

Antimicrobial Resistance from a One Health Perspective in Zambia: A Systematic Review

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Abstract

Background:

Antimicrobial resistance (AMR) is widely acknowledged as a global health problem, yet its extent is not well evaluated, especially in low-middle income countries (LMICs). It is challenging to promote policies without focusing on healthcare systems at a local level, therefore a baseline assessment of the AMR prevalence is a priority. This study aimed to look at published papers relating to the prevalence of AMR in Zambia as a means of establishing an overview of the situation, to help inform future decisions.

Methods:

PubMed, Cochrane Libraries, Medical Journal of Zambia and African Journals Online databases were searched from inception to April 2021 for articles published in English in accordance with the PRISMA guidelines. Retrieval and screening of article was done using a structured search protocol with strict inclusion/exclusion criteria.

Results:

A total of 716 articles were retrieved, of which 25 articles met inclusion criteria for final analysis. AMR data was not available for six of the ten provinces of Zambia. Twenty-one different isolates from the human health, animal health and environmental health sectors were tested against 36 antimicrobial agents, across 13 classes of antibiotics. All the studies showed a degree of resistance to more than one class of antimicrobials. Majority of the studies focused on antibiotics, with only three studies (12%) highlighting antiretroviral resistance. Antitubercular drugs were addressed in only five studies (20%) despite an epidemic in sub-Saharan Africa. No studies focused on antifungals. The most common organisms tested, across all three sectors, were *Staphylococcus aureus*, with a diverse range of resistance patterns found; followed by *Escherichia coli* with a high resistance rate found to cephalosporins (24%-100%) and fluoroquinolones (20%-100%).

Conclusions:

This review highlights three important findings. Firstly, AMR is understudied in Zambia. Secondly, the level of resistance to commonly prescribed antibiotics is significant across the human, animal, and environmental sectors. Thirdly, this review suggests that improved standardization of antimicrobial susceptibility testing in Zambia could help to better delineate AMR patterns, allow comparisons across different locations and tracking of AMR evolution over time.

Background

The SARS-COV-2 pandemic has highlighted the importance of implementing working systems at a local level to mitigate and prevent spread of infectious disease. Antimicrobial resistance (AMR) has been highlighted by the World Health Organization (WHO) as a prominent threat to global health. (1) There is specific concern of low-middle income countries (LMICs) where there is poor surveillance, poor diagnosis measure and a lack of guidelines indicating therapy procedures. (2) A regional and national understanding of AMR is needed to improve human health, animal health and agricultural productivity per country. (3)

The term "One Health" was first described by the Wildlife Conservation Society in 2004 as a link between human and animal health that that predisposes to diseases in the food sector. (4) The concept focuses on the consequences, responses and actions across the human-animal-environment sectors highlighting the importance of balance and interconnectedness. AMR understanding and control should be approached ideally from a One Health perspective since resistance can arise in the human, animal or the environment and spread from one to another. (5)

LMICs have unique socioeconomic and cultural settings that challenge the strategies from policy makers on the world stage, (6) as a result of this, antimicrobial stewardship strategies must be tailored specifically from the ground level. In many LMICs, the use of antimicrobials used for treatment remain undocumented and unregulated. (7)

A report was developed by the Zambian National Public Health Institute (ZNHPI) and the Centre for Science and Environment (CSE) India highlighting the need to prepare a surveillance system for Zambia. (8) Zambia faces a generalized HIV epidemic, with most deaths resulting from opportunistic infections. Malaria is considered to be the main cause for hospitalization, and the biggest contributor to morbidity and mortality rates. (8,9) There have also been outbreaks of cholera, meningococcal meningitis, pneumonia, and typhoid in Zambia. (8) Standard infections are becoming increasingly difficult to treat with standard first-line antibiotics because of AMR, leading to the necessary use of newer, more targeted, but also more expensive antibiotics. (10,11)

A consolidated approach is needed to address the complexity and scale of the problem which includes incorporating the various fields of governance and policy makers. (12) When an overview of antimicrobial practice is known, more tailored implementations and control measures can be planned; and understood. Unique insight into antibiotic prescribing, ideas about AMR, and insights into use of antimicrobials in the animal and agriculture sectors. We conducted a systematic review assessing the prevalence of AMR in Zambia as a means of establishing an overview of the situation, to help inform future decisions.

Methods

Search strategy

A systematic review was performed in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines. (13) The search terms [(*multiresistant* OR *multi-drug resistant* OR *antimicrobial resistance* OR *drug resistance* OR *bacterial resistance*) AND (*Zambia*)] were used to identify relevant literature from Cochrane Libraries, PubMed, Medical Journal of Zambia and African Journals Online databases. Various spellings were considered. A total of 994 articles were identified from the four databases that were searched using Boolean search strategies to obtain English articles relating to AMR and Zambia. No limitation on publication dates were set. Literature search began in March 2021, with an update on April 30, 2021. Reference list of relevant articles were checked for additional titles for inclusion in the review. No limitation was set on the bacteria in animal and human health sectors.

Inclusion and exclusion criteria

Full-text articles on the prevalence of antibiotic resistance among clinical pathogenic bacteria isolated from humans (inpatients, outpatients, healthy volunteers), animals (avian, cattle, sheep, swine, and fish) and environment (water, outbreak studies, hospital surfaces, health care tools, markets) in Zambia were used for the review. Publications were initially screened independently by three reviewers (AAN, NNT, OYM) to determine eligibility. Articles were reviewed by at least two reviewers and disagreements were resolved by a third author. Studies related to human sector included both adult and pediatric populations, inpatients and outpatients, and healthy volunteers in institutions such as prisons and schools. There were no limitations on the disease or microorganism tested. Publications identified through the literature search that reported AMR in human, animal, and environment but that did not report prevalence data were not included; specific site of genetic mutations resulting in AMR were not included.

Data extraction

Data was extracted from each study using a database developed by AAN for the purpose of this review using Microsoft Office 365: Excel. The data extraction was independently done by AAN and verified by co-authors NNT and OYM. Articles that met the inclusion criteria and reported prevalence data for AMR were included in the systematic review.

Information extracted included article information (first author, year of publication, duration of study, location, and specific sites), and study design (samples size, cross-sectional design, or longitudinal study). The specific information extracted for the human sector considered: category of patients (in- or out-patients, healthy persons and reason admitted if inpatient), and type of samples extracted (pus, blood, throat swabs, stool, nasal swabs, urine, vaginal or wound swabs). Regarding the animal sector: species, number of sites (including farms, sanctuaries, and veterinary sites), number of animals sampled in analysis,

sample type (feces, meat, milk, blood), sampling point (farm, slaughterhouse, or retail market) were extracted. The environmental/ agricultural sector included information of interest such as water, outbreak studies, vegetables, markets, clinic/hospital surfaces and medical tools were considered. Articles that studied more than one sector was classified as a One Health paper and extracted to the subsections mentioned above. The samples that were studied had to have undergone a laboratory procedure in which the type of microorganism was identified, and prevalence of antibiotic-resistant bacteria were taken into consideration for the human, animal, and environment articles. Specific site of genetic mutations was noted, highlighting the degree of resistance a microorganism has, however the specific sites were not included in this systematic review.

Data analysis

Articles were characterized based on Zambia as a geographic location (including the region and specific site if this information was available; if the study included other countries, specific information regarding Zambia was extracted if available), the type of antimicrobial resistance described in the study (antibacterial, antiviral, antifungal or antimalarial), context of the study (human, animal or environmental; or a combination of any of the sectors i.e. One Health), study design, and outcome of the studies (specifically prevalence rate of antimicrobial resistance).

Meta-analysis was not conducted due to the diversity of the study types and identified data, and therefore present descriptive findings. Visualizations were performed using Microsoft Office 365.

Results

Data

The initial search of the online databases identified a total of 994 publications (PubMed (n=234), Cochrane Libraries (n=376), African Journals Online (AJOL) (n=377) and Medical Journal of Zambia (MJZ) (n=7)) from inception of database to 2021; of which only 717 were accessible. A total of 5 duplicates were removed. Additional 4 records were retrieved after screening references. The African Journals Online identified 372 studies, of which only 100 articles were accessible from the database due to an internal error within AJOLs system. A total of 716 studies were screened for eligibility based on the title and abstract contents. Overall, 614 articles were excluded for non-relevance to this systematic review. 102 full-text articles were assessed for eligibility with 25 articles meeting the inclusion criteria for the study (Fig. 1). Table 1 summarizes the characteristics of the analyzed articles; a full list of the included articles and breakdown of findings is provided in Additional File 1/ Supplementary Data.

[INSERT TABLE 1]

Fig 1. PRISMA flow-chart illustrating the study selection process on antimicrobial resistance in Zambia

Study Characteristics

A total of 15 studies reported on the outcome of AMR in humans, two reported on the outcome of AMR in animals and two on the environment (Table 1a). Three studies used a One Health approach; with one study reporting outcomes of AMR in both human and animal sectors, while one study reporting on the outcome of AMR in animals and environmental sectors, one study reflected on the outcomes of AMR within the human and environmental sector (Table 1a). Across the sectors, 21 (84%) of studies were focused on antibacterial, with 5 studies specific for antitubercular drugs. The antimicrobials that underwent surveillance were antibiotics (antibiotic classes were aminoglycosides, cephalosporins, penicillin, sulfonamides, fluoroquinolones, beta-lactamases, macrolides, tetracyclines, chloramphenicol and glycopeptides), antivirals (nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs). Only one paper reported data on antimalarials. No antifungals were surveilled.

The largest number of studies originated from Lusaka (n=16), followed by Ndola (n=5), Mongu (n=1), Livingstone (n=1), Kaoma (n=1), Chingola (n=1), Eastern Province (n=1), while three studies mentioned multiple sites within the regions of the country (Fig. 2.) however, it was noted that several provinces had no studies conducted. These studies investigated isolates from diarrheal diseases (2; 10%), breast abscesses (1; 5%), chronic supportive otitis media (1; 5%), hospital acquired infections (1; 5%), malaria (1;5%), neonatal sepsis (1;5%), typhoid (1;5%), HIV (4; 20%), and tuberculosis (4, 25%) (Table 1c). Overall, 27 samples were reported from the human and animal studies, the most abundant being blood (7; 26%) followed by sputum samples (5; 19%), stool samples (4; 15%), wound swabs (4; 15%), nasal swabs (2; 7%), aspirates (1; 4%), rectal swabs (1; 4%), urine swab (1; 4%) and oral swabs (2; 7%) (Table 1d). Samples from the environmental sector were obtained from (1) fish markets, (2) veterinary hospital surfaces, (3) healthcare white coats and (4) the hydrotherapy bathtub of the burns unit at the Department of Surgery. Twenty-one types of pathogens across all sectors were isolated from samples with the most common organisms isolated were *Staphylococcus aureus* (13; 17%) followed by *Escherichia coli* (11; 14%), *Klebsiella species* (7; 9%), *Mycobacterium tuberculosis* (5; 7%), *Proteus species* (4; 5%), *Streptococcus* (4; 5%), *Pseudomonas species* (4, 5%), *Enterobacter species* (4; 5%), *Coliform* (3; 4%), *Shigella species* (3; 4%), *coagulase negative Staphylococci* (3; 4%), HIV (3; 4%), *Vibrio cholerae* (2; 3%), *Salmonella typhi* (2; 3%), *Salmonella paratyphi B* (1; 1%), *Non-Typhoidal Salmonella* (NTS) (1; 1%), *Citrobacter species* (1; 1%), *Yersinia species* (1; 1%), *Plasmodium falciparum* (1; 1%), *Campylobacter jejuni* (1; 1%) and *Staphylococcus pseudointermedius* (2; 3%) as summarized in Fig. 3. These isolates were tested against 36 antimicrobial agents, across 13 classes of antibiotics.

The animal, environmental and One Health studies focused on bacterial pathogens and resistance patterns. The most found pathogens isolated were *E. coli* and *S. aureus*. *Salmonella* was only studied in the human sector. The 25 included studies focused on resistance profiles of microbes. No articles included described the process or outcomes of AMR stewardship programs at a local level or focused on policy aspects of AMR prevention or management. No studies were conducted that relayed information about antifungal resistance.

Discussion

Antimicrobial Resistance has been highlighted by the World Health Organization (WHO) as a global health threat that needs urgent intervention (11,14). Zambia has a National Action Plan (NAP), aimed to have been implemented by 2020, (8) however the effects of these interventions may be inaccurate without a baseline investigation. As an LMIC, there are multiple challenges Zambia must overcome, such as the unavailability of diagnostic tests, lack of microbiologists, lack of reagents or inadequate equipment within hospitals and laboratories. Availability of routine and research data on antimicrobial resistance is an important step in the development of local strategies to curb the global AMR crisis. (15) The One Health approach is a progressive development of multi-disciplinary action across the human health sector with animal and environmental health. (16) A report was developed by the ZNHPI and the CSE India highlighting the need to prepare a surveillance system for Zambia. (8) An integrated baseline using information collected from secondary research was developed with the hope to accurately implement a NAP. The report mentions commonly used antimicrobials, disease burdens and estimates the trends of AMR from secondary studies conducted in Zambia. (8)

This current review describes published data on antimicrobial drug resistance from Zambia, revealing a high rate of resistance of microorganisms isolated in hospital settings, animal health and environment against typical antibiotics used in Zambia. Lusaka province had majority of the studies, with various provinces having no data on AMR, indicative that more AMR data is needed for several provinces to have a more complete understanding of the status of AMR in the country. A couple of articles mentioned Zambia in a multi-country study, however in these cases, the specific region or location of the study or sample collection was rarely mentioned, resulting in limitations of the study in findings specific to the Zambian context. A 2017 systematic review reported that about 42% of African countries do not have published studies on AMR,(17) and the lack of information available in Zambia is evident. Many LMIC's, such as Zambia, are resource limited. The allocation of resources is crucial hence an up-to-date baseline is needed to develop, coordinate and apply surveillance systems at all levels. (8)

Many studies in sub-Saharan Africa focus on antibacterial resistance with few studies on antivirals and antifungals. Countries with high prevalence of HIV, TB and malaria had high numbers of studies on these diseases; (8) this does not align with our observations from Zambia. Despite Zambia having an HIV epidemic, only four studies made mention of HIV, with one study testing the resistance to opportunistic infections in HIV patients: *S.pneumoniae*. HIV prevalence in Zambia was estimated 11.3% among adults ages 15 to 49 as of 2018. (18) This represents a substantial burden of disease, and it was surprising to identify only three studies focused on prevalence to antiretroviral resistance in Zambia: particularly because of the emerging resistance to antiretroviral regimens across Africa. (19) Zambia has a high prevalence of tuberculosis with 455/100 000 cases recorded in a study in 2019. (20) Despite the tuberculosis epidemic, only five studies showed specific resistance to antitubercular drugs. The prevalence of *M. bovis* in Zambia and LMICs is limited due to poor laboratory facilities and lack of trained personnel. (20) Bovine tuberculosis (BTB) has been reported in traditional cattle in Zambia, with a high prevalence of 49.8% within the Kafue basin region; while abattoirs in Namwala district found a 16.8% cattle slaughtered were infected with BTB. (20) The spillover effect from the animal sector to the human sector has not yet been established.

Most studies on AMR in Zambia focused on resistance in the human sector, with a handful of studies in the animal and environmental sectors, despite the known importance of the interconnectedness of all three sectors and the vital role they play in preventing and mitigating AMR. The One Health approach should assist and encourage future researchers to consider the methodologies that explicitly look at the interlink across human-animal-environment frameworks, specifically focusing on the zoonotic diseases that have the high potential of resulting in resistance antimicrobials. With only three studies focusing on multiple sectors, yet these studies are on microorganisms that are not epidemiological microorganisms, it was noted that there are not enough studies using the 'One Health' approach in Zambia.

Numerous studies found resistance of more than 50% suggesting high resistance or possible sampling/testing errors. It was observed that studies are diverse in samples type, study design and identified data and no standardized tool was used across the studies. Antibigrams were not found in the systematic review, and the most recent antibiogram found in a ZNHPI report was from 2016 for only one hospital (8). Recent communication with the laboratory mentioned a shortage of reagents hence the main third level hospital cannot conduct yearly antibigrams, as recommended by the Clinical and Laboratory Standards Institute (CLSI). (21)

Several studies showed a 100% resistance to commonly prescribed drugs in Zambia, as well as multidrug resistance amongst clinical isolates. This review highlights concerns relating to the use of common antimicrobials as the choice for optimal therapy of common pathogens in Zambia. Our study highlights concern regarding second-line treatment options, such as azithromycin for cholera, in the country have also been highlighted by this study. However, the high rate of antimicrobial resistance does bring into question the testing methods and accuracy of the testing in Zambia as there may have been sample contaminations at certain studies since there were a variety of contradicting results, as seen with B-lactamase use for *S. aureus* ranging from 0% resistance to 100% resistance for second line antibiotics (gentamycin, ceftazidime, nalidixic acid and norfloxacin). Similarly, it was noted that resistance has emerged and been detected for *K. pneumonia* and *E. coli*, however there is a diversity of results with majority showing resistance greater than 50%. These findings demonstrate antibiotic resistance, regardless of testing method, site, year and region, to new and extended spectrum, more efficacious antibiotics.

The most common pathogen identified across the human-animal-environmental sectors was *Staphylococcus aureus*. *S. aureus* is frequently found on the human skin and is recognized as the main contributor of infections in humans. (22) There are high rates of AMR to gentamycin, ceftazidime, amoxicillin-clavulanic acid, cotrimoxazole, nalidixic acid, norfloxacin and oxacillin found in this study. Gentamycin, ceftazidime (third generation cephalosporin) and the fluoroquinolones (nalidixic acid and norfloxacin) are considered second line for *Staphylococcus spp.* is a serious concern as we see a prominent resistance rate across multiple studies.

Special consideration needs to be addressed in Zambia regarding the surveillance techniques across the several regions. It is imperative to include rural and urban informal settlements, as well as community studies. To prevent an AMR pandemic, it is important to establish surveillance systems that also address and incorporate investigations into the knowledge, attitudes and practices across the human, animal and environmental sectors. It is also recommended to establish systems to map

antimicrobial use, resistance profiles and genetics. No known system to address AMR mapping is in place in Zambia at the time of this review. Studies on antifungals, a group that is neglected, should be considered a field of interest. Researchers should be encouraged to collaborate within the human-animal-environmental sectors and conduct studies from a One Health perspective; as well as establish appropriate means to ensure a system can be in place to potentiate future studies on AMR in Zambia.

Our research is one of the first systematic reviews assess antimicrobial resistance in Zambia. Our results provide critical information that can be used towards policy development and patient management. The different sectors should be more involved and share information to ensure that there is a holistic approach when it comes to combatting AMR.

Conclusion

To safeguard our current collection of antibiotics it is imperative to address the gaps in AMR diagnostic standardization and reporting; and improve surveillance, stewardship, infection control, and implementations of updated treatment guidelines and monitoring. Overall, this review suggests that improved standardization of antimicrobial susceptibility testing in Zambia could help to better delineate AMR patterns and allow comparisons across different locations and allow tracking of AMR evolution over time.

The findings further emphasize the need to address and implement effective AMR surveillance through continued data sharing, multidisciplinary collaborations, and coordination of all stakeholders. This is essential to understand and manage the AMR national burden especially in Zambia.

Abbreviations

AJOL

African Journals Online

AMR

Antimicrobial Resistance

BTB

Bovine Tuberculosis

CLSI

Clinical and Laboratory Standards Institute

CSE

Centre for Science and Environment

LMIC

Low-middle income countries

MJZ

Medical Journal of Zambia

NAP

National Action Plan

NRTI

Nucleoside reverse transcriptase inhibitors

NNRTI

Non-nucleoside Reverse Transcriptase Inhibitors

PI

Protease Inhibitors

PRISMA

Preferred Reporting Items for Systematic Reviews and Meta-Analysis

WHO

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data

The data and materials of the study will be available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Contributions

AAN, AWA and LRS conceived the idea. AAN prepared the systematic review protocol and was involved in the literature search, screening, extraction of data, data analysis and developed the drafts of the manuscript. OYM and NNT performed the screening, extraction of data and developed the first draft of the manuscript. LRS and AWA provided critical review of the manuscript and contributed to the final version. All the authors read and approved the final version of the manuscript.

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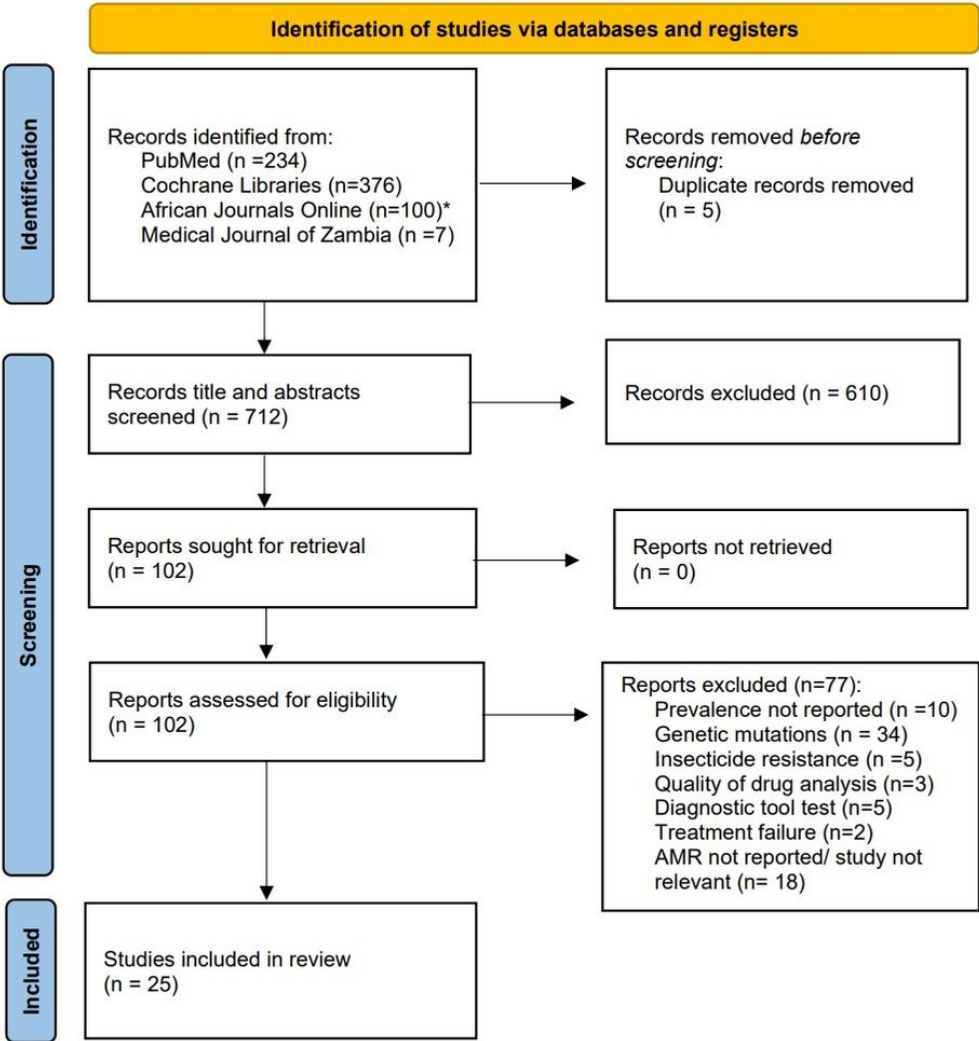
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Table

Table 1 is only available in the Supplemental Files section.

Figures



* African Journals OnLine (AJOL) identified 377 studies, of which only 100 articles were accessible from the database due to an internal error within AJOLs system.

Figure 1

PRISMA flow-chart illustrating the study selection process on antimicrobial resistance in Zambia

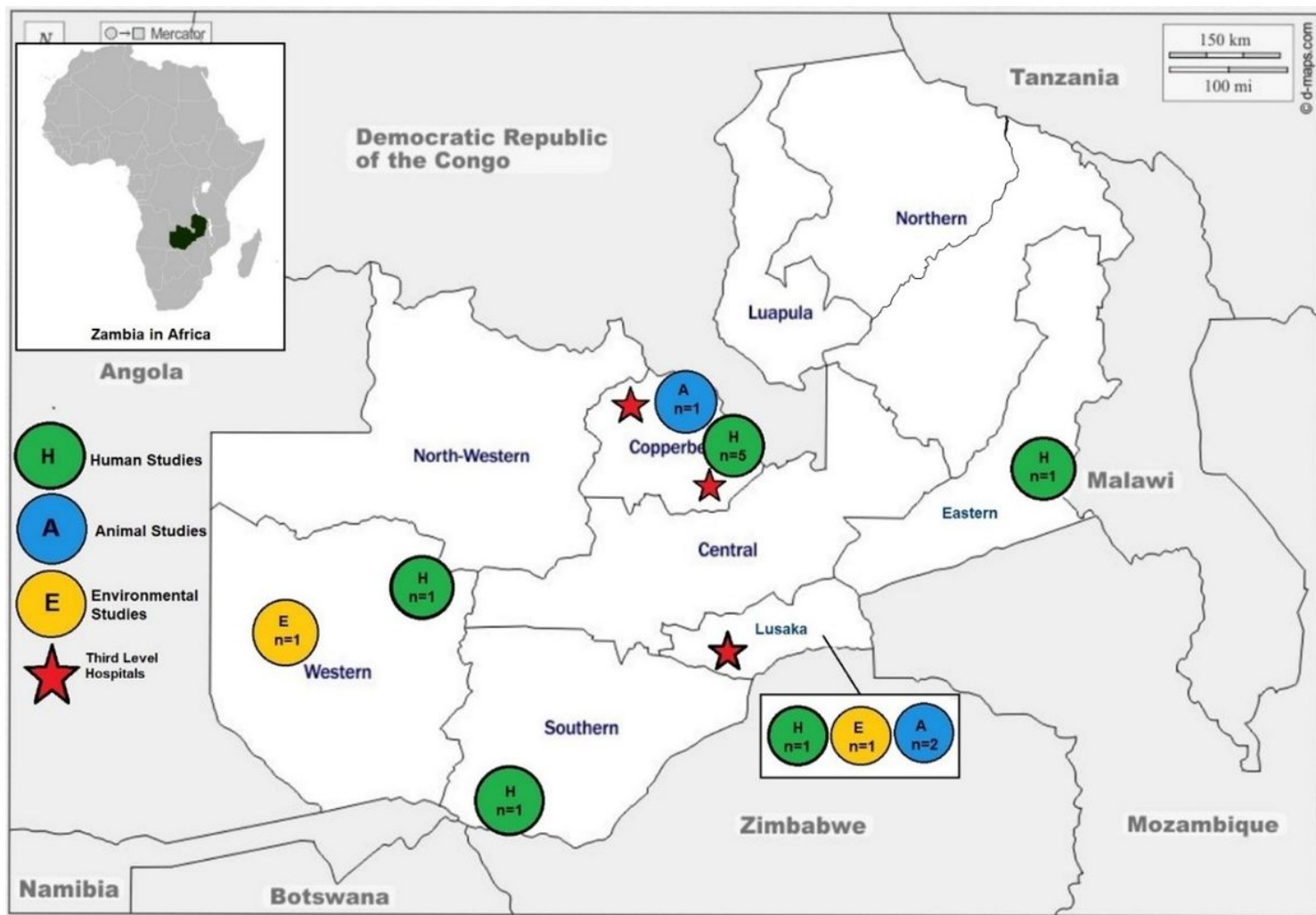


Figure 2

Map of Zambia showing study sites and number of articles used in the review.

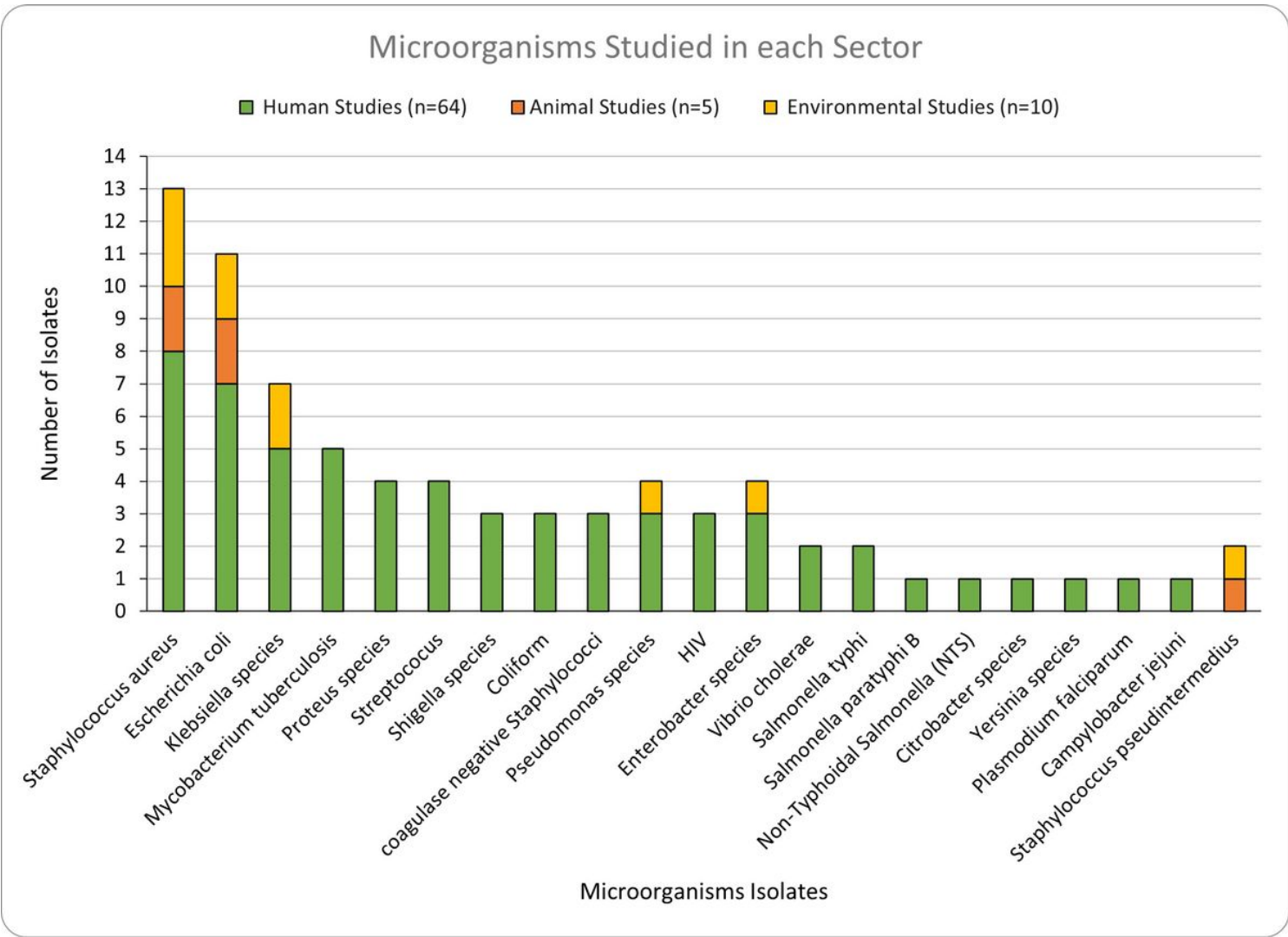


Figure 3

Microorganisms isolated across human, animal, and environmental sectors in Zambia

Supplementary Files

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- [Table1.docx](#)
- [Additionalfile1.pdf](#)