Antibiotics resistance in Sub Saharan Africa; literature review from 2010 – 2017

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SUMMARY

Antibiotics saves millions of lives in human and animal from bacterial infections, but resistance has been occurred and spreading borderless which pose health and economic problems. This study aimed to describe epidemiology (prevalence) of antibiotic resistant bacteria in human and animals and describing risk factors with strategic control efforts in Sub-Sahara Africa countries. Total 72 articles published from 2010 to 2017 were reviewed which reported on bacterium resistance to commonly-used antibiotics of different groups. Majority of isolated bacteria were highly resistant to b-lactams, Tetracycline and Sulphonamide, moderate resistant to Gentamycine and Aminoglycoside with low resistant to cephalosporin and quinolones for bacteria isolated from human while isolates from animal have high resistance to majority of antibiotic. High antibiotic resistant was associated by presence of weak/no regulation and irrational antibiotics use in Animal and Human health system, despite there is paucity of published data from central and southern African countries, lack of data sharing among laboratories and presence of few initiatives on control strategies of antimicrobial resistance while most of them are faced by resource limitations (skilled personnel, Equipments and Fund allocation). This study recommend that awareness on rational antibiotic use must be created, strong regulation to limit accessibility of antibiotics over the counter prescription, strengthening laboratory based diagnosis and surveillance, Infection control and prevention in hospitals with strong biosafety and biosecurity in animal farms are crucial. Adoption of "One Health Approach" is very important through multisectoral involvement, information sharing and networking.

Keywords: *Antibiotic resistance, epidemiology, control strategies, sub-sahara Africa countries*.

INTRODUCTION

The use of antibiotics for control of infectious diseases saves millions of lives in human and animal from infectious diseases, although some of them are becoming ineffective as pathogen develop resistance. Antibiotic resistance has health and economic consequences due to increased costs of treatments and economic losses associated with reduced productivity caused by sickness and long stay in hospital (Wegener, 2012). It is expected that by 2050 AMR could cause more global economic crisis, in Europe alone health care costs Euro 1.5 billion in annually.

The AMR is estimated to account for more than 700,000 deaths per year worldwide, in which if action is not taken it will reach a point that the global health will enter a post antibiotic era whereby even simple injuries

with infection threatening our life (UN, 2016).

In developing countries countries antibiotics are irrationally used in animal production system by nonprofessional treating animals without adhering to dose, regime of treatment and withdraw period which leaves Animal foods products to contain antimicrobial residues (Caudell et al., 2013).

Uncontrolled antibiotic drugs sell to the markets and easily accessibility, over the counter use of antibiotics, symptomatic treatments and self-medication in the community with infections control and hygiene in health care facilities which contributes to emergency and spread of bacteria resistance in Animal and human population locally and globally (Ocan et al., 2015; Okeke et al., 1999).

AMR is a global problem that threatened achievement of Millennium Development Goals (MDG) and is also bringing challenges to Sustainable Development Goals (SDG) on health promotion, poverty reduction and productivity which made the tripartite (WHO, FAO and OIE) in 2015 to meet and discuss on the strategies control.

These public health problems require global attention for harmonized containment and control strategies from regional and international community. Recommendation was made that for effective control of antibiotic use and antibiotic resistance each country must develop AMR Action plans (WHO, 2016).

In Africa majority of countries are in lower and middle incomes (LMI) are associated by presence of poverty, high prevalence of infectious disease with uncontrolled antimicrobial use in animal and human (Maron and Nachman, 2013).

Majority of studies conducted on antibiotic resistance in animal and humans separately, hence as far as "One Health approach" is concerned our study aimed to describe the epidemiology (prevalence and Risk factors) and strategic control efforts of antibiotic resistant bacteria in human and animals holistically in Sub-Saharan Africa.

METHODS

Study Design

A review of literatures for published articles was conducted to collect and analyze data that answer objectives of our study on prevalence and risk factors of antibiotic resistance plus control strategies.

Study Area

Sub Saharan African region; countries from *Western, Eastern, Central and Southern Africa with exception on Northern Africa* as described by the UN scheme of geographic regions.

Search strategy

Data were collected from online databases by using search engines such as PubMed, BMC, Cochrane, Google Scholar, Research Gate and AJOL libraries by using key words such as "review of antimicrobial resistance", antibiotics use", prevalence", "epidemiology of antibiotics resistance" "risk factors of antibiotics resistance"," strategic control", "stewardships program", "action plan", "Sub-Saharan African" "2010 to 2017".

Information obtained from the search databases and other sources were saved using Zotero software for citation and referencing.

Selection of Articles for eligibility and Screening

Free Online PRISMA software generator for reporting systematic review as a guide was used to screen eligible documents for

selection based on inclusion and exclusion criteria (Liberati et al., 2009).

Review, Research and Reports papers published between 2010 and 2017 in English language from human and animal population in sub-sahara Africa countries were included. While all studies that focussed on TB, HIV, Malaria, Influenza virus and fungal infection, Articles published before 2010 and after 2017 in language other than English.

Critical Appraisal tools (Assessment of quality)

Validity of included studies were assessment for quality prior to inclusion in the review by using standardized instrument Joanna Briggs Institute (JBI) and (CASP) as adapted by Guyatt et al (Martin, 2017). The instrument had 11 criteria whereby each study was evaluated for each question as "Yes", "Cannot tell", or "No", with assigned values of 2, 1, and 0 respectively.

Data collection and analysis

Data were collected and organized into table for extraction necessary information's from each study. Qualitative descriptive analysis was used to describe epidemiology (prevalence and risk factors) of antibiotic resistance with control strategies used.

RESULTS

Search results

A total of 432 articles were identified from databases searching, after initial screening 222 were removed. 58 studies discarded of 210 articles remained after review of their titles and abstracts as their full text was not available

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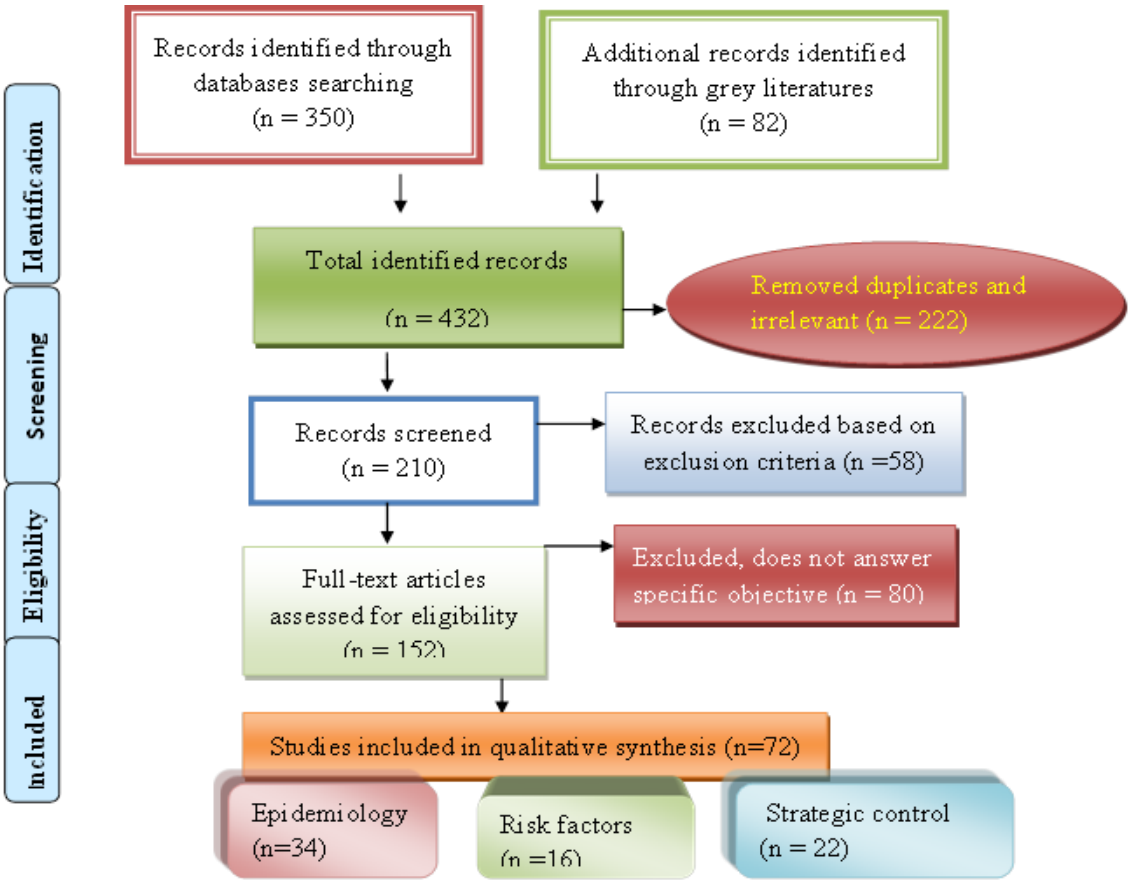

Figure 1. PRISMA Flow diagram for systematic review (Liberati et al., 2009)

152 full texts were assessed for eligibility in detail, 80 studies excluded while 72 studies were included in this review as they give data that needed to answer research objectives whereby 34 studies described prevalence, 16 studies on risk factors and 22 studies on control strategies as summarized in PRISMA Flow diagram Figure 1.

Characteristics of included studies

Both human and animal population were included where by 62% from human, 29% from animal while 9% were from animal and human.

Among of 34 epidemiological studies included conducted laboratory based on 47% bacteria culture and sensitivity, 21% genetic/molecular technique while 32% were on both bacteria culture and sensitivity & genetic/molecular technique. Of the included studies in this review 36 studies (50%) were from Eastern Africa, 20 studies (28%) from Western Africa, 10 studies (14%) from Sub-Saharan Africa, 4 studies (6%) from Southern Africa while 2 studies (3%) studies from Central Africa. These studies obtained from 12 Sub-Sahara Africa countries namely Tanzania, Uganda, Kenya, Ethiopia, Ghana, Nigeria, Benin, Bukinafaso, South Africa, Zambia, Zimbabwe and DRC.

Quality of included studies

Critical appraisal showed most studies were of high quality 85% whereas 14% were of medium quality. No difference was observed between high and medium quality studies that were included for analysis while those studies with low quality were excluded from this review.

Prevalence of antibiotic resistant bacteria

Among of the included studies; 34 articles discussed the prevalence of antibiotic resistant bacteria, in which a total of 10 bacteria were isolated from Animal (4 isolates) and human (9 isolates) whereby hospital based had 8 isolates while community based had 4 isolates, these isolates were from enteric infection, Urinary Tract Infections and Blood stream infection.

The isolates were tested against several antibiotics commonly used for treatments; these include b-lactams (penicillin, cephalosporin), quinolones, Aminoglycoside, tetracycline and Cotrimoxazole.

Significant variation of resistance rate among bacteria from different studies, in which the data for prevalence were pooled into mean resistance of bacteria to antibiotic are shown in Table 1 (for animal), while prevalence in human are shown in Table 2A (for hospital based) and Table 2B (for community based).

Risk factors for development of antibiotic resistant bacteria

risk factors for development of antibiotics resistant bacteria have been categorized into behavioural and environmental factor which have been classified into six (6) factors/causes of bacteria resistance namely over-prescription of antibiotics, patients not finishing the entire antibiotic dose, overuse of antibiotics in livestock and fish farming.

Poor infection control in health care settings, poor hygiene and sanitation and absence of new antibiotics being discovered (Larson, 2007; Duong, 2015) are other factors.

22 published articles reported risk factors for development of antibiotic resistant bacteria as summarized in supplementary Table 1.

Table 1. Prevalence of antibiotic resistant bacteria in Animal (Mean bacterial resistance)

Antibiotic groups	Antibiotic classes	*E. Coli*	*Salmonella spp*	*Campylobacter*	*S. Aureus*
	Oxacillin	-	100	-	-
B-lactams	Procaine Penicillin	-	-	-	74
	Ampicillin	90	96	-	-
Quinolones	Norfloxacin	-	-	60	100
	Enrofloxacin	-	87	71	-
Aminoglycosides	Gentamycine	68	-	-	-
	Streptomycin	71	-	-	-
Tetracycline	Chlortetracycline	90	-	75	-
	Oxytetracycline	88	-	71	85
Macrolides	Amikacin	62	-	-	-
	Clindamycine	-	-	-	60
	Erythromycin	-	-	-	80
	Azithromycin	-	-	29	-
	Tylosin	-	94	39	-
Suphonamides	Cotrimoxazole	80	-	-	-
	Sulfamethoxazole	51			
	Trimethoprim	67			
**MDR*		80	100	61	68

* (MDR) Multidrug Resistance, (-) No data available/found

Table *2A*. Prevalence of antibiotic resistant bacteria in Human (Mean bacterial resistance for Hospital based).

Antibiotic groups	Antibiotic classes	*E. coli*	*Klebsiella spp*	*Shigella spp*	*S. aureus*	*Salmonella spp*	*Pseudomonas*	*Enterococcus*	CNS*
	Penicillin	-	-	-	95	-	-	-	92
B-lactams	Ampicillin	87	88	93	88	91	-	88	-
	Amoxicillin	63	37	-	47	-	-	-	-
	Cefepime	15	-	-	52	-	-	-	-
cephalosporin	Cefoperazine	48	48	-	74	-	-	-	-
	Ceftazidime	68	-	68	31	-	-	-	-
Quinolones	Nalidixic acid	62	52	-	-	-	-	-	-
	Ciproflaxin	62	25	-	50	12	-	-	-
	Froloquinolone	-	-	-	-	-	-	-	-
Aminoglycosides	Gentamycine	30	33	-	75	-	-	-	-
Tetracycline	Tetracycline	41	41	-	55	-	84	-	-
Macrolides	Vancomycin	-	-	-	-	-	-	68	-
Suphonamides	Cotrimoxazole	80	75	-	100	91	100	73	76
	Nitrofurans	80	79	-	-	-	83	-	-
	Furantoin	87	-	-	-	-	-	-	-
**MDR*		15	-	-	-	60	-	-	93

MDR (Multidrug Resistance), CNS (Coagulase Negative Staphylococcus), (-) No data available/found

Table *2B.* Prevalence of antibiotic resistant bacteria in Human (Mean bacterial resistance for Community based).

Antibiotic groups	Antibiotic classes	*E. coli*	*Klebsiella spp*	*Shigella spp*	*S. aureus*
	Penicillin	-	-	-	81
B-lactams	Piperacillin	84	-	-	-
	Amoxicillin	83	-	-	-
	Amoxyclav	77	-	-	-
cephalosporin	Ceftazidime	22	46	22	40
Quinolones	Nalidixic acid	17	-	-	-
	Ciproflaxin	60	11	-	-
Aminoglycosides	Gentamycine	30	11	-	-
	Chloramphenicol	-	19	-	-
Tetracycline	Tetracycline	83	-	-	-
Macrolides	Erythromycin	-	0	-	-
Suphonamides	Cotrimoxazole	89	69	-	91
Others…	Colistin	61	-	-	-
	Nitrofurans	4	4	-	-
**MDR*		34	60	90	-

*MDR (Multidrug Resistance), (-) No data available/found.

DISCUSSION

Antimicrobial resistance (AMR) is estimated to account for more than 700,000 deaths per year worldwide. In 2014 Global AMR Surveillance reported high antibiotic resistance which is of global concern however the paucity of published data in many African countries (WHO, 2014).

This study also found that most of pathogenic bacteria frequently isolated from hospital, community and animal in sub sahara African countries (2010 – 2017) they are resistance to several drugs including Sulphonamides, Tetracycline and b-lactams (penicillinase) groups.

However the possibility of being under-reported is high as published data are sparse and varies throughout sub-regions of eastern and western Africa, central and southern Africa.

Majority of bacteria isolated from Animals reported to have higher resistance to all groups of antibiotics tested including b-lactams (penicillinase), Tetracycline and Quinolones with a medium resistance to Sulphonamides for E coli isolates.

Streptococcus spp isolated in Uganda from blood stream had higher resistance to Penicillin (81%) and Cotrimoxazole (91%) (Rutebemberwa et al., 2015) as compared to Campylobacter infection which had low resistance to Macrolides at 29% Azithromycin and 39% Tylosin.

Most of bacterial isolated from human reported to have a medium resistance (11-53%) to Quinolones, Aminoglycosides and Macrolides group with low resistance to Cephalosporins and Nitrofurans among E. coli, Klebsiella, Shigella and Streptococcus while E. coli and Klebsiella had higher resistance to 80% Nitrofurans for hospital infection but low 4% Nitrofurans for community infection.

Erythromycin is highly sensitive (with 0% resistance) for community infections as compared to Vancomycin with 68% resistance for hospital infections, hence Erythromycin can be used as the first line/choice treatment for streptococcus infection due to its highly sensitivity.

MDR in human was reported to be very high (93% for CNS, 60% for Salmonella) (Donkor et al., 2012) in Hospital and (90% for Shigella, 60% for Klebsiella) (Sang et

al., 2012) in community. *Salmonella spp* in animal isolated from poultry in Nigeria had higher MDR (100%) as compared to that in human (60%). Also E.coli in animal had higher MDR (80%) (Nguyen et al., 2016) while low MDR in human (15% for hospital and 34% for community based).

High MDR in animal brings concerns to public health as if it spreads to human through laterally or vertically from animal's farm. MDR for ESBL producers (*E coli and Klebsiella)* was higher at 94.5% than ESBL non producer at 49.9% for hospitalized patient in the population (Najjuka et al., 2016), this brings a concerns in health facilities due to hospital acquired infections as it can spread to the community and animal farms.
Ocuurances and spread of Antiotics resistance is associated by human factors (behavioural and governance) on antibiotic use including self-medication and non-adherence to dose regime by patients as some people skip doses in favour for the consumption of alcohol when they are invited for a party (Sanya et al., 2013; Tafa et al., 2017).

Although Ceftriaxone resistance reported to be less than 25% but its over-use /over-prescription of third generation cephalosporin without bacteria culture and sensitivity test to patients for prophylactic use by physicians (Nyongole et al., 2015) can be a source of emergency and spread of resistance among pathogenic bacteria in hospitals.

While low level of awareness among farmers on antibiotic use; withdraw period and residuals effects, weak regulation on antibiotic accessibility and use, untrained person treating animals and sell & dispensing of antibiotics without prescription form in veterinary facility (Rugumisa et al., 2016).

This study found that bacteria resistance to antibiotic in Africa are very high and increasing while MDR being a big challenge, Thus if appropriate actions are not taken to control AMR, the achievements gained in reducing mortality and morbidity through the use of antibiotics will be in serious threats.

Despite of those global health challenges but in Africa there are few control strategies of antimicrobial resistance had been initiated, while most of them are faced by resource limitations (skilled personnel, Equipments and Fund allocation) and Antibiotic Sensitivity Testing capability like laboratory technical training, accreditation and limited comparability of standards (Ampaire et al., 2016).

Due to globalization and science & technology with rapid movement across borders these resistant bacteria do not remain within Africa countries. As AMR threatens the effective control and treatment of various bacterial diseases worldwide; therefore this study recommends that every country should consider antibiotic resistance as a public health priority by (1) creating awareness on rational Antibiotic use through education, (2) reducing infection through effective sanitation and hygiene control in hospitals with strong Biosafety and biosecurity in animal farms, (3) Imposing strong regulation to limit accessibility of antibiotics over the counter prescription, (4) Strengthening Lab based Diagnosis and Surveillance, (5) Adoption of "One health approach" is very important through multisectoral involvement, information sharing and networking.

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Supporting information

Supporting Table 1. Risk factors for development of antibiotic resistant bacteria in Africa

Factor category	Factors	Reasons
Behavioral facrors	Inappropriate/irrational antibiotic use in Human	Poor prescription and dispensing practice, Non adherence to dose and self-medication, Patient request without prescription foam, low KAP.
	Inappropriate/irrational antibiotic use in Animal	Poor farm management, self-treating their animals, non-adherence to dose and withdraw period.
	Animal-Human movement and contact	Importation and Travelling.
	Poor Hygiene and Sanitation	Low KAP,
	Poor Antibiotic storages	Low KAP,
	Poor Waste disposal	Low KAP, high infectious wastes are produced
Environmental factors	Absence of regulation, week enforcement	Drug quality control, accessibility and treatment guideline
	Poor Laboratory capacity for Diagnosis and Surveillance.	Lack of Equipments, skilled personnel, Lack of data sharing
	Access to health services.	Poverty, out of stock drug.
	Lack of collaboration and sharing of data/information.	Poor information , communication and intersectoral networking
	Social-Economic and Politics.	Political instability/war, conflicts.

***** Knowledge Altitude and Practice (KAP).

Supporting Table 2. Strategies efforts for control of Antibiotic resistance in Africa

Control strategy	Classification of strategies	Strategy outcomes
Behavioral change	Continuing education and Antibiotic Stewardships Program (ASP) to health workers.	Increased KAP on rational antibiotic use among health workers and Veterinarians
	Education intervention to livestock keepers and patient/public.	Increased KAP on adherence to dose regime among livestock keepers and pmatients
Good governance	Political willingness to Formulation of policy/action plan on AMR control	Increased number of countries with action plan from 1 country in 2015 to 9 countries in 2017.
	Drug quality control and enforcements of regulation	*****NMRA is present to all counties in sub Saharan except Morocco.
	Laboratory capacity building and strengthening surveillance system	
	Infectious disease control and prevention (Vaccination)	Reduced outbreak of infections, reduced antibiotic use

*(KAP) Knowledge Altitude and Practice, (NMRA) National Medicine Regulatory Authority