogens were of human origin, with comparatively few zoonotic transmissions. Importantly, the same clones were shown to spread between countries and between animals, humans, plants, and the environment, including *E. coli* ST103, *K. pneumoniae* ST101, *S. enterica* ST1/2, and *V. cholerae* ST69/515. The authors suggested *Enterobacter* spp. or *K. pneumoniae* as sentinel species for AMR surveillance. In conclusion, single and multiple clones of gram-negative clinical pathogens with MDR profiles are spreading in Africa, disseminating different resistomes from animals, foods, plants, and the environment to humans.

Another study did a comprehensive review and meta-analysis to determine the global prevalence of ESBL in co-existing *E. coli* and *K. pneumoniae* isolates from humans, animals, and the environment [116]. A total of 126 studies from Asia ($n = 80$), Africa ($n = 37$), Europe ($n = 11$), and North America ($n = 8$), published from 1990 to 2022, were analyzed. ESBL-producing *E. coli* (33%, 34%, 57%, and 27%) and *K. pneumoniae* (33%, 19%, 24%, and 7%) were common in humans, animals, the environment, and animals/environment, respectively. The three types of resistance genes that encode ESBL have been found in isolates from humans, animals, and the environment. Based on their findings, the authors concluded that ESBL-producing bacteria should be included in national surveillance systems.

The fight against the AMR hurdle in Sub-Saharan Africa has used a variety of currently available approaches. According to Gahamanyi et al. [117], these important weapons against AMR include vaccine production, promotion of AMR education and awareness among health professionals and the community, and strengthening infection prevention and control by improving water, sanitation, and hygiene facilities. Using alternative treatment options, adopting the “One Health Approach”, initiating AMR surveillance, developing and implementing national action plans on AMR, applying antimicrobial stewardship programs, and promoting good governance and regulations are also possible measures against AMR. Advanced techniques, like metagenomics, whole-genome sequencing to track resistance tendencies, and artificial intelligence for AMR prediction, should be gradually implemented to rapidly detect outbreak etiologies. The authors emphasized the need for financial support for improving diagnostic capabilities in healthcare settings.

From the studies discussed above, it is uncontroversial that African countries would benefit from thorough One Health molecular surveillance to map AMR and AMR transmission routes [115].

5. Conclusions

The potential for antibiotic resistance to cause high mortality and morbidity rates in LMI countries may be even greater than in developed countries, because of the higher burden of bacterial infections, poor diagnostic capability, and less access to quality antibiotics.

In Angola, the information available on antimicrobial resistance is scarce, mainly focusing on bacteria associated with human infections, indicating the existence of data gaps, especially in the veterinary and environmental settings. Public in general, veterinarians, and pharmacists need more knowledge about the correct and conscious use of antibiotics. Counterfeit antibiotics and over-the-counter antibiotic sales must be stopped through strict government regulations that reflect awareness of antibiotic misuse. International and cooperative surveillance programs

should be implemented, properly followed, and reported. It is necessary to proceed with the national health development plan until 2025, not forgetting to include AMR monitoring, and to comply with the “One Health Approach”, and continuously monitor humans, animals, and the environment, for the presence of resistant strains. Both surveillance systems and national health plans will allow to obtain more information about this public health problem, and thus be able to define strategies for the control of antimicrobial resistance in Angola with the government commitment.

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Romay Coragem da Costa: Conceptualization, Writing – original draft, Writing – review & editing, Visualization. **Isa Serrano:** Conceptualization, Writing – review & editing, Visualization. **Lélia Chambel:** Conceptualization, Writing – review & editing, Visualization. **Manuela Oliveira:** Conceptualization, Writing – review & editing, Visualization, Project administration.

Declaration of competing interest

None.

Data availability

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