PREVALENCE OF CARBAPENEM RESISTANCE AND FACTORS INFLUENCING ANTIBIOTIC MISUSE/OVERUSE IN NIGERIA USING THE ONE HEALTH APPROACH

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Prevalence of carbapenem resistance and factors influencing antibiotic misuse/overuse in Nigeria using the One Health approach

A thesis submitted in partial fulfilment of the requirement for the degree of Master of Science in Public Health by Oluwafemi J. Adewusi

Nigeria

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DEDICATION

Now unto the King eternal, immortal, invisible, the ONLY WISE GOD, be honour and glory for ever and ever. Amen (1 Timothy 1:17)

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GLOSSARY

Antibiotic misuse/overuse	refers to irrational use and abuse of antibiotics including use of antibiotics to treat viral infections, use of antibiotics without prescription, use of antibiotics for non-therapeutic purposes in sublethal dose.
Antimicrobial resistance	refers to a phenomenon where the activities of infection-causing bacteria can no longer be terminated or inhibited by antibiotics/antimicrobial agents that are previously used for these purposes as a result of bacteria modification to these agents.
Carbapenem-resistance	refers to a phenomenon where bacteria are no longer treatable with carbapenem, a set of beta-lactam antibiotics.
One Health	refers to working together of local, national and international stakeholders from different sectors in a collaborative approach to ensure healthy human, animal and the environment.

ABBREVIATIONS

AMR	Antimicrobial resistance
bla	beta lactamase
CLSI	Clinical and Laboratory Standards Institute
CR	Carbapenem resistance
CRE	Carbapenem-resistant enterobacterales
ESBL	Extended broad-spectrum lactamase
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FAO	Food and Agricultural Organization of the United Nations
FMoH	Federal Ministry of Health
IMP	imipenem-resistant Pseudomonas beta-lactamase
KPC	Klebsiella pneumoniae carbapenemases
MBL	Metallo-beta lactamases
NCDC	National Centre for Disease Control
NDM	New Delhi metallo-beta-lactamases
NRL	National Reference Laboratories
OTC	Over the counter
OXA	oxacillinase
PPMVs	Patent Proprietary Medicine Vendors
VIM	Verona integronencoded metallo-beta-lactamases
WHO	World Health Organization

ABSTRACT

Background: Increasing rates of carbapenem resistance (CR) are reported in Africa, driven primarily by misuse and overuse of antibiotics for humans and animals. Still, the extent of occurrence of CR and drivers of antibiotics misuse/overuse in Nigeria are not comprehensively understood due to lack of effective CR and antimicrobial use surveillance systems. This scoping review was conducted to describe the prevalence of CR as well as determinants of antibiotics misuse/overuse in Nigeria using One Health Approach.

Methodology: Peer-reviewed articles published in English language from January 1, 2000, to June 30, 2020 were retrieved from the MEDLINE and AJOL databases in two searches: CR prevalence, mechanism, and geographical distribution; and determinants of antibiotics misuse/overuse. Using the PRISMA guideline for a scoping review with established inclusion and exclusion, data from eligible studies were extracted in an Excel spreadsheet. Findings were reported using appropriate frameworks.

Results: Of the 1361 and 1617 articles identified, 94 and 33 were eligible in the first and second search, respectively. The majority, 75(79.8%) and 38(40.4%) of the CR studies utilized clinical samples and from Southwestern Nigeria, respectively. CR range from 0%-100% mainly due to carbapenemase production. Antibiotics misuse/overuse determinants include drive for profits, availability of leftover antibiotics, cost and lack of diagnostics.

Conclusion: CR varies widely but prevalent across the country and socio-economic, health system and policy factors continue to drive the misuse/overuse of antibiotics among the prescribers and consumers. It is essential to establish a national CR surveillance system and design antimicrobial stewardship interventions in the country.

Keywords: carbapenem resistance, antimicrobial resistance, antibiotics misuse/overuse, One Health

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CHAPTER 1: BACKGROUND

The discovery and development of penicillin in the 1940s and other antibiotics in subsequent years is one of the landmarks in modern medicine (1). Antimicrobial therapy has therefore been an important component of prevention and treatment of infections as well as surgical operations. The significant contribution of antibiotics to human existence cannot be overemphasized as it has significantly improved outcomes in disease treatment, contribute to decreased mortality and increased life expectancy as well as improved productivity (2)(3). Antibiotic use has become an essential part of modern-day human medicine evidenced in the consumption rates. Recent global antibiotic consumption estimation showed that between year 2000 and 2015, the mean rate of antibiotic consumption increased by 28% from 16.4 (SD 9.9) defined daily dose (DDD) per 1,000 inhabitants per day to 20.9 (SD 9.8) across the countries although this upsurge was largely driven by increased consumption in low and middle-income countries. In 2015, total global antibiotics consumption was 42.3 billion DDD (15.8 DDDs per 1,000 inhabitants per day) and without any policy intervention, this will increase by over 200% in 2030 (4).

Similarly, antibiotics are used in livestock farming, fish and poultry management and as well as in food processing procedures. These medicinal agents are vital to the expansion of industrial farming over the years thus contributing to food productivity, security and animal health. Antibiotics are used in veterinary and aquaculture and in crop production for prophylactic, curative and growth promoting purposes. Although used to treat and prevent infections in animals, a significant proportion of the antimicrobials is used to enhance and promote rapid growth in animals. These antimicrobials are administered in low doses with potentially grave implications for resistances (5). Antibiotic consumption is relatively low in crop production compared to livestock production, where 67% of the estimated increase in future consumption of antimicrobials is expected to take place (6)(7).

1.1 Occurrence and burden of antimicrobial resistance

The gains of antimicrobial discovery and use are slowing down and taking a downward trend as bacteria are beginning to develop resistance to the world's classes of antibiotics (8). Antimicrobial resistance describes a situation when bacteria no longer respond to antibiotic agents that impede their development or destroy them. Most bacteria develop resistance to antibiotics as a result of rapid change of the bacterial genome due to mutation or horizontal gene transfer although bacteria can be intrinsically resistant to some antibiotics. The latter phenomenon occurs when a bacterium has natural structural and functional characteristics which makes it able to withstand the actions of the antibiotic. Bacteria also develop or acquire antibiotics resistance through three main ways: firstly, by minimizing the concentration of the antibiotics in the cell due to inadequate entry into the microorganism or of the antibiotic efflux; secondly, through modification of the antimicrobial target as a result of mutation or po-translational alteration of the target; and thirdly, through inactivation of the antimicrobial via alteration or hydrolysis (9). Acquired resistance occurs under continuous selective antibiotic pressure due to routine antibiotics consumption (10) and as shown in figure 1, the timelines for antibiotics discovery is relatively slower than the rate of bacterial resistance.

AMR has increased significantly over the years and the rising trend of AMR has become a public health threat that requires urgent attention. The WHO global report on surveillance of AMR in 2014 revealed resistance of many pathogenic micro-organisms to the commonly used antibiotics across the globe making it difficult to manage the bacterial infections. For instance, the prevalence of *Klebsiella pneumoniae*'s resistance to third-generation cephalosporins was higher than 30% globally and *Escherichia coli* was resistant to fluoroquinolones, exceeding 50% in almost all WHO regions (11). Similarly, a 2017 systematic review revealed increasingly high rates of antimicrobial resistance in Africa. The review showed that bacteria causing urinary tract infections were notably highly resistant to common first line regimens, and *Klebsiella spp* resistance to second generation fluoroquinolones were increasingly high West Africa (12).

The impact of AMR is enormous, and this will increase without any policy intervention. Globally, an estimated 700,000 are attributable to AMR annually and 100 trillion USD is estimated as potential global production loss by year 2050 if no effort is directed towards curbing the AMR menace (13). AMR potentially challenges efforts to improve human and animal productivity, reduce poverty and improve the quality of life. The World Bank estimated that by 2050, annual global GDP and real exports will be reduced by 1.1% in in a low AMR-impact scenario, at least 2.6% reduction in global livestock production, rise in global healthcare of at least $300 billion per year and possibilities of additional 26.2 million extreme poverty cases in the LMICs in a high impact situation (8). Similarly, increase healthcare cost, increased health workers' burn out, depersonalization and stress due to preventable death of patient are potential consequences of AMR on the health system (13)(14).

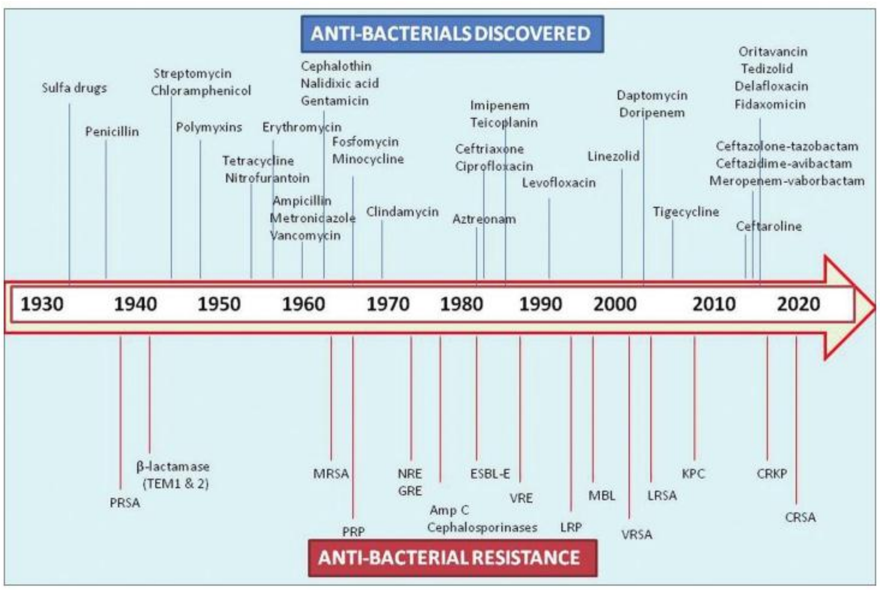

Figure 1: Time line of anti-bacterials discovery and development of resistance. Annexure to Figure 1 of new and promising anti-bacterials. PRSA = penicillin resistant *Staphylococcus aureus*; MRSA: methicillin resistant staphylococcus aureus; PRP = penicillin resistant pneumococcus; NRE = nalidixic acid resistant enterococci; GRE = gentamicin resistant enterococci; ESBL-E = ESBL producing Enterobacteriaceae; VRE = vancomycin resistant enterococci; LRP = Levofloxacin resistant pneumococcus; MBL = metallo β-lactamases; VRSA = vancomycin resistant *staphylococcus aureus*; LRSA = Linezolid resistant *staphylococcus aureus*; KPC = Klebsiella pneumoniae producing carbapenamases CRKP = Colistin resistant Klebsiella pneumoniae; CRSA = Ceftaroline resistant *staphylococcus aureus*

Figure 1: Timeline for antibacteria discovery and development of resistance (15)

1.2 Factors influencing antimicrobial resistance

Antibiotics become less effective over time because bacteria develop resistance to the drugs. However, the rate at which antimicrobial resistance occur can be enhanced by clinical, environmental and behavioural factors which are preventable (10). Inappropriate human and animal antibiotics use has notably been identified as a key driver to AMR and this is coupled with other direct and indirect factors such as environmental transmission, healthcare transmission, suboptimal rapid diagnostics, suboptimal vaccination, suboptimal dosing including from substandard and falsified drugs, travels and mass drug administration for human health (16).

In the Agricultural sector, the rapid growth of industrial farming over the years in a bid to meet up with the rising world population is a major factor fueling the use of irrational antibiotics use in the sector (17). Other factors influencing AMR in the Agricultural sector include price of antibiotics, farmers' expertise, and availability and access to diagnostics (18).

The WHO, in it's country level situation assessment, identified other broader factors contributing to AMR which include weak surveillance and laboratory diagnostic capacity, weak regulatory capacity on the use of antimicrobials, weak or lack of infection prevention and control programmes and inefficient monitoring and supervision of antibiotic use (AMU). AMR and AMU surveillance mechanism carried out by experts and relevant stakeholders, using appropriate tools to detect resistant organisms and corresponding risks is central to control AMR epidemics (19).

1.3 AMR in a One Health context

The occurrence of AMR, including carbapenem-resistant Enterobacterales (CRE), listed among WHO's critical priority pathogens (20), has been primarily considered from a human health perspective (21). However, AMR is also being reported in wildlife, food-producing and companion animals (22). José Graziano da Silva, director general of the FAO emphasized at the United Nations (UN) meeting that the challenge of AMR is evidenced in the hospitals and farms (23). Similarly, Forsberg et al (24) also described in their study, the possibilities of spread of AMR genes from soil bacteria to clinical pathogens which suggests availability and transmission from AMR across different reservoirs. This implies that AMR is highly inter-connected among the human, animal, plant, food and the environment (25).

Although the pathway and mechanism of resistant bacteria transmission among the three AMR domains are complex and yet to be fully understood, potential routes of transfer of resistant exist. Human-to-human transmission is possible via contact with infectious body fluids while animal to human transmission could occur via contact with animal feaces, consumption of contaminated uncooked or improperly cooked foods and water or breathing in of air from farms or abattoir. Similarly, the use of bacteria-resistant wastewater for irrigation as well as release of household, farms, hospitals and industries bacteria-resistant pollutants such as fecal matter into the environment increases surface contamination and consequently risk of exposure (26).

The irrational use of antibiotics in humans, food and animal production as well as uncontrolled environmental pollution fuels the emergence and spread of AMR (Figure 2). In humans, the practice of treating viral infections with antibiotics and misuse or over-use of broad-spectrum antimicrobial agents for bacterial infections creates antibiotic selection pressure which tends to eliminate the susceptible pathogens, leaving the resistant ones to reproduce, thus increasing the rate of AMR development (10). In the same vein, AMR is driven in food and animal industries because of use of antimicrobials as growth promoters and prophylactics. These therapeutic agents are administered in sublethal doses which provides an environment for pathogenic bacteria in the animals to thrive and develop resistance to the antibiotics (5).

The rising trend and potential consequences of AMR among humans, animals, plants and environment reinforce the need to address it using a coordinated and multi-prong approach such as 'One Health'. The One Health approach refers to the working together of relevant sectors in designing and implementing research, policies and interventions through effective communication in order to achieve better health outcomes for humans, animals and the ecosystem (27). In addressing AMR with this approach, burden and risks through interactions of humans, animals and the environment are assessed and mitigated.

In 2016, the UN made a political declaration to use a One Health strategy to address AMR as contained in the WHO action plan. These leaders indicated commitment to allocate resources in this direction, with her tripartite human, animal and food agencies charged with the responsibilities of planning and coordination (23). The National Centre for Disease Control of Nigeria (NCDC), in 2017 developed a five-prong Action Plan in line with the WHO global plan. This plan aimed to increase awareness and knowledge of AMR and related topics; build a 'One Health' AMR surveillance system; intensify infection prevention and control in the tripartite sectors; promoting rational access to antibiotics and antimicrobial stewardship; and invest in AMR research and development. Execution of this plan was hinged on the collaborative efforts from the Ministries of Agriculture, Environment and Health (28).

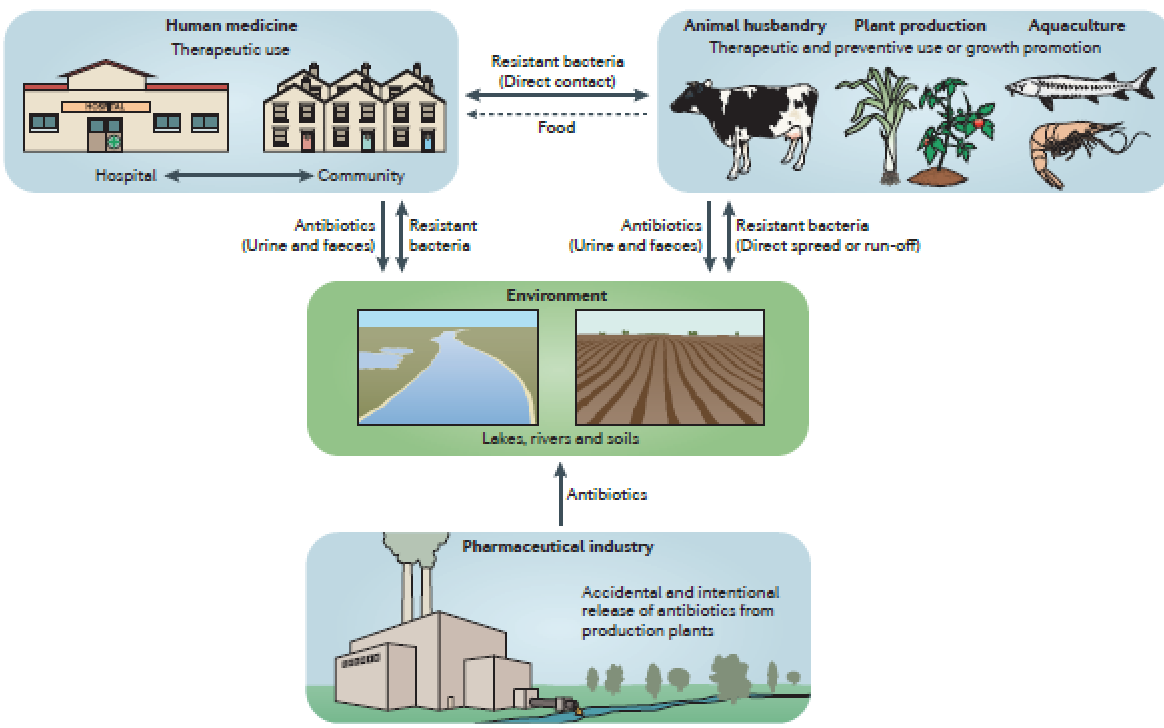

Figure 2: Ecology of antibiotics and antibiotic resistance (Cycling of antibiotics among the One Health domains) (29)

1.4 Antimicrobial resistance in Nigeria

Until 2017, there was little or no nationally coordinated response to AMR in Nigeria. In 2017, the Ministries of Health, Agriculture and Environment developed the national action plan for AMR from year 2017 to 2022, coordinated by the NCDC (28). A situational analysis conducted by the NCDC revealed a high prevalence of AMR from both nosocomial and community-acquired infections in the country (30). Systematic reviews reported increasing prevalence of methicillin-resistant *Staphylococcus aureus* from 18.3% in 2009 to 42.3% in 2013, high rise in AMR among food animals and environment and a 34.6% pooled prevalence of extended spectrum beta lactamase-producing Enterobacterales (ESBL-PE) in Nigeria (31)(32)(33). A 2020 systematic review reported high prevalence of ESBL-producing Gram-negative bacteria resistance across all the geopolitical zones in the country (34) and recent reports also indicated the occurrence of CR pathogens from clinical and veterinary samples (35)(36)(37).

The emergence of CR in the country has severe implications for mortality rates, length of hospital stay, health expenditure as well as economic loss and inability to achieve universal health coverage (38). This is because CR bacteria have very limited treatment options (39) and recently, the WHO classified ESBL-producing and CRE as critical priority pathogens and highly drug-resistant microorganisms (HRMOs) (20) as a result of their increasing rates of resistance to most beta-lactam antibiotics (40). Currently, carbapenems are considered as antibiotics of last resort for treatment of bacterial infection; generally prescribed as next line of treatment when the other antibiotics are failing especially in the treatment of causative agents from the Enterobacterales group (39). Common carbapenem agents include meropenem, imipenem, ertapenem, doripenem and panipemen (41). Carbapenems possess wider broad spectrum antimicrobial actions, independent of concentration (40)(42) however, factors such as prolonged hospital admission, immunosuppression, age, amechanical ventilator, stem-cell or organ transplantation, initial exposure to antibiotics, and admission to the intensive care unit could increase the risk to CR (43)(44).

In accordance with the five strategic objectives from the WHO Action Plan (45), the NCDC identified gaps in addressing AMR in the country: low public awareness among the different stakeholders, lack of coordinated multi-sectoral surveillance system, non-existence of AMR laboratory surveillance system, high incidence of infectious disease, weak antimicrobial stewardship drive in the government and private sectors, vertical implementation of control programmes, non-existence of guidelines for national Infection Prevention and Control (IPC), lack of data on AMR health and economic impact and poor funding (28). Despite laws to ensure antimicrobials are only dispensed with prescription, health system and economic factors such as shortage of licensed prescribers especially in the rural areas, increased activities of under-regulated patent drug vendors and hawkers, low awareness among the public and health workers, poor infection control, production of low-quality antibiotics and poverty promotes inappropriate antimicrobial use by patients and farmers, (30).

Considering the cardinal role of surveillance to AMR stewardship, the NCDC developed blueprints for the nationally coordinated AMR surveillance and generation of data for the Global antimicrobial Surveillance System (GLASS) amongst other strategic objectives but the actual implementation commenced in 2018 (30). As illustrated in the 2020 WHO report (figure 3), there were three surveillance sites and twenty-six outpatient facilities linked with two National Reference Laboratories (NRL) (46).

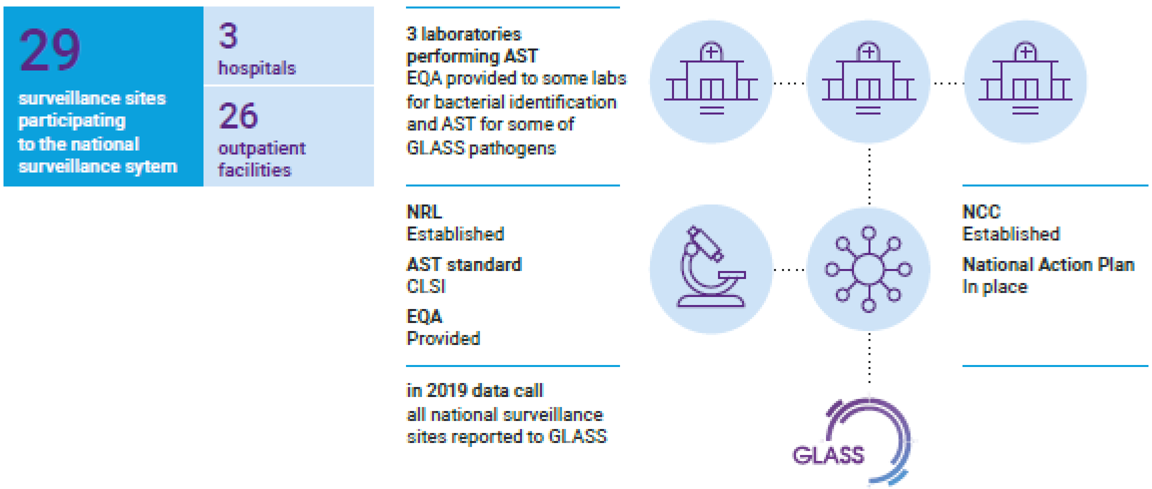

Figure 3: Nigeria National AMR surveillance systems key indicators (46)

1.5 Antibiotic use in Nigeria

Antibiotic use in Nigeria can be categorized into two: prescription and non-prescription usage. Interestingly, evidence shows that usage is highly prevalent in the two categories. A survey on rational drug use conducted in 12 LMICs revealed that Nigeria's overall prescription rate is 3.8 prescriptions/encounter and antibiotic prescription rate is 48%, making the country rank highest in the number of prescribed drugs and third highest prescriber of antibiotics (47). A study reported over 85% antibiotics prescription rate for children with watery diarrhea (48) and another recent multi-center hospital point-prevalence survey in the country reported 80.1% prescription rate with broad spectrum antibiotics in one of every three prescription and protracted use of surgical prophylaxis and needless antibiotic combinations (49).

Similarly, several studies revealed high rates of non-prescription antibiotics rate among Nigerians. A study reported that 31.7% of university students use antibiotics without prescription and only 42% of the those that used antibiotics following a doctor's prescription did not complete the recommended dosage (50). More than 15% of mothers of under five children were reported to initiate antibiotic use for watery diarrhea without a doctor's prescription in a study (48) and another 24.4% use antibiotics for their children without a clinician's prescription (51).

A comparable high rate of antibiotic use in the Agricultural sector is recorded among farmers in the country. Ojo et al (52) reported widespread non-prescription use of fluoroquinolones among livestock farmers in a multi-state study. Other prohibited antibiotics such as furazolidones and chloramphenicol were being freely used by these farmers. Another similar study documented about 58.3% self-prescription of antibiotics used on animals by pastoralists and these drugs are used for prevention, treatment and growth promoting in animals (53).

1.6 Country Profile

1.6.1 Demographic and geographic context

Nigeria is a country in the West Africa located between 3^o and 14^o East Longitude and 4^o and 14^o North Latitude. It is bounded in the west by the republics of Benin and Niger, Niger in the north, Lake Chad in the northeast, Cameroon in the east and the Atlantic Ocean in the south. The country has an area of 923,769 $SqKm^2$ (made up of 909,890 $SqKm^2$ of land area and 13,879 $SqKm^2$ of water area) and an estimated population of 195,874,740, the largest population in Africa (54).The country operates a federal system of government and is divided into 6 geopolitical zones namely North-central, Northeast, Northwest, Southeast South-south and Southwest. These are further divided into 36 states and the Federal Capital Territory, Abuja (which is usually categorized with the North Central zone). The 36 states are subdivided into 774 Local Government Areas (LGAs). About 49.3% of the population is women and the country has a young population with the national median age of 17.9 years (54). The official language adopted in the country is English but there are more than 250 ethnic groups in the country with Hausa, Yoruba and Igbo as the major ones (55).

1.6.2 Health System

The Nigerian healthcare system is pluralistic in nature consisting of public, private sectors, modern and traditional providers. It is structured into three levels: primary, secondary and tertiary with about 34,176 health facilities in the country. Primary health facilities make up 88%, secondary 11.7% and tertiary 0.25%. The public tertiary health facilities are managed by the Federal government while secondary facilities by the State government and the primary healthcare facilities by the Local government. There is considerably financial and health service autonomy at each level of the healthcare system with guidance from the Federal Ministry of Health (FMoH). There is at least a public tertiary health facility in every state of the country and the a spread of public primary health facilities across the country (56). The primary healthcare facilities including health posts, dispensaries and health centres which are closest to the population, serve as entry point into the health system and provides an estimated at 61% of the health services in the country. Health workers in Nigeria range from the less skilled Community Health Workers (CHWs) who provide mostly preventive and referral services at the lower level of the health system to the specialists at the tertiary level (56). The private sector plays significant roles in healthcare delivery with about 11,323 facilities and numerous unregistered patent medicine stores, contributing actively to antibiotics distributions and use in the country (56)(57).

Indicators	
Population	195,874,740
Gross Domestic Product (US$)	397.27
Life expectancy at birth (years)	54.3
Domestic Health Expenditure (DOM) as % of Current Health Expenditure (CHE)	92
Domestic General Government Health Expenditure (GGHE-D) as % Current Health Expenditure (CHE)	14
GNI per capita (US$)	1,960
Gross Domestic Product (GDP) per Capita in PPP Int$	5,887
Current Health Expenditure (CHE) per Capita in PPP	221
Current Health Expenditure (CHE) as % GDP	4
Poverty rate (%)	40.1
Unemployment rate (%)	23

Table 1: Nigeria Profile (54)

CHAPTER 2: PROBLEM STATEMENT, JUSTIFICATION, OBJECTIVES AND METHODOLOGY

2.1 Problem statement

Globally, there are increasing reports of incidence of human and animal infections resistant to available antimicrobials (58)(59) and presence of resistant pathogens in sewage water (60). The rising trend is alarming especially because of significant role played by the misuse of antibiotics and other factors as drivers of this phenomenon (61). Of these resisting pathogens, CR pathogens are one of the top priorities for global health in recent times. The WHO classified CR pathogens as ‘critical’ pathogens, in its recently published list of priority pathogens with the aim to attract global attention and actions on life-threatening pathogens (20).

With over 77% of the current health expenditure in Nigeria coming from out-of-pocket spending (62) and 40.1% of the population below the poverty line (63), prolonged hospital stay to due AMR and particularly CR is a potential trigger for catastrophic spending and poverty cycle within the population thus undermining other efforts geared towards attaining universal health coverage (UHC) (64). In addition, AMR could have an overwhelming effect on the human resource for health as well as the motivation of the health workers; increasing the stress level with the number of in-patients unlikely to reduce with AMR, creating stress condition for the health system (14). The high incidence of infectious diseases in Nigeria makes carbapenems, the last line antibiotic drugs, a reliable therapy however, resistance to this set of antibiotics translates to increased mortality due to exhaustion of antimicrobial therapy.

Reports showed high level of irrational antibiotics prescription and use among the health workers and the general population. Despite increasing awareness, misuse/overuse is still prevalence. This is as a result of interacting factors driving the phenomenon. However, these factors and their interlinkages are poorly understood thus undermining the antimicrobial stewardship efforts in the country.

Unlike in Europe where the use of antimicrobials is well regulated and there is a good coordination of CR surveillance (65), many low and middle income countries including Nigeria are yet to set up a surveillance system for CR and therefore unable to monitor the phenomenon and its trend. Similarly, risk factors contributing to AMR from humans, animals and environment are not well understood and poorly reported, limiting evidence-informed interventions which can effectively control AMR in Nigeria.

2.2 Justification

Addressing the epidemic of AMR including CR in Nigeria is only possible in the presence of an efficiently coordinated surveillance system. The WHO stressed the need for a one health approach in surveillance to bridge the gaps across the relevant sectors. The situation analysis of AMR conducted by the NCDC was focused primarily on clinical samples (30) and the study by Oloso et al (32) complemented this with a review of AMR in food and animals in Nigeria. Similarly, other studies described the geographical distribution and the trend of AMR in Nigeria using a systematic review (33)(34). However, CR prevalence was out of the scope of these studies thus creating a gap in knowledge on the prevalence and distribution of CR in Nigeria. This gap is detrimental to efforts geared toward addressing the growing rates of CR in the country.

Convincing evidence showed that AMR is highly associated with the level of inappropriate (misuse/overuse) antibiotics consumption in the human and non-human settings. Therefore, understanding the factors contributing to antibiotics misuse/overuse is key to antimicrobial stewardship in Nigeria and hence the focus of this study. The 2017 situation analysis by the NCDC on these factors was focused on humans leaving out the drivers in the non-human settings.

Therefore, this study aims to fill these gaps, using the one health approach in describing the prevalence and distribution of CR in Nigeria and factors contributing to antibiotic misuse/overuse in all the sectors including the agricultural and environmental domains. The results from this study will provide systematic information on the burden of CR, contributing to how to incorporate carbapenem surveillance in the existing plans for AMR surveillance of Nigeria. It will also provide evidence on indirect fueling factors from a one health approach which are vital to effective policy formulation and program design for antimicrobial stewardship.

2.3 Objectives

2.3.1 Broad objective: To describe the prevalence of carbapenem-resistance in Nigeria and to conduct a situation analysis of factors influencing antibiotics misuse/overuse in order to make recommendations on strategies for effective carbapenem-resistance surveillance and antimicrobial resistance stewardship in Nigeria.

2.3.2 Specific objectives

1. To describe the prevalence of CR in humans, livestock and environment in Nigeria.
2. To describe the mechanisms for CR in humans, livestock and environment in Nigeria
3. To describe the geographical distribution of CR in humans, livestock and environment in Nigeria.
4. To analyze factors influencing misuse/overuse of antibiotics in Nigeria.
5. To give recommendations on strategies for effective carbapenem-resistance surveillance and AMR stewardship in Nigeria.

2.4 Methodology

2.4.1 Study design

This study is a scoping review on the prevalence of CR and factors contributing to the misuse and overuse of antibiotics in Nigeria using One Health approach. Although a scooping review share similar processes with systematic review, it however aims to rapidly map out existing literature on a broad subject with a range of methodologies without critically evaluating each study quality nor combining their results (66). This selection of articles for this study was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (67). This study was focused on CR because of the current gap in knowledge in Nigeria. Nevertheless, contributory factors to inappropriate use of antibiotics were extended to all AMR pathogens as these apply to CR pathogens as well.

2.4.2 Search strategy

An electronic literature search was conducted using Google Scholar search engine and through MEDLINE and AJOL databases. Two broad searches were conducted with identified keywords using Boolean operators 'OR' and 'AND' to separate the keywords: the first for the first three objectives and the second search for the fourth objective. Keywords used in the first literature search are "carbapenem*", "meropenem", "imipenem", "ertapenem", "doripenem", "panipemen", "carbapenem-resist*", "enterobacteriaceae antibiotics susceptibility", "enterobacteriaceae multidrug resist*", "carbapenem multidrug resist*", "enterobacterales resist*", "humans", "patients", "hospital-acquired", "community-acquired", "animal", "livestock", "cattle", "cow", "horse", "pig", "poultry", "chicken", "birds", "broiler", "dairy", "farm", "seafood", "fish", "aquatic", "Nigeria". The second literature search was conducted using the following keywords: "factors", "risks!, "determinants", "drivers", "reasons", "motiv*", "antimicrobial use", "antibiotics use", "self-medicat*", self-treat*", "patient use", "antimicrobial use" "non-prescription", "over-the-counter", "irrational use" "overuse" "non-prudent" "drug misuse", "medicine misuse", "community pharmacy", "patent medicine vendor", "drug seller", "animal treatment", "farm use", "poultry use", "aquatic farming", "livestock use", "veterinary use". The combination of the keywords in the search process is shown in tables 4 and 5 (Appendix)

The population, intervention, comparison and outcome (PICO) framework considered in selecting the articles for the first and second literature searches are presented in the table below.

Criteria	**Determinants**	
	Search 1	**Search 2**
Population	*Patients/Farmers*	*Humans, animals, environment*
Intervention	*Antimicrobial/antibiotics use*	*Carbapenem resistance*
Comparison	*Not applicable*	*Not applicable*
Outcome	*Factors/Determinants/Drivers*	*Prevalence, geographical distribution, mechanism of resistance*
Settings	*Nigeria*	*Nigeria*

Table 2: PICO framework for eligibility of articles to include in the study

2.4.3 Inclusion criteria

Literature search was limited to publications in English language from January 1, 2000 to June 30, 2020 and only peer-reviewed articles from original studies conducted in Nigeria were selected for review. For the first three objectives, studies using any type of sample from humans, animals and environment, and reporting phenotypic or genotypic antibiogram with at least one carbapenem antibiotic were included. Only studies that included numerator and denominator were included to be able to report prevalence. Studies with antimicrobial susceptibility data from all methods and guidelines including use of VITEK machine were included in the review. All types of study designs were also included in the search and selection. Additionally, for the fourth objective, articles with all study designs documenting association or outlining contributing factors to antibiotics misuse/overuse by all categories of people were selected.

2.4.4 Exclusion criteria

Studies reporting other antibiotic resistance without any carbapenem antibiotics or studies done outside Nigeria and before January 1, 2000 were excluded. Similarly, case reports and multi-country studies aggregating prevalence of CR with other countries were also excluded. Conference abstracts or studies without access to full the paper, meta-analysis, reviews editorials, letters to the editor on AMR and grey literature were excluded from this review. However, references of these materials were checked using snowballing technique for additional articles not part of the search. In the same vein, articles reporting the drivers or factors contributing to the use of other drugs such as antimalarial, antiretroviral were excluded. Literature reporting only the pattern of antibiotics misuse/overuse without the factors or reasons were also excluded.

2.4.5 Data extraction/variables of interest

Data extraction was carried out from all the selected studies after thoroughly reading through them to ensure inclusion of relevant articles. Relevant information linked to the study objectives were extracted and analysed using an Excel spreadsheet. The following variables were extracted from reviewed studies in the first search; title, author, year of publication, subject, study setting, study design, sample size, specimen/sample used, pathogens recovered, carbapenem antibiotics tested, location and geopolitical zone of study, hospital type, level of care of hospital, diagnostic methods used, prevalence of CR, mechanism of CR and resistant genes reported. In the same vein, article title, author, year of publication, sample size, category of respondents, study design, group of respondents, location, geopolitical zone, source of antibiotics, factors influencing antibiotic misuse/overuse were extracted from the selected articles in the second search.

2.4.6 Ethical Consideration

This was not applicable to this study.

2.4.7 Conceptual framework

The conceptual frameworks by Harbarth et al (68) and Lhermie et al (18) were utilized in this study to describe the identified factors of misuse/overuse of antibiotics, their interactions and contributing factors for which there is no evidence available in the humans and non-humans, respectively. These frameworks were selected because they provide comprehensive structures beyond the clinical/microbiological and farm settings to analyze antibiotics use contributory factors. They considered individual and macro-level factors influencing antibiotic use and hence provide different points for possible interventions. The lack of a One Health framework describing the drivers of antibiotic misuse/overuse in human and non-human necessitated the use of two different frameworks. Most One Health frameworks analyzed AMR from the perspectives of research and surveillance (69)(21), stakeholders and interactions (70) among the three domains of AMR. In the same vein, other frameworks describing factors influencing drivers of antibiotic use were limited to prescriber factors (71), AMR interventions (72)(73), while frameworks focusing on the patients/farmers considered only the individual and interpersonal determinants of antibiotic use (74).

Although the framework by Harbarth et al (68) used in this study was limited to outpatients in Europe, evidence suggests that majority of antibiotics use in humans is used in the outpatient setting (75) and this is related to the prescribers' influence described by Harbarth et al and the framework was adapted to Nigeria for lack of more context-specific framework. It is noteworthy that there are few similarities among all frameworks reviewed for use in this study, Harbarth et al and Lhermie et al frameworks were selected because of their strengths in analysis of factors across the socio-ecological levels and results in this study were classified and presented under appropriate sections of the framework and linkages were also reported where relevant.

The framework by Harbarth et al (68) considered the non-microbiological factors which influence the use of antibiotics. It describes the five categories of influencing factors namely prescribers, patient, cultural influences, social determinants and regulatory. This framework proposed that clinician's or prescribers' choice of antibiotic agents, dosing and instructions affect the use antibiotics by the patients. The prescription behaviour of the clinician influenced by intrinsic or extrinsic factors influence how and what antibiotics are used by the patients. Similarly, the health beliefs of the patients influence the use of antibiotics. Health perceptions and beliefs such as delayed health-seeking behaviour or adopting a less aggressive approach in a non-life-threatening infection could influence the use of antibiotics. This also contributes to the demand of antibiotics by the patients from the clinicians. The cultural factors such as acceptance of traditional or alternative medicine, cultural perception of signs and symptoms of infections that determine antibiotics influence the use of antibiotics. In addition, other social determinants such as child-care, workplace and other systems contribute to acquisition of infections and subsequently antibiotics use. Furthermore, policies and regulations such as control of availability of pharmaceutical products, pricing, advertisement and other commercial activities of pharmaceutical companies are examples of macro-level factors influencing the use of antibiotics by the patients.

The framework by Lhermie et al (18) considered the factors influencing antimicrobial use in food-animal production. The framework highlighted the influence of several broad factors on farmers' decision to use antibiotics. These include research, voluntary approaches, institutional influences, regulations, possibilities of substitution and disease occurrence or pathogen expression. Others are surveillance, exogenous factors and endogenous factors such as disease appraisal, cost-benefit evaluation of treatment, farmers' attitude and behavior, farmers' expertise, risk aversion and diagnostic test. According to Lhermie et al, exogenous factors refers to factors imposed on the farmers such as the climate, regional pathogen prevalence or general factors such as changes in markets. These factors directly contribute to the minimal level of infectious disease and antibiotics use in a given production system. They concluded that farmer's decision to use antibiotics is primarily influenced by: (a) the cost-benefit analysis of antibiotic use; (b) the farmer's expertise, attitude towards risk and behaviour, and; (c) ability to detect the disease. This study will therefore focus on these primary factors because they largely represent the production factors that lie within the control of the farmers, and they are responses to the exogenous factors which cannot be controlled by the farmers. (18).

2.4.8 Limitation of the study

The quality of articles reviewed in this study was not assessed. Most of the studies reported CR pooled prevalence for multiple specimens used and for pathogens recovered making it difficult to describe CR for specific organisms and samples. In addition, the sample size varies widely for all the study.

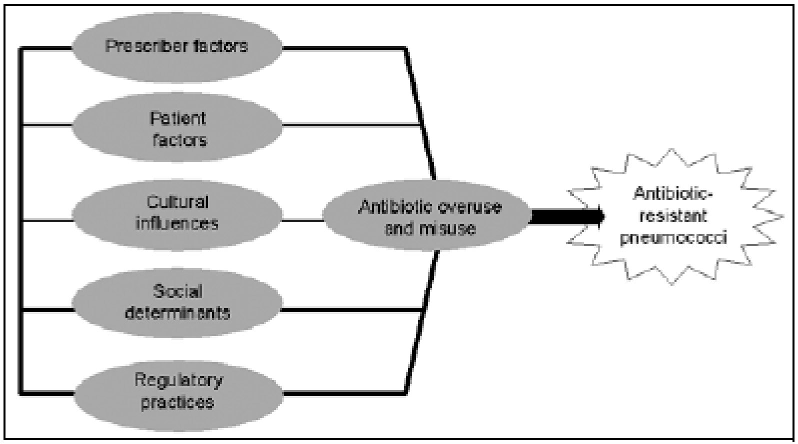

Figure 4: Framework for factors influencing antibiotic use among humans (68)

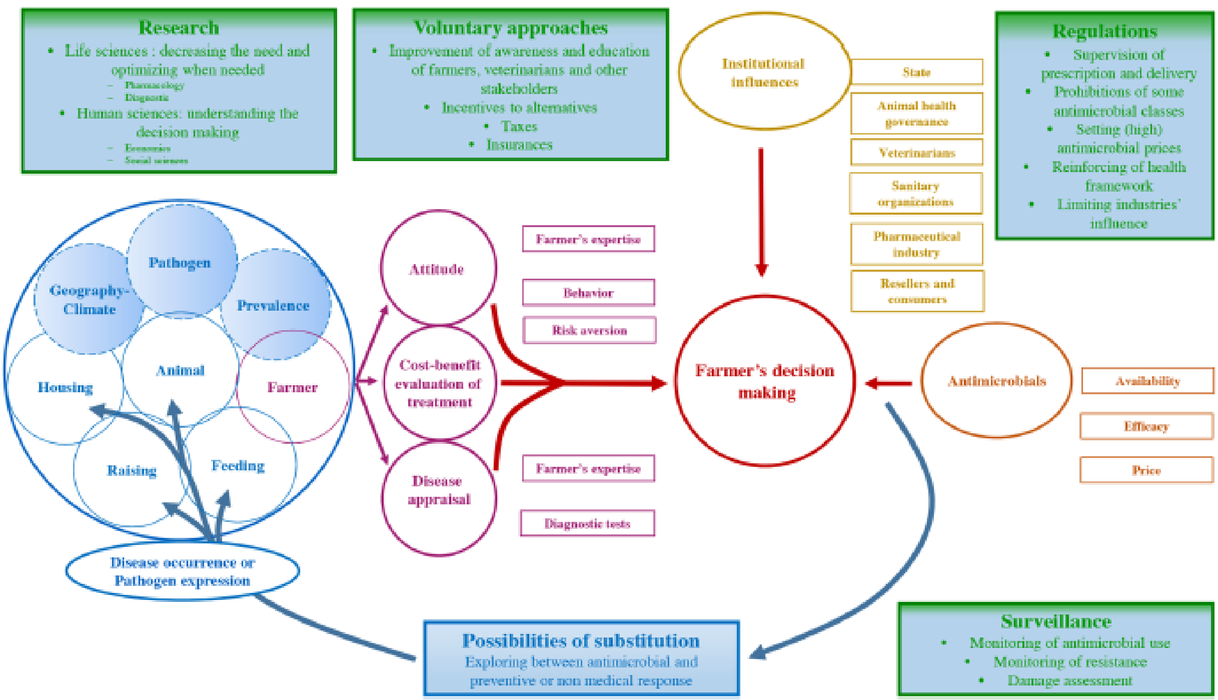

Figure 5: Framework for factors influencing antimicrobial use in food-animal production (18)

3.0 RESULTS

3.1 Literature search results for prevalence of CR

The first broad literature search across the two databases yielded 1,361 articles. Only 94 of these articles were included in the review after screening using the inclusion and exclusion criteria (Figure 6). While this study reviewed articles published between 2000 and 2020, 57(60.6%) of these articles were published between 2015-2020. As shown in figure 7, the majority of the articles reviewed were from southwest Nigeria 38(40.4%), South-south 15(16.0%), Southeast 14(14.9%), Northwest 10(10.6%), Northcentral 8(8.5%), Northeast 6(6.4%) and 3(3.2%) multi-zonal studies. Of the 94 reviewed articles, 90(95.8) employed a cross-sectional study design (80(88.9%) used active sampling for study purpose and 10(11.1%) were observational studies using routinely collected samples), and 4(4.3%) adopted a prospective cohort research design.

As shown in figure 6, 75(79.8%) were carried out in the human sector, animal sector 10(10.6%), environment sector 7(7.5%) and 3(3.2%) from combination of the sectors. Imipenem and meropenem antibiotics were mostly used for susceptibility testing to identify carbapenem resistance across all the sectors. The disc diffusion susceptibility testing method using the CLSI guideline was employed in 60(80.0%), 8(80.0%) and 5(71.4%) of the human, animal and environmental studies respectively. Of the 25 studies reporting mechanism of carbapenem resistance across the sectors, 10(26.6%) utilized the Modified Hodge Test method (MHT). Other susceptibility testing methods and guidelines, and carbapenemase detection techniques are summarized in table 3 below.

The human studies were conducted in hospital 72(96.0%) and community 3(4.0%) settings. The hospital-based studies employed patients from public hospitals in 53 studies (73.6%) and private hospitals in 2 studies (2.8%) while the rest were unspecified. Fifty-nine (81.9%) and 5(6.9%) of these hospitals were tertiary and secondary healthcare facilities, respectively. The community-based studies were conducted among asymptomatic university students, farm and abattoir workers. The type of samples utilized in the studies are presented in table 3. Six (60.0%) of the animal susceptibility data were recovered from poultry samples and a study (11.1%) utilized rectal swab from horses. The environmental samples utilized by the studies were pond water, wetland water, wastewater, sewage, soil and vegetables.

As presented in table 3, *Escherichia coli* 54(72.0%), *Klebsiella spp* 48(64.0%), *Pseudomonas spp* 32(42.6%) and *Proteus spp* 24(32.0%) were the commonly reported bacteria from the human studies while *Escherichia coli* 5(50.0%), *Klebsiella spp* 2(20.0%) and *Salmonella spp* 2(20.0%) were commonly reported in the animal studies and *Pseudomonas spp* 2(28.6%), *Enterococcus spp* 2(28.6%), *Citrobacter spp* 2(28.6%), *Escherichia coli* 2(28.6%) and *Salmonella spp* 2(28.6%) were reported in the environmental studies.

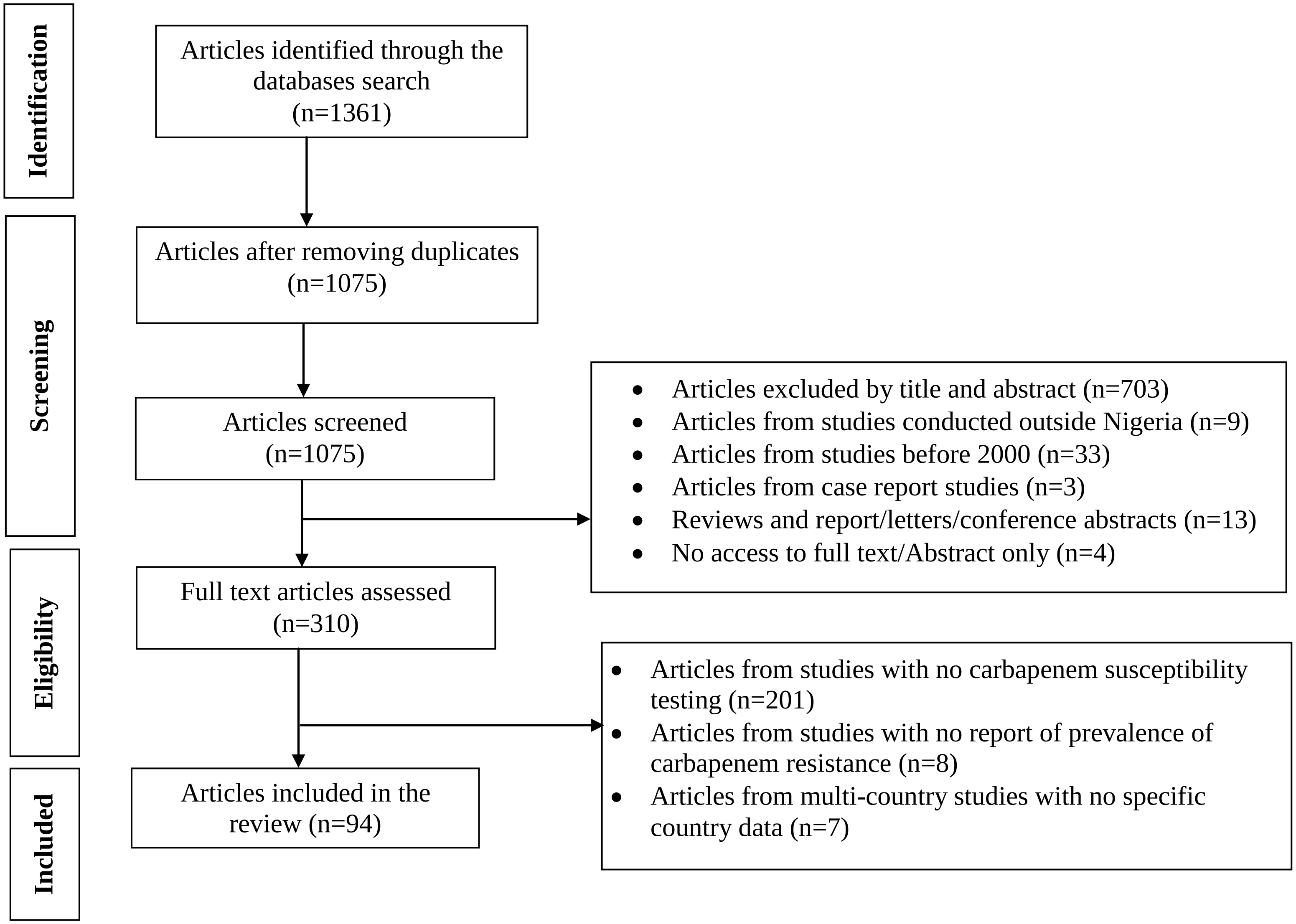

Figure 6**:** PRISMA diagram of the article selection procedure in the first literature search

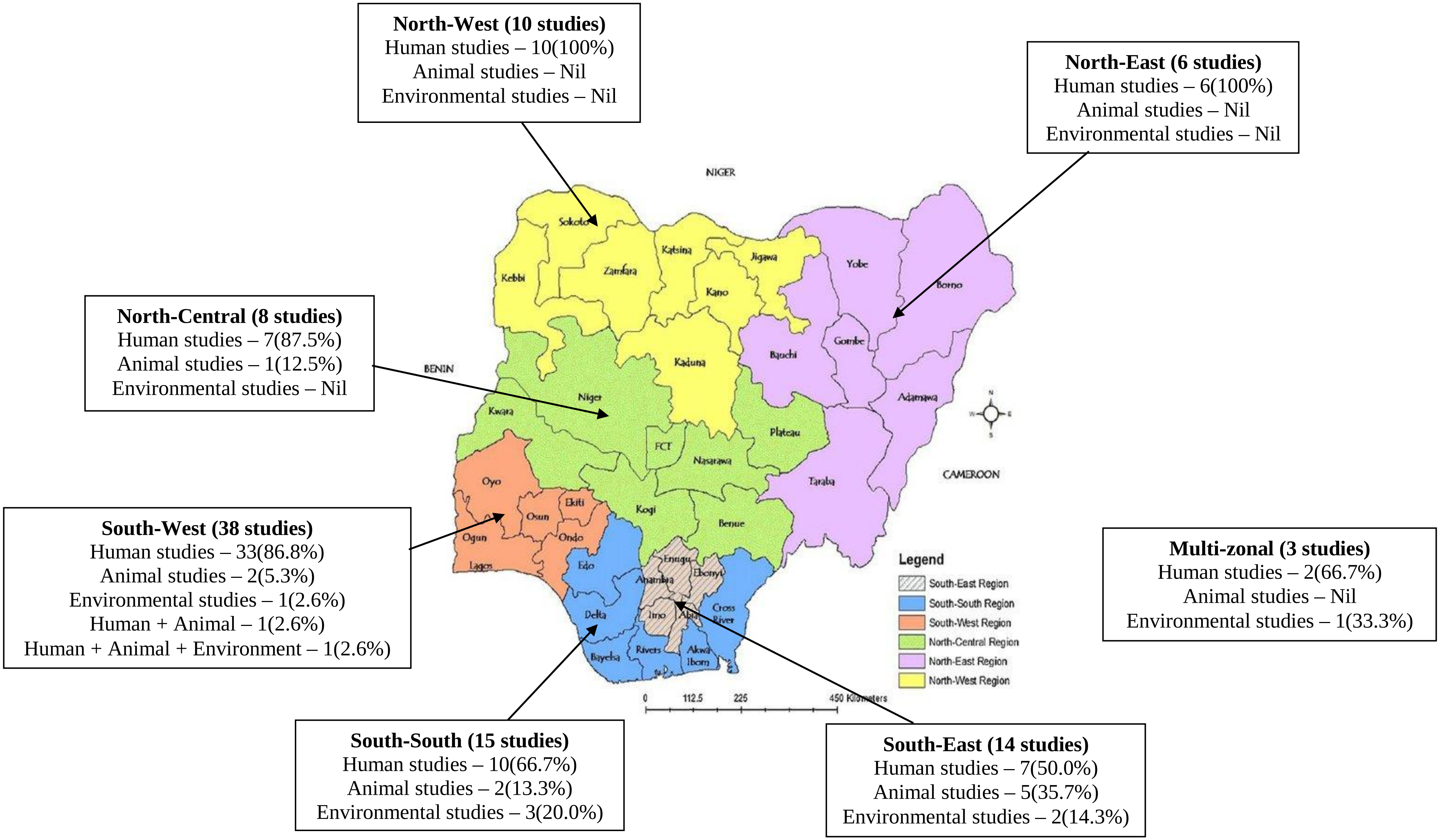

Figure 7: Geo-political distribution and domain of studies included in the review

3.2 Literature search results for factors influencing misuse/overuse of antibiotics

As shown in figure 7, 1,617 papers were identified in the second broad search. A total of 33 articles were selected for review after screening using the inclusion and exclusion criteria. All the articles employed a cross-sectional study design with the exception of two studies which employed a mixed method approach. Of the 33 studies considered for review, 23(69.7%) focused on determinants for patients antibiotic misuse/overuse, 2(6.1%) described factors influencing clinical prescribers and 3(9.1%) described factors influencing patent proprietary medicine vendors (PPMVs) who dispense for human and animal use. Similar to the first literature search, studies were from all the geo-political regions in Nigeria with the majority of studies conducted in the Southwestern Nigeria 12(36.4%) and the least number of studies conducted in the North-eastern region of the country 1(3.0%). Non-prescribed antibiotics were reportedly sourced from the PPMVs or local drug shops, community pharmacy stores, hawkers, or left-over drugs.

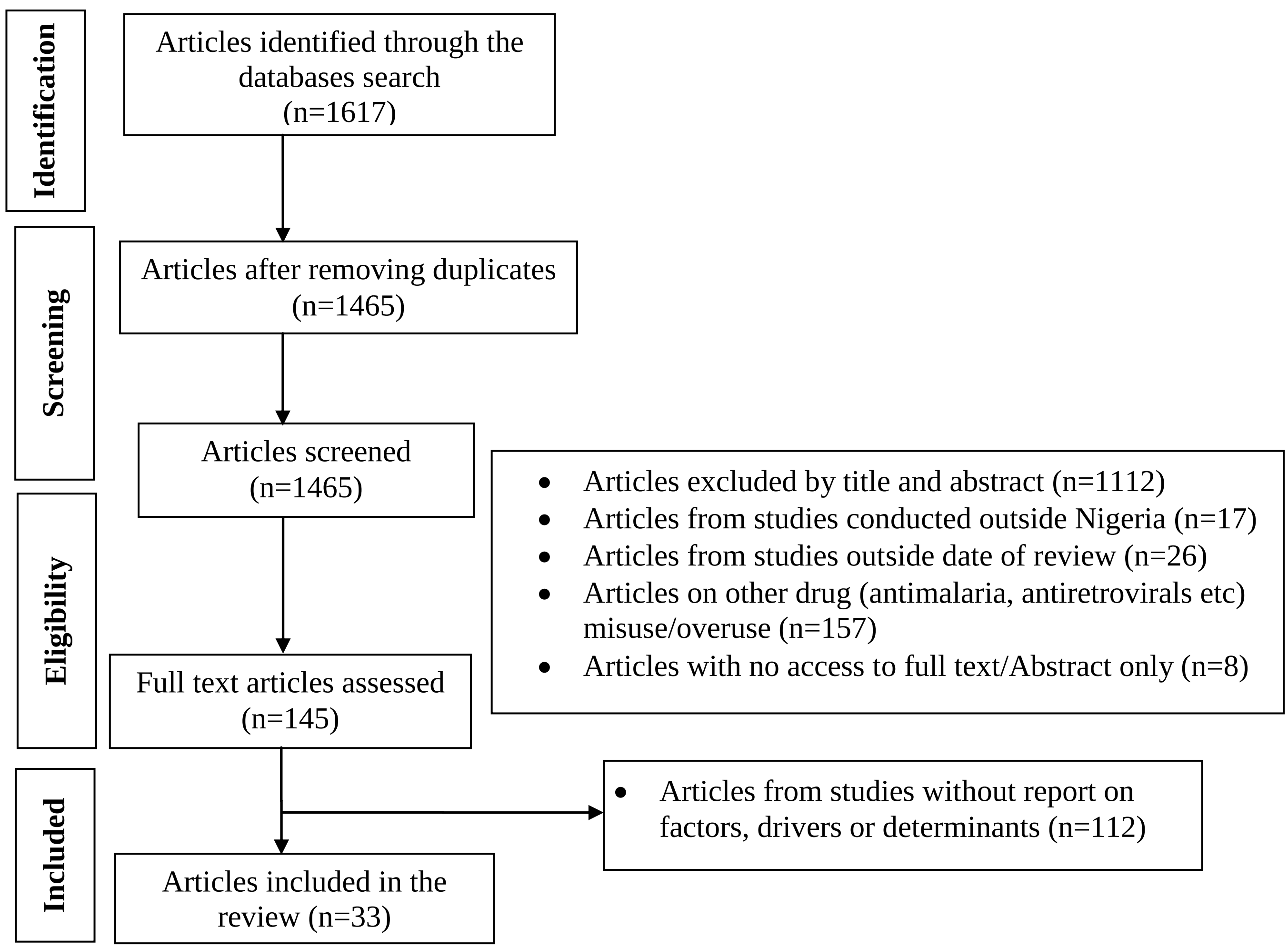

Figure 8: PRISMA diagram of the article selection procedure in the second literature search

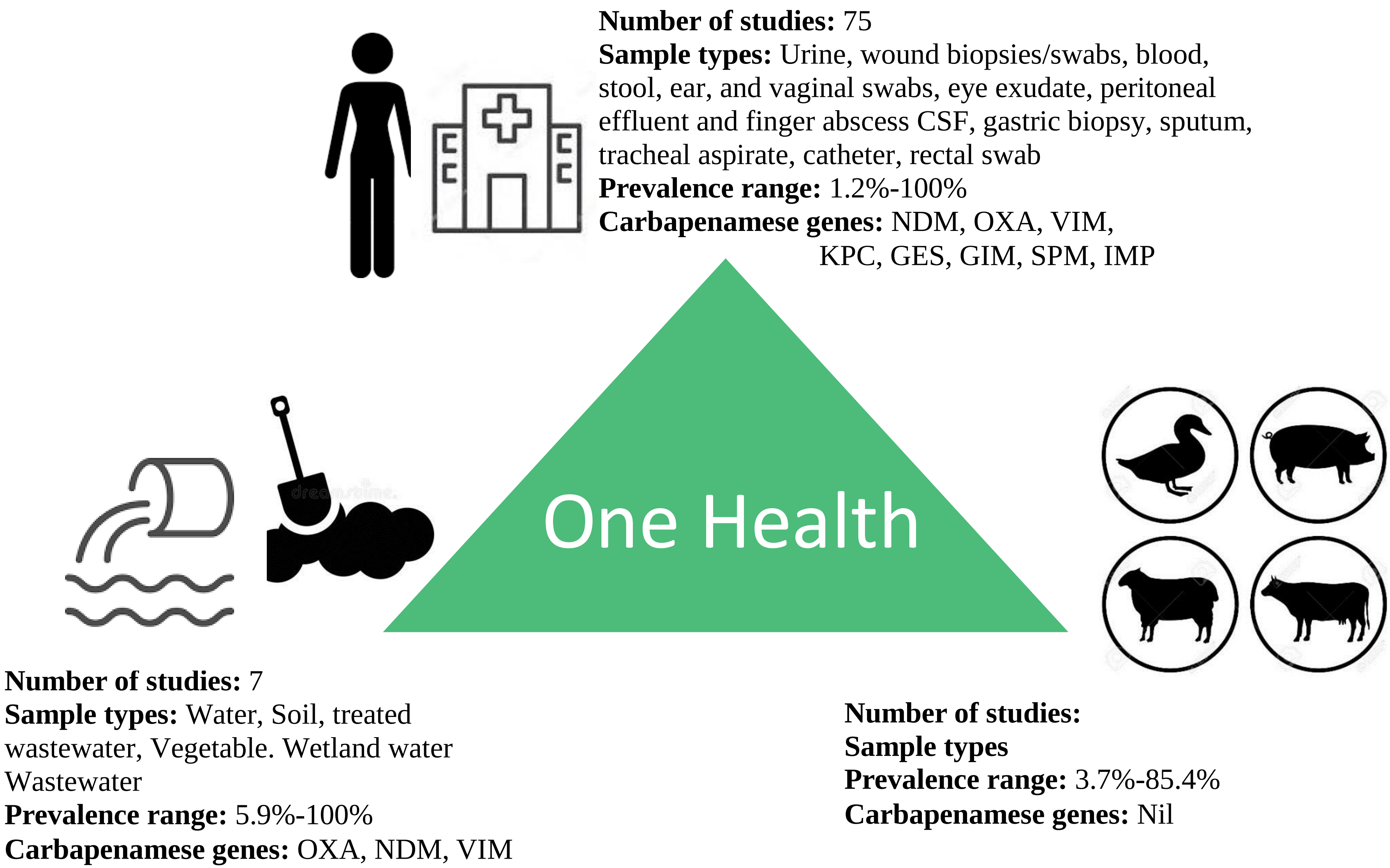

Figure 9: Pictorial representation of characteristics and summary findings of studies identified from the three One Health domains

3.3 Prevalence of carbapenem-resistance in Nigeria

The result from studies conducted in Nigeria showed varying but high prevalence of CR to pathogens causing common infections in humans, animals and the environment.

3.3.1 Prevalence of carbapenem-resistance in humans

A total of 22(29.3%) of the human studies (21 hospital-based and 1 community-based) reported complete susceptibility to carbapenem antibiotics tested (76)(77)(78)(79)(80)(81)(82)(83)(84)(85)(86)(87)(88)(89)(90)(91)(92)(93)(94)(95)(96)(97). Eleven of these studies (50.0%) tested carbapenems on *E. Coli*, *Klebsiella spp* 9(40.9%), *Salmonella* enterica serovars, *Enterobacter spp*, *Proteus mirabilis, P. aeruginosa* 3(13.6%) each. Others were *Acinetobacter baumanni* 2(9.1%), *Stenotrophomonas maltophilia* 1(4.6%) and *Staphylococcus aureus* 1(4.6%). Forty-eight studies (64.0%) reported varying CR prevalence between 1.2% to 80% (98)(99)(100)(101)(102)(103)(104)(105)(106)(107)(108)(109)(110)(111)(112)(113)(114)(115)(116)(117)(118)(119)(120)(121)(122)(123)(124)(125)(126)(127)(128)(129)(130)(131)(132)(133)(134)(135)(136)(137)(138)(139)(140)(141)(142)(143)(144)(145) and 5(6.7%) studies reported complete *Escherichia fergusonii, Acinetobacter spp, S. aureus. E. coli, Klebsiella spp.* and *Salmonella spp* (146)(147)(148)(149)(150)

3.3.2 Prevalence of carbapenem resistance in the animals

Findings from this study showed CR prevalence among the animals ranged between 3.7%-85.4%. From the six poultry studies, 4(66.7%) reported complete susceptibility of different pathogens (*K. pneumonia, Morganella morganii, Leclercia adecarboxylata, C. freundii and Ocnrobactrum spp*) to carbepenems (151)(152)(153)(154) while the other two reported *E. coli* and *Klebsiella spp* resistance rates of 12.0% (37) and 62.5% (155) respectively. One of the two pig studies reported *E. faecalis and E. faecium* resistance rates of 5.1% and 3.7% respectively (156) while the other reported 80% resistance of *S.* Enteritidis resistance to imipenem and 9.1% resistance of *S.* Typhimurium to meropenem (157). *E. coli*, *Salmonella spp* and *Proteus spp* recovered from rectal swabs in horses were completely susceptible to meropenem (158) but E. coli isolated from cattle in Abattoir were 85.4% resistant to imipenem and meropenem (159).

3.3.3 Prevalence of carbapenem resistance in environment

This review showed that most of the studies conducted on environmental samples such as wastewater, soil and sewage documented high prevalence of CR. A study conducted in Lagos using wetland water documented complete susceptibility to imipenem antibiotics (160). However, Igbinosan (161) reported that *Vibrio spp* isolated from pond water showed 5.9% resistance to imipenem while an aggregated resistance prevalence of 47.9% was reported for *A. baumannii, Aeromonas caviae, Enterobacer, cloacae, Pseudomonas putida, K. pneumoniae, Citrobacter freundii* isolated from soil and water (162). Similarly, *E. coli* recovered from the soil reportedly showed 76% resistance to imipenem while *E. coli* isolated from treated wastewater and vegetable in the same study were completely susceptibility to imipenem (163). In two different studies conducted in Benin city in 2017 and 2019 using wastewater from abattoirs, *Salmonella* enterica serovars showed 8% resistance to imipenem while *Enterococcus spp* showed 84.4% and 100% resistance to meropenem and ertapenem respectively (164)(165).

The study by Onuha (166) reported 50% imipenem-resistance rate from *K. pneumoniae* and *Pseudomonas spp* recovered from water while *E. coli, P. aeruginosa, S. aureus, Shigella, Salmonella*, *Enterococcus spp*, *Streptococcus spp* were completely susceptible to the carbapenem agent.

Adefioye et al (167) reported an aggregated *E. coli*-meropenem resistance prevalence of 40% from human and animal samples while Odumosu et al (168) reported that *P. aeruginosa* isolated from vegetables and poultry samples showed complete susceptibility to imipenem but the same pathogen recovered from clinical samples showed 1% resistance to imipenem.

Region	One Health Domain (number of studies)	Study design	Specimen/Sample	Pathogens	Antibiotic tested	Susceptibility Method	CR Prevalence	CR Mechanism (number of studies)	Mechanism method	Carbapenemase genes (number of studies)	References
South-west	Humans (n=33)	CS 30/33(90.9%), PC 3/33(9.1%)	Urine 14/33(42.4%), Blood 15/33(45.5%), Stool 5/33(15.2%), Gastric biopsy 1/33(%), Wound 14/33(42.4%), Sputum 6/33(18.2%), Peritoneal effluent 1/33(3.0%), Finger abscess 1/33(3.0%),Tracheal aspirate 3/33(9.1%), Vaginal swab 3/33(9.1%), Catheter 2/33(6.1%),Ear swab 5/33 (15.2%), CSF 2/33(6.1%), Rectal swab 1/33(3.0%),	Klebsiella spp 23/33(69.7%), E. Coli 20/33(60.6%), Proteus spp 9/33(27.3%), Pseudomonas spp 13/33(39.4%), Salmonella spp 3/33(9.1%), Acinetobacter spp 6/33(18.2%), Staphylococcus aureus 5/33(15.2%), Enterobacter spp 4/33(12.1%), Enterococcus spp 3/33(9.1%),H. pylori 1/33(3.0%), Hafnia alvei 1/33(3.0%), Shigella spp 1/33(3.0%), S. mercesens 1/33(3.0%), Stenotrophomonas maltophilia 1/33(3.0%), C. freundii 1/33(3.0%), Serratia rubidaea 1/33(3.0%)	IMI 24/33(72.7%), MEM 16/33(48.5%), ERT 4/33(12.1%)	Disk diffusion (CLSI guidelines) 24/33(72.7%), VITEK 3/33(9.1%), Disk diffusion (EUCAST guidelines) 3/33(9.1%), Modified Stokes method 1/33(3.0%), National Committee for Clinical and Laboratory Standards Method 1/33(3.0%)	1.2%-100%	Carbapenemase 10(30.3%	Hodge Test (MHT) method 3/33(9.1%), PCR 3/33(9.1%), DDST and a combined disk test MBL detection methods 1/33(3.0%),Carba NP test version I 1/33(3.0%), Inhibitor combination disc test called the KPC, MBL and OXA-48 detection discs for Enterobacteriaceae 1/33(3.0%),Isothermal amplification (eazyplex SuperBug CRE Kit; AmplexDiagnostics GmbH, Gars Bahnhof, Germany) 1/33(3.0%)	NDM 3/33 (9.1%), VIM 2/33(6.1%), GES 2/33(6.1%), OXA 2/33(6.1%)	(96)(141)(131)(145)(143)(132)(97)(133)(78)(121)(101)(134)(135)(104)(149)(106)(82)(136)(137)(84)(108)(109)(110)(88)(89)(146)(126)(113)(115)(116)(117)(128)(94)
	Animals (n=2)	CS	Different samples, Stool	E. coli 1/2(50%), K. pneumonia 1/2(50%), Morganella morganii 1/2(50%), Leclercia adecarboxylata 1/2(50%), C. freundii 1/2(50%)	IMI 2/2(100%), MEM 2/2(100%), ERT 1/2(50%)	VITEK					(154), (152)
	Environment (n=1)	CS	Wetland water	Escherichia spp, Enterobacter spp, Citrobacter spp, P. monteilii, P. taiwanensis, P. plecoglossicida, C. segnis, Achromobacter insuavis, Achromobacter spanius, Stenotrophomonas spp	IMI		0%				(160)
	Humans (n=2) 2/2(100%), Animals 2/2(100%), Plants 1/2(50%)	CS	Vegetable, animal stool, human isolates, Stool, beef	E. coli 1/2(50%), P. aeruginosa 1/2(50%)	IMI 2/2 (100%), MEM 1/2(50%)	Disk diffusion (CLSI guidelines)	1%-40%				(167)(168)
	Humans (n=7)	CS	Blood 4/7(57.1%), Stool 2/7(28.6%), Urine 3/7(42.9%), Wound	E. coli 3/7(42.9%), Klebsiella spp 3/7(42.9%), P. Aeruginosa 2/7(28.6%), Proteus spp	IMI 6/7(85.7%), MEM	Disk diffusion (CLSI guidelines) 6/7(85.7%), Disk	3%-100%	Carbapenemase 1/7(14.3%)	Total MBL Confirm Kit from ROSCO Diagnostica (ROSCO Diagnostica A/S,	VIM 1/7(14.3%)	(150)(102)(81)(111) (114) (93)

North-central			2/7(28.6%), Sputum 2/7(28.6%), Ears swab 2/7(28.6%),, Eye swab 2/7(28.6%),, Nasal swab 2/7(28.6%), , Bone Tissue 1/7(14.3%)	1/7(14.3%), S. aureus 1/7(14.3%), Salmonella spp 1/7(14.3%)	2/7(28.6%), DRP 1/7(14.3%)	diffusion (NCCLS guidelines) 1/7(14.3%)			Taastrupgaardsvej, Denmark 1/7(14.3%)		(118)
	Animals (n=1)	CS	Stool	E. coli	Imipenem	Disk diffusion (CLSI guidelines)	12.0%				(37)
North-east	Human (n=6)	CS	Urine 5/6(83.3%), Stool 4/6(66.7%), Blood 2/6(33.3%), Sputum 2/6(33.3%), Wound 2/6(33.3%), Vaginal swab 2/6(33.3%), CSF 1/6(16.7%)	E. coli 6/6(100%), Klebsiella spp 3/6(50%), Proteus mirabilis 2/6(33.3%), Pseudomonas spp 3/6(50%), Enterobacter spp 2/6(33.3%), Morganella morganii 1/6(16.7%), C. freundii 1/6(16.7%), Serratia marcescens 1/6(16.7%), Hafnia alvei 1/6(16.7%), Citrobcter sedlakii 1/6(16.7%), Providencia rettgeri 1/6(16.7%), Stenotrophomonas maltophilia 1/6(`6.7%), Aeromonas spp 1/6(16.7%)	IMI 4/6(66.7%), ERT 3/6(50%), MEM 2/6(33.3%)	Disk diffusion (CLSI guidelines)	6.8%-10.2%	Carbapenemase 4/6(66.7%)	Hodge Test (MHT) method 2/6(%), PCR 2/6(33.3%)	NDM 2/6(33.3%), VIM 2/6(33.3%), KPC 1/6(16.7%)	(76) (99) (80) (103) (86) (91)
Northwest	Human (n=10)	CS	Urine 9/10(90%), Wound 6/10(60%), Stool 5/10(50%), Blood 3/10(30%), Catheter tips 5/10(50%), Vaginal swab 3/10(30%), Ear swab 3/10(30%), Semen 1/10(10%) Urogenitals 2/10(20%), Abscesses 2/10(20%), Sputum 2/10(20%), Rectal swab 1/10(10%), Bed linen swab 1/10(10%), CSF 1/10(10%), Nasal feed tube 1/10(10%)	Klebsiella spp 9/10(90%), E. coli 8/10(80%) Proteus spp 7/10(70%), Pseudomonas spp 7/10(70%), Salmonella spp, 3/10(30%), C. freundii 1/10(10%), Enterobacter spp 2/10(20%), Shigella spp 1/10(10%), Staph aureus 1/10(10%), Acinetobacter spp 1/10(10%), Streptococcus spp 1/10(10%)	IMI 9/10(%), MEM 4/10(40%)	Disk diffusion (CLSI guidelines) 9/10(90%)	10.5%-100%	Carbapenemase 5/10(50.0%)	Hodge Test (MHT) method 3/10(30%), EDTA-disc synergy test 1/10(10%), Combined discs method 1/10(10%)		(130) (140) (123) (142) (100) (85)(147) (139) (129) (95)
	Humans (n=7)	CS 6/7(85.7%), PC 1/7(14.3%)	Urine 5/7(71.4%), Blood 3/7(42.9%), Sputum 2/7(28.6%), Wound 2/7(28.6%), Rectal swab Stool, Anal swabs 1/7(14.3%), Pleural and peritoneal aspirate 1/7(14.3%), CSF 1/7(14.3%)	E. coli 7/7(100%), Klebsiella spp 4/7(%), Salmonella spp 3/7(42.9%), P. aeruginosa 2/7(28.6%), S. aureus 2/7(28.6%), Citrobacter freundii 1/7(14.3%), E. aerogenes 1/7(14.3%)	MEM 6/7(85.6%), IMI 1/7(14.3%), ERT 1/7(14.3%)	Disk diffusion (CLSI guidelines) 6/7(85.7%), Widal test 1/7(14.3%)	2.9%-36%	Carbapenamase 1/7(14.3%)	Hodge Test (MHT) method 1/7(14.3%)	SPM 1/7(14.3%), IMP 1/7(14.3%), GIM 1/7(14.3%), GES 1/7(14.3%), NDM 1/7(14.3%), VIM 1/7(%)	(98) (77) (105) (122) (87) (127) (112)
	Animals (n=5)	CS	Anal swabs 2/5(40%), Cloacal swabs 1/5(20%), Stool	E. coli 3/5(60%), Salmonella spp 1/5(20%), Proteus spp 1/5(20%), Ochrobactrum spp 1/5(20%),	IMI 4/5(80%), MEM	Disk diffusion (CLSI guidelines)	4.2%-85.4%	Carbapenemase 1/5(%)	Inhibition based assay 1/5(20%)		(158) (151) (155) (159) (153)

Southeast			1/5(20%), Rectal swab 1/5(20%)	Klebsiella spp 1/5(20%)	3/5(60%), ERT 1/5(20%)						
	Environment (n=2)	CS	Water, Treated wastewater, Soil, Vegetable	E. coli 2/2(100%), P. aeruginosa 1/2(50%), S. aureus 1/2(50%), Shigella spp 1/2(50%), Klebsiella spp 1/2(50%), Salmonella spp 1/2(50%), Enterococcus spp 1/2(50%), Streptococcus spp 1/2(50%)	IMI	Disk diffusion (CLSI guidelines)	50% -76%				(166) (163)
South-south	Humans (n=10)	CS	Urine 7/10(70%), Wound 4/10(40%), Sputum 2/10(20%), Ear swab 2/10(20%), Eye 2/10(20%) swab, Throat swab 1/10(10%), Vaginal swabs 1/10(10%), swab, Catheter tip 1/10(10%), Stool 1/10(10%), Rectal swab 1/10(10%), Aspirates 1/10(10%), Blood 1/10(10%)	E. coli 9/10(90%), Klebsiella spp 6/10(60%), Proteus spp 5/10(50%), Enterobacter spp 4/10(40%), Pseudomonas aeroginosa 4/10(40%), Citrobacter spp 4/10(40%), Acinetobacter spp 3/10(30%), Providencia spp 3/10(30%), S. aureus 2/10920%), Serratia marcescens 1/10(10%), Alcaligenes spp 1/10(10%), Atlantibacter hermannii 1/10(10%)	IMI 8/10(80%), MEM 7/10(70%), ERT 2/10(20%)	Disk diffusion (CLSI guidelines) 6/10(60%), British Society for Antimicrobial Chemotherapy (BSAC) method 2/10(20%), Disk diffusion (EUCAST guidelines) 1/10(10%)	4%-100%	Carbapenemase 1(10%)	Hodge Test (MHT) method 1(10%)		(124) (79) (107) (148) (90) (144) (92) (138) (119) (120)
	Animals (n=2)	CS	Anal swab, Stool, Feeds, water trough, water source	Enterococcus spp 1/2(50%), Salmonella spp 1/2(50%)	IMI, MEM	Disk diffusion (CLSI guidelines)	3.7%-80%				(157)(156)
	Environment (n=3)	CS	Pond water 1/3(33.3%), Wastewater 2/3(66.7%)	Vibrio spp, Enterococcus spp, Salmonella spp	IMI 2/3(66.7%), MEM 1/3(33.3%), ERT 1/3(33.3%)	Disk diffusion (CLSI guidelines)	5.9%-100%				(161) (164)(165)
Multi-zonal	Humans (n=2)	CS	Blood 2/2(100%), Urine 1/2(50%), Wound 1/2(50%), Sputum 1/2(50%), CSF 1/2(50%), Tissue 1/2(50%)	A. baumannii, Salmonella spp	MEM 2/2(100%), IMI 1/2(50%)	Disk diffusion (CLSI guidelines) 1/2(50%), Epsilometer test (Etest, bioMérieux) methodology 1/2(50%)	33.3%	Carbapenemase 1/2(50%)	Disc-based 'carbapenemase and ESBL detection set' from Mast Group (Bootle, UK) 1/2(50%)	NDM 1/2(50%), OXA 1/2(50%)	(125) (83)
	Environment (n=1)	CS	Water, Soil	A. baumannii, Aeromonas caviae, Enterobacer, cloacae, Pseudomonas putida, K. pneumoniae, Citrobacter freundii	IMI, ERT	Disk diffusion (EUCAST guidelines)	47.9%	Carbapenamase 1(100%)	Rapidec Carba NP test (bioMérieux) /PCR	OXA, NDM, VIM	(162)

Table 3: Summary of findings based on geopolitical CR distribution

CS – Cross-sectional, PC – Prospective Cohort, IMI – Imipenem, MEM – Meropenem, ERT – Ertapenem, DRP – Doripenem

3.4 Mechanisms for carbapenem-resistance in Nigeria

Carbapenem resistance may be intrinsic to the bacterial species or mediated by carbapenemase-encoding genes such as metallo-beta lactamases (MBLs) and other carbapenemases. As presented in table 3, 23(92.0%) of the 25 studies that investigated and reported mechanism of carbapenem were from human studies, 1(4.0%) from an animal and environmental study each. Almost half, 10(40.0%) of the studies reporting CR mechanism were from the Southwest.

The reported prevalence of carbapenemase-producing bacteria ranges from 8.9%-91.7% (121)(108)(80)(99)(103)(130)(123)(100)(122)(131)(133)(134)(162)(143)(125)(129) with prevalent MBL-producing bacteria from humans (96)(101)(118)(142)(124) and (41.7%) from animal pathogens (155). The carbapenemase-producing bacteria in the environmental study was 47.9% (162)

Carbapenemase encoding genes reported were bla_{KPC}, bla_{VIM}, bla_{NDM}, bla_{OXA}, bla_{SPM}, bla_{IMP}, bla_{GIM} and bla_{GES}. The bla_{NDM} and bla_{VIM} genes were reported by most of the studies (80.0% and 70.0% respectively) while bla_{OXA} and bla_{GES} were reported in 40% and 30% of the studies respectively and other genes in a single study each. While the bla_{KPC} gene was only reported in a hospital study in Northeastern Nigeria (99), others were observed in studies in different parts of the country including multi-zonal environmental study (101)(103)(118)(121)(122)(133)(134)(162)(125).

3.5 Geo-political distribution of carbapenem-resistance in Nigeria

Findings from the reviewed studies showed slightly varied pattern of CR discussed under each geopolitical zone below.

3.5.1 Southwest Zone

Of the 38 studies conducted in this geopolitical zone, 33(86.8%) focused primarily on humans, 2(5.2%) on animals, 1(2.6%) on environment and 2(5.2%) combined samples from humans and non-humans. All the human studies were hospital-based, and almost half of the isolates recovered 15/33(45.5%) were from blood (mostly in combination with other samples as presented in table 3). Twenty-four (72.7%) were from tertiary hospitals and the disc diffusion method using CLSI guidelines was used by 24(72.7%) for susceptibility testing

A total of 8(24.2%) studies reported complete susceptibility of *E. coli, H. pylori, Pseudomonas spp, Klebsiella spp, Acinetobacter baumanii, Acinetobacter lwoffi, Acinetobacter calcoaceticus, Stenotrophomonas maltophilia, Proteus spp, Enterobacter spp* and *Salmonella* enterica serovars to carbapenems (78)(82)(84)(88)(89)(94)(96)(97) while CR prevalence range between 1.2% and 72.7% was reported by 23(69.7%) studies (101)(104)(106)(108)(109)(110)(113)(115)(116)(117)(121)(131)(132)(133)(134)(135)(136)(137)(141)(143)(145)(143)(126) and 2(6.1%) studies documented complete resistance of *Klebsiella pneumoniae* to imipenem and *Escherichia fergusonii* to imipenem, meropenem and ertapenem respectively (149)(146).

Antimicrobial susceptibility results in one of the two animal studies conducted in five states in the zone (Oyo, Ondo, Ogun, Ekiti and Osun) using different poultry samples revealed complete *E. coli, K. pneumonia, Morganella morganii, Leclercia adecarboxylata* and *C. freundii* susceptibility to imipenem and meropenem (152). Similarly, fecal samples collected from cattle, chicken and pigs yielded *E. coli* completely susceptibe to carbapenems (154). The environmental study using wastewater reported *Escherichia spp, Enterobacter spp, Citrobacter spp, P. monteilii, P. taiwanensis, P. plecoglossicida, C. segnis, Achromobacter insuavis, Achromobacter spanius* and *Stenotrophomonas spp* complete susceptibility to imipenem (160). The two studies with combined samples from humans, animal and environment reported 1% *P. aeruginosa* resistance to imipenem and 40% E. coli resistance to meropenem (168)(167).

3.5.2 South-south Zone

As presented in table 3, 10(66.7%) of the 15 studies in this zone focus on humans while 2(13.3%) on animals and 3(20.0%) on environment. Most of the studies, 11(73.3%) including the three environmental and two animal studies were from Edo state. Nine (90%) of the human studies were hospital-based and 1(10%) study was conducted in the hospital/community setting. Susceptibility testing was commonly carried out using disc diffusion method (CLSI guideline) 6(60%). Table 3 showed that urine was commonly used as testing sample 7(70.0%) and E. coli 9(90.0%) was mostly recovered (in combination with other bacteria as shown in table 3). CR prevalence by clinical pathogens range from 0% (79)(90)(92) to 4%-63.6%) (107)(119)(120)(138)(124)(144) and 100% (complete resistance) (148).

The two animal studies were carried out using pig samples. In one of the studies, CR prevalence rates of 5.1% and 3.7% was reported by *E. faecalis* and *E. faecium* recovered from anal swabs respectively while *S*. Enteritidis and *S*. Typhimurium isolated from feaces, feeds and water trough showed 80.0% and 9.1% CR respectively (156)(157). Similarly, the three studies conducted using environmental samples (wastewater and pond water from abattoir and farm) isolated *Vibrio spp, Salmonella* enterica serovars and *Enterococcus spp* with CR prevalence of 5.9%, 8% and 100%, respectively (161)(164)(165).

3.5.3 Southeast Zone

A total of 7(50%) of the 14 CR studies carried out in this region was focused on humans, animals 5(35.7%) and environment 2(14.3%). Six (85.7%) and 1(14.3%) of the human studies were carried out in the hospital and community settings, respectively. Urine was used more than other human samples 5(71.4%) while the disc diffusion method for susceptibility testing using CLSI guidelines was commonly employed 6(85.7%) and *E. coli* was isolated from all the human studies. Other samples, susceptibility methods used and bacteria isolated are presented in table 3. Two of the human studies including the community-based study among asymptomatic students reported complete susceptibility of *E. coli* and *Salmonella spp* to carbapenems (77)(87). The other five studies reported CR ranging from 2.9% to 36% from *E. coli, Salmonella spp, C. freundii, E. aerogenes, E. coli, P. aeruginosa, S. aureus, Klebsiella spp* (105)(98)(122)(127)(112). While three of the animal studies reported complete carbapenem susceptibility, the other (158)(153)(151), the other two documented *E coli* and *Klebsiella spp* CR prevalence of 85.4% and 62.5% respectively(155)(159). *K. pneumoniae* and *Pseudomonas spp* isolated from water and *E. coli* recovered from the soil showed a CR prevalence of 50%, 50% and 76.0%, respectively (166)(163).

3.5.4 Northwest Zone

All 10 studies conducted in this zone were carried out in the hospital setting using clinical samples, mostly urine 9(90.0%) in combination with other samples presented in table 3. Eight, (80.0%) of the studies were carried out in Kano State and the disc diffusion susceptibility method (using CLSI guidelines) was used most of the time 9(90.0%). CR prevalence range from 0% in two studies (85)(95) to 10.5%-71.4% in seven studies (100)(130)(139)(140)(123)(129)(142) and 100% in a study., others recorded resistance ranging from 10.5% to 100% (147).

3.5.5 North Central Zone

Seven, (87.5%) out of the eight CR studies conducted in this zone investigated isolates recovered from clinical samples and 1(12.5%) from animal samples. Disc diffusion susceptibility testing using CLSI guidelines was mostly employed in the human studies 6(85.7%), blood was commonly sampled 4(57.1%) than other human specimens (mostly in combination), and *E. coli* and *Klebsiella spp* were recovered from 3(42.9%) of the human studies. Two of the human studies reported complete susceptibility of *Klebsiella spp* to carbapenem (81)(93), four reported CR range of 6.3% to 24.7% (102)(111)(114)(118) and a study documented complete CR of *Samonella spp* to meropenem (150). E. coli isolated from poultry fecal sample was 12.0% resistant to imipenem (37).

3.5.6 Northeast Zone

All the six CR studies from this geopolitical zone were conducted in the tertiary hospital setting. The disc diffusion method using CLSI guidelines was used in all the studies and urine sample was used in 5(83.3%) of the studies (in combination with other samples as presented in table 3). E. coli was recovered from all the studies alongside other pathogens. A relatively low prevalence of CR was reported with four studies reporting complete susceptibility of *E. coli, K. pneumoniae, Proteus mirabilis*, and *P. aeruginosa* to imipenem and ertapenem (76)(80)(86)(91). The two other studies yielded *P. aeruginosa, K. pneumoniae, E. coli, Providencia rettgeri, Klebsiella spp, Enterobacter spp, Stenotrophomonas maltophilia, Aeromonas spp,* and *Pseudomonas spp* documented 6.8% and 10.2% CR rates (99)(103).

3.5.7 Multi-zonal studies

Two of the three studies conducted across more than one zone focused on human CR while the third study investigated isolates recovered from water and soil. Susceptibility testing was carried out in the human studies using disc diffusion and Epsilometer test (Etest, bioMérieux) methods. While *Salmonella* spp from blood was completely susceptible to carbapenems in one of the studies (83), *A. baumannii* isolated from urine, wound, blood, sputum, cerebrospinal fluid and tissue in the second study showed a CR of 33.3% (125). Similarly, Terrier et al (162) reported aggregated CR 47.9% prevalence from bacteria isolated from water and soil samples collected from Ibadan (Southwest), Akwa Ibom (South-south), Nnewi (Southeast), Kano (Northwest), Yola (Northeast) and Abuja (North Central) .

3.6 Factors contributing to misuse and overuse of antibiotics

Based on the Harbarth et al (68) framework, factors influencing antibiotics misuse/use in humans can be categorized into:

3.6.1 Prescribers factors

Clinicians and others health workers including the community pharmacists and the PPMVs play significant roles as prescribers of antibiotics misuse/overuse. Students and mothers of under five children reportedly overuse antibiotics as a result of recommendations from the health workers (51)(169)(170). Interestingly, these prescribers are also influenced by other factors to either overprescribe or under-prescribe antibiotics. For instance, clients' high demand and crave to maximize profits were major reasons for PPMVs over-prescription of antibiotics (171). Abubakar and Tangiisuran (172) reported that community pharmacists in Kaduna, North-western Nigeria were influenced by their confidence in their knowledge of antibiotics therapy, consideration of patients' long waiting time and financial incapability to pay for medical consultation at the health facility, consideration of patients' inaccessibility to the health facility in addition to fear of loosing their clients to other community pharmacy (172). In a similar study conducted in Warri, Southern Nigeria, Erah et al reported that the availability of antibiotics and feedback from the patients as well as consideration of the socio-economic status of the patients were determinants to antibiotics misuse among community pharmacists (173).

Orthopaedic surgeons from a study conducted in 2015, in Lokoja, North Central Nigeria used prophylactic antibiotics for reasons of just following instructions from medical training school and doubt of the hospital hygienic environment and practices (174). A more recent study reported that the antibiotic prescribing behaviour of doctors in a tertiary hospital in Lagos were determined by consideration of cost to patients, clinical experience, availability of drugs, decisions by senior colleagues, evidence from literature, laboratory results and hospital drug policy (175).

3.6.2 Patient factors

The patient individual factors such as the socio-economic background, perceptions and beliefs as well as behaviours were determinants of antibiotic misuse/overuse.

3.6.2.1 Socio-economic background (Age, gender, marital status, level of education and socio-economic status)

Two studies reported significant association between age and antibiotics misuse (176)(177). Although the association was not linked with any pathway in the studies, middle-aged individuals (25-44years) were more likely to misuse antibiotics than their younger and older counterparts. In the same vein, mothers of under-five children were less likely to administer antibiotics to infants compared to mothers with children above one year of age because infants were perceived as frail and thus require clinician's prescription before antibiotics use (178). Four of the studies, conducted among university students reported that the level of study in the university was associated with the misuse/overuse of antibiotics (176)(177)(169)(179). Students in the lower level of study tend to misuse antibiotics more than those in higher levels of study. This relates to the age of the students as both are not mutually exclusive. While higher education qualification was reportedly significant in reducing the likelihood of misusing/overusing antibiotics as a result of increase increased awareness and knowledge of the antibiotics and AMR

(178)(180), another study reported that higher education was significantly associated with misuse of antibiotics because of intentional use as a result of the knowledge of the efficacy of the drugs (181).

Significant associations between gender and misuse use of antibiotics were reported by three studies (176)(177)(180) with women were more likely to stay away from clinical consultations for fear of medical and dental procedures and thus resort to non-prescription and misuse of antibiotics (182). Lawan et al (183) also reported that marital status was significantly associated with the misuse of antibiotics. In addition, four studies reported that lack of money or financial incapability contributes to self-prescription of antibiotics (50)(182)(184)(185). Patients who are unable to bear the cost of going to the health facility easily resort to self-prescription of antibiotics from the patent medicine store which is perceived as a cheaper alternative (178)(180)(186)(187).

3.6.2.2 Perception and attitude towards illness and the efficacy of antibiotics

Perceptions about illness and antibiotics were reported contributory factors to antibiotic misuse. Patients result into self-prescribed antibiotic use when they perceive their illness or infection as mild and simple and do not require clinical consultation or antibiotic prescription (183)(188)(187)(170). Similarly, three studies reported that patients/consumers' perception of antibiotics as efficient drugs of cure for infections encourages the misuse/overuse of the drug (178)(186)(184). These perceptions are fuelled by previous antibiotics use and experience, another contributory driver of antibiotic misuse. Left over drugs are kept and used for occurrence of infections with similar signs and symptoms (51)(187)(189) as the patients exaggerates their knowledge and ability to treat themselves of any infection with antibiotics (177)(187)(170).

Another determinant of inappropriate use of antibiotics identified in the studies was lack of time to visit the healthcare facility due to busy schedule. Four studies reported that the need to save time required in visiting the hospital, consult with a doctor drives the faster option of self-prescription of antibiotics (176)(177)(182)(187)(188). A study reported that students inconsistently take prescribed antibiotics medication because of the number and size of the tablets they are required to take and the side effects of the medication (50).

3.6.3 Cultural influences

Cultural perspectives and interpretation of health, signs and symptoms of infections as well as treatment options influences the health seeking behaviour including use and misuse of antibiotics. Although, huge gap in knowledge exist as a result of lack of studies on cultural influences on antibiotic use and misuse in Nigeria, the influence of friends, family, neighbours, and colleagues documented in five of the reviewed studies (51)(178)(180)(186)(190) indicates significant social pressure as a determinant of antibiotics misuse and overuse as described by Harbarth and Monnet (191).

3.6.4 Socio-determinants

As described by Habarth et al (68), the social factors represents other broader determinants in the society such as practices, structures and systems. However, there is a wide gap in this aspect as many of the societal and system factors addressed and reported by studies reviewed were within the health system. Of the eight studies that described reasons for antibiotic misuse/overuse relating to the health system, three reported far distance to the health facility as a barrier to seek care at the health facility (176)(182)(192) therefore resorting to indiscriminate use of antibiotics. Similarly, long queue and waiting time were reported by three studies as reasons for preferring to self-treat with antibiotics to visiting the doctors for antibiotics prescription (50)(177)(183). This is related to lack of time due to busy schedule as the feeling of having to wait for a long time at the healthcare facility just to consult with a clinician or to get antibiotics prescription may not be productive and hence their use of unprescribed antibiotics.

Two studies reported that high cost of healthcare services contributes to the motivation to self-medicate with an antibiotics (183)(188). This is connected to the low socio-economic status as poor people are unable to afford the high user fee in the health facility thus resorting to a seemingly cheaper alternative of self-treating with OTC antibiotics. Lack of trust and confidence in the health facility prescriber was also reasons for self-medicating with antibiotics. As a result of past experience, students reported that drugs dispensed at the healthcare facility do not improve their health conditions and so are not confident in the prescribers, therefore preferring to buy OTC antibiotics for use (50)(176). In contrast, PPMVs are gaining the confidence of the patients which promotes seeking care from them (182). The unfriendly attitude of health workers and non-readily availability of antibiotics at the health facilities were addition reasons for embarking on non-prescribed use of antibiotics (176)(184).

3.4.5 Regulatory practices

Harbarth et al (68) described regulatory practices as determinant of antibiotics prescription, availability and use. Regulatory mechanisms such as enforcement of policies on pharmaceutical products including antibiotic, pharmaceutical promotional activities, prescription and dispensing guidelines affect the extent of antibiotics misuse/overuse. For instance, four studies reported that unrestricted, relatively cheaper and available OTC antibiotics from PPMVs was a motivating factor to use antibiotics anytime without doctors' prescription (178)(186)(188)(192). Doctors in a Lagos teaching hospital also reported being influenced by drug promotional and marketing activities to prescribe antibiotics (175).

3.5 Factors influencing antibiotics misuse/overuse in food animal production

Factors influencing antibiotics misuse/overuse in food animal production were described based according to Lhermie et al (18) framework:

3.5.1 Cost-Benefit Analysis

Antibiotics are used for both therapeutic and non-therapeutic purposes in animal production and the latter is targeted towards optimization of profits via use as growth promoters. Therefore, the cost of antibiotic use vis-à-vis evaluation of benefits derived from it such as cure for infections, prevention of diseases and economic gains as a result of rapid growth of the animals influences the decision to use antibiotics (18). Three of the studies reported the use of antibiotics as growth promoters (52)(193)(190) and another study reported that the drive to maximise profit motivates the irrational use of antibiotics on the farm. Animal signs such as diarrhoea and loss of appetite which reduces the economic value of the animals immediately prompt the use of antibiotics even when these signs are not as a result of infections and as a result antibiotics were being used to boost animal appetite (190)(194). The expected economic profits are reasons for use of antibiotics as treatment in spite of the cost of treatment (52).

The expectation of immediate antibiotics outcomes and need to maximise gains facilitated extensive husbandry system which was also reported as an important contributor to antibiotics misuse in Nigeria (53). A study from Southwestern Nigeria reported that farmers were motivated to administer antibiotics to animals in order to boost farm production, an indication of positive consideration of benefits over cost of antibiotics use (190). However, cost-benefit analysis is closely related to cost and the level of knowledge and expertise of the farmers (52)(53).

3.5.2 Farmer's expertise, attitude toward risk and behaviour

The decision to use or not use antibiotics is influenced by the technical ability of the farmers to detect, appraise, interpret and evaluate the need for it; forming the linkage among other endogeneous factors such as cost-benefit analysis and disease appraisal (18). As described by Harbarth and Monnet (191), farmer's personal perceived efficacy of antibiotics and potential benefits from its use influence decisions to use antibiotics in animals and these perceptions and expertise are in turn related to the age, level of education, and previous practical experience. One of the reviewed studies reported that level of education of farmers predicts misuse of antibiotics with farmers having low level of education administering more antibiotics irrationally to the animals (53). Likewise, previous experience with antibiotic use was associated with misuse of antibiotics for animals and over 85% of the farmers based their decision to use antibiotics on their previous experience (52)(190)(194). Another example of expertise-related factor is the route of antibiotics administration which require skills. Most farmers prefer to administer antibiotics to animals orally and antibiotics involving intramuscular administration were used personally by a few or through the engagement of a veterinarian thus limiting the extent to which farmers can use such antibiotics(52)(190).
In addition, the attitude and behaviour towards risk are determinants of antibiotic misuse/over. Two studies reported that farm hygiene practices as a contributory factor to use or not use antibiotics (52)(194). Poor hygiene practices do not only exposes the animals to infections which consequently require antibiotic use, the awareness of unhygienic environment by the farmers promotes the use of antibiotics as prophylaxis (193).

3.5.3 Disease Appraisal

The availability and accessibility to diagnostic test as well farmer's knowledge and experience contributes to the ability to detect diseases in the animals and consequently impact the decision to use or not use antibiotics without prescription. The likelihood of indiscriminate use of antibiotics is higher in a situation where farmers are unable to access diagnostics due to cost or other reasons (18). Ojo et al (52) reported that the limited and in some cases non-existence of animal disease diagnostic laboratory contributed to irrational use of antibiotics by the farmers (52). Non-use of laboratory diagnostics can also be linked with the nomadic and transhumance culture of the pastoralist reported by Alhaji and Isola (53).

Ojo et al (52) and Alhaji and Isola (53) also reported that lack of awareness and knowledge about animal disease and antimicrobial agents fuelled the misuse of antibiotics. This explained the farmers' ability to appraise animal infections and decide on the use of antibiotics as described by Lhermie et al (18).

3.5.4 Other factors

A study reported the influence of advertisement of antibiotics on use (52). The farmers get stimulated by the effect of the advertisement to try new antibiotics without prescription.

Similarly, the availability of antibiotics is a one of the drivers for misuse/overuse of antibiotics by the animal farmers. Ready and unrestricted access to OTC antibiotics was reported by two of the studies as reasons for antibiotic abuse (52)(194). The ease at which farmers access antibiotics coupled with the cheaper cost of the drugs promotes indiscriminate use. Alhaji and Isola also reported that the farmers are motivated to purchase and use antibiotics wherever and whenever they choose because there is no enforcement of law limiting availability and restricting usage (53).

4.0 DISCUSSION

This study compiled research on the prevalence, geographical distribution and mechanism of carbapenem resistance as well as factors influencing antibiotics misuse/overuse in humans and animals in Nigeria. The results revealed widespread, varied but high prevalence of CR, ranging from 0% up to 100%. This is similar to the systematic review findings of Tanko et al, where the prevalence of ESBL gram-negative bacteria in Nigeria ranged from 7.5% to 93.4% (34). However, the CR rates were higher compared to many other African countries (195)(196) although the different sample types and pooled prevalence reporting could possibly explain the variations. The use of various samples and limitation in geographical scope make comparison of data challenging, underscoring the need for a nationally coordinated and standardized CR surveillance. Considering the high burden of infectious diseases in Nigeria (197), high CR is an indicator for imminent risk of treatment failure for common infections and reduced chances of recovery from minor and major surgeries as CR presents with limited treatment options (39).

The few CR susceptibility studies for animal and environmental isolates confirmed the huge lack of AMR data from this domain reported by the O'Neill report (6). Nevertheless, the high CR prevalence of 85.4% and 100% from the scanty animal and environmental studies, respectively could be linked with the high antibiotics usage for livestock reported in different parts of Nigeria (52)(53). This is in congruence with the previous AMR prevalence results from food animals in Nigeria (32) and a review report of 2%-26% prevalence of CRE in animals from Africa compared to less than 1% in Europe (22) where the use of antibiotics for animals is well regulated (65).

A notable finding of this review is that the susceptibility data on CR were generated mostly from cross-sectional, hospital-sampled studies, suggesting a gap in knowledge of CR in the community. This is similar to the pattern observed by Tanko et al (34) and could possibly be attributed to easy access to patients, access to rountinely collected clinical diagnostics data from hospital settings and relatively easier research logistics compared to community-based studies. Similarly, the CR prevalence from this review may not have shown the true picture of the phenomenon in the country because most of the hospital-based studies were from tertiary, public hospitals. This finding corroborates past reports by the NCDC and the FMoH that susceptibility data is almost absent in the non-tertiary health facilities (30) and there is very little or no reporting structure from the private sector in Nigeria (56). Yet, reports showed that the tertiary facilities constitute only 0.25% of the health facilities in the country and the private sector contributes about 60% to healthcare service provision through the 30% conventional healthcare facilities (56). Evidence of polypharmacy and over-prescription of antibiotics exist in private clinics in Nigeria (198) still the prevalence of AMR especially CR in these facilities remain unresearched.

The CR prevalence was lowest in the Northeast geopolitical zone of the country but there were little variations in studies among the remaining zones. Certain factors could be responsible for this pattern which requires further research. The geopolitical distribution of studies reviewed showed a skewed pattern towards specific regions and states within regions. The number of studies from the Southwest were more than twice that from any other region with the Northeast having the lowest number of studies conducted. Tanko et al (34) reported similar pattern from their studies and this may not be unconnected with the concentration of Higher Education

Institutions that facilitates research activities in the country in the Southwest (199) and the unrest and conflict in the region (200). As revealed in this study, CR mechanism was mostly through carbapenemase production and predominant carbapenemase genes were bla_{NDM} and bla_{VIM}. Similar patterns were also reported in many other African countries (195)(196).

The review on factors influencing misuse/overuse of antibiotics revealed that patients are influenced by recommendations from prescribers in the formal and informal health sectors. In line with findings from a 2015 review, PPMVs and community pharmacists in Nigeria were motivated by customers' demand and drive for economic gains, to sell antibiotics without prescription (57). The customers' demand for antibiotics, mostly linked to their perceptions and previous experience of antibiotics suggests low level of knowledge about antibiotics and AMR (187)(194). Getting away with considerations for personal gains over the public health impact of AMR by the PPMVs and community pharmacists indicate weak enforcement of antibiotics dispensing regulations in Nigeria

Consideration of the cost of antibiotics and medical consultation antibiotics misuse/overuse in this review. While the patients preferred non-prescribed OTC antibiotics because of its relatively cheaper cost compared to seeking prescription, the prescribers also consider the financial capability of the patients and this may lead to under-prescription or over-prescription. Other prescribers' factors identified in this review have been reported in other parts of the world with slight context-specific variations (201). For instance, performance-based financing factor reported in Cameroon was uncommon and unreported in the Nigerian setting (202).

Several patient-related factors were highlighted in this review similar to findings from other previous studies (201)(203). However, it is worthy to take note that these factors could be linked with one another and with other social determinants. For instance, the perception of antibiotics efficacy could be linked with previous experience, side effects, level of antibiotics awareness and level of study or education. Likewise, financial incapability could be related with availability of leftover antibiotics and cost of antibiotics. Similarly, the long waiting time at the facility could be linked with busy schedule reported in the study.

This review revealed that the intention to maximize profits from animal production has been reported to often drive the use of antibiotics as growth promoters in Nigeria. The use of growth-promoting antibiotics is still rampart in many African countries unlike in the European countries where it has been banned (204). Antibiotics use for non-therapeutic purposes accounts for significant proportion of the total antibiotics use in Agriculture and it is estimated to primarily drive the increase in antibiotics consumption by 67% in 2030 without any policy intervention (7). Growing evidence shows that the use of antibiotics as growth promoters was not significantly associated with increased economic gains and profits as previously thought (205). While farmers' poor perception of illness and antibiotics efficacy reported in this review could possibly translate into low technical expertise influencing the demand and misuse/over of antibiotics in animal production, weak regulatory structure could also enhance the sales of non-prescribed antibiotics for animals just like for humans. This review showed the role of farmers' access to veterinary diagnostics as determinant of antibiotics misuse/overuse. Laboratory diagnostics for infection and susceptibility detection has been reported as a tool to prevent AMR in food animal production. However, limited diagnostic facilities, cost as well as the mobile nature of the pastoralist undermine the accessibility of the farmers to diagnostics. Previous NCDC assessment reported weak veterinary regulatory capacity and inadequate veterinary diagnostic services in Nigeria thus creating a gap for enforcement and diagnosis respectively (30).

4.1 Strengths and weaknesses of the study

There are limitations to this study. Firstly, articles reviewed were from studies conducted mostly in public and tertiary health facilities, making it difficult to generalize the results for prevalence of CR in a country where the majority of the population seek healthcare services from the private and non-tertiary health facilities. Secondly, most of the studies reported pooled CR prevalence for multiple samples and bacteria tested thus, making it difficult to report resistance rates by specific sample or bacteria type. A qualitative description of pooled prevalence was therefore adopted since more appropriate meta-analyses estimation was beyond the scope of this study. In addition, this study carried out a qualitative description of determinants of antibiotic misuse/overuse without critical appraisal of studies. It also did not provide insight to the magnitude or importance of the identified determinants relative to antibiotics misuse/overuse.

Nevertheless, one main strength of this study is its representativeness in the description of CR across all the geopolitical regions in the country, giving an overview of CR occurrence rates. It also clearly revealed the One Health sector and geopolitical regions not covered in the country. In addition, this study broadly identified factors associated with antibiotics misuse/over pointing to areas for further research and likely AMR interventions.

5.0 CONCLUSION AND RECOMMEDATIONS

5.1 Conclusion

This study reviewed the prevalence, mechanisms and geographical distribution of CR in addition to factors influencing the misuse/overuse of antibiotics in Nigeria. The prevalence of CR is relatively high in Nigeria with many infection-causing bacteria from humans, animals and environment showing varying degree of resistance to the three mostly used carbapenems in Nigeria. This calls for urgent integrated One Health-approach national surveillance based on standard and uniform diagnostics and laboratory guidelines and data management. This is required for evidence-based interventions to prevent the looming consequences of post-antibiotics era. Worrisome but not surprising is the existence of very few susceptibility studies from animal, environmental and non-hospital-based isolates pointing to the need to engage all relevant stakeholders in human, animal and environmental health. There is a need to also conduct more community-based research in order to fully understand the burden of CR in the country. The geographical distribution of CR across the country showed similar pattern with little variations in geographical areas studied.

Addressing antibiotic misuse/overuse is not a linear simple challenge considering the country's socio-economic and cultural context. However, the analysis of factors influencing the misuse/overuse of antibiotics provides useful information that can be used to determine entry points for antimicrobial stewardship interventions. This study identified interrelated intrinsic and extrinsic factors, influencing antibiotics misuse/overuse by both prescribers and consumers from descriptive studies in the country pointing to need for multi-layer antimicrobial stewardship initiatives. Nevertheless, there is need to understand in detail, the weight and relationships among these factors using qualitative and interventional studies. This would help to determine the best strategies to address these factors with consideration of the social determinants of health prevalent in the country-context. For instance, while creating awareness on rational antibiotic use and AMR is an important strategy, its optimal success is hinged on availability and accessibility to quality diagnostics services when needed. Therefore, a multi-faceted approach and collaboration is required for the fight against misuse/overuse of antibiotics and by extension, antimicrobial resistance.

5.2 Recommendations

Based on the aforementioned findings, the followings are recommended:

1. **Creating antibiotics rational use and AMR awareness among the public, informal and formal healthcare workers:** The government and other stakeholders need to direct more concerted efforts towards creating awareness on antibiotics irrational use. AMR specialists should work with the health promotion department of the FMoH to design targeted awareness campaigns for the general population and health workers (both in the formal and informal sector). Awareness and education campaigns using behavioural change communication platforms such as mass and social media platforms; seminars for health professional associations including PPMVs; use of billboards; and promotion of the world antibiotics awareness week (WAAW). It is also essential to revise and incorporate antibiotics prescribing training for doctors-in-training at all levels.

2. **Optimizing antibiotic use through recall/withdrawal of leftover antibiotics:** Since leftover antibiotics is a source for non-prescribed antibiotics, initiatives aimed at returning leftover antibiotics could address this. Incentivising the return of unused or expired antibiotics with financial/non-financial tokens such as voucher towards future treatment could motivate the patients/farmers to return leftover antibiotics.
3. **Building nationally representative AMR surveillance system, including CR:** A surveillance system with sentinel of healthcare facilities across the different facility types and routine point prevalence surveys in the predominant farm animals are recommended. These should be integrated into the country surveillance system.
4. **Incorporating the private and non-tertiary healthcare facilities and veterinary laboratories into the current national AMR surveillance system:** The government through the NCDC need to design initiatives to network and incorporate all health and veterinary facilities into the current surveillance system. This can be through retrieval of susceptibility data from a sentinel of healthcare facilities, with or without transport of isolates to designated reference laboratories. This will also require establishing more NRL and surveillance sites in addition to the existing ones in the country.
5. **Regulating the dispensing and use of antibiotics:** There is need to build stronger monitoring of antibiotics sales system and ensure enforcement of antibiotics dispensing especially among the PPMVs and community pharmacists. Disciplinary measures should be enforced on defaulting dispensers to deter others from the act. Similarly, the use of antibiotics as growth promoters should be banned with strong enforcement among the farmers
6. **Strengthening the health system:** Since health system factors indirectly contribute to the irrational use of antibiotics, there is need to improve physical and financial accessibility to infection prevention and control as well as curative health system services.
7. **Improving access to veterinary diagnostics:** There is need to provide adequate veterinary diagnostic facilities in the country. This could be done through public-private partnership. The different categories of animal farmers including nomadic pastoralists should engaged in planning and setting up of these facilities to optimize usage by these mobile farmers.

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APPENDIX

Terms 1	Terms 2	Term 3
(carbapenem* OR meropenem OR imipenem OR ertapenem OR doripenem OR panipemen OR carbapenem-resist* OR enterobacteriaceae antibiotics susceptibility OR enterobacteriaceae multidrug resist* OR carbapenem multidrug resist* OR enterobacterales resist*)	AND (humans OR patients OR hospital-acquired OR community-acquired OR animal OR livestock OR cattle OR cow OR horse OR pig OR poultry OR chicken OR birds OR broiler OR dairy OR farm OR seafood OR fish OR aquatic)	AND Nigeria

Table 4: Combination of keywords for the first broad literature search

Terms 1	Terms 2	Term 3	Term 4
(factors OR risks OR determinants OR drivers OR reasons OR motiv*)	AND (antimicrobial use OR antibiotics use)	AND (self-medication OR self-treatment OR patient use OR non-prescription OR over-the-counter OR irrational use OR overuse OR non-prudent OR underconsumption OR overconsumption OR underdosed OR inappropriate OR overprescribing OR unnecessary OR drug misuse OR community pharmacy OR patent medicine vendor OR drug seller OR farm use OR livestock use OR veterinary OR food-animal OR animal husbandry OR growth promotor)	AND Nigeria

Table 5: Combination of keywords for the second broad literature search