One Health Approach and Antimicrobial Resistance: From Global to Ethiopian Context

Dejen Nureye1*, Mohammed Salahaddin1,2 and Workineh Woldeselassie1

1Department of Pharmacy, College of Medicine and Health Sciences, Mizan-Tepi University, Mizan Campus, Southwest, Ethiopia
2Department of Biomolecular Sciences, Pharmacology division, University of Mississippi, United States of America

*Corresponding Author: Dejen Nureye, Department of Pharmacy, College of Medicine and Health Sciences, Mizan-Tepi University, Mizan Campus, Southwest, Ethiopia.

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Abstract

Recently, antimicrobial resistance is considered as a global health crisis. Some are thought that we are now in post-antibiotic era. Despite data gaps are largest; it creates particularly significant intimidation to low- and middle-income countries. Many factors are responsible for the development of resistance to antimicrobials by microorganisms. Weak regulations and usage inaccuracies are the major causes for the occurrence of antibiotic resistance. In the last three decades, greater than thirty new infectious diseases, most originated from animals, have been emerged. There is also rising of antimicrobial consumption across the world. The growth of human populations and an increase in contact with wildlife contribute to the spread of resistance and making it a global health concern. Since there are many routes by which drug metabolites and resistant microbes can disseminate among humans, animals and the environment, One Health Approach is urgently required to address antimicrobial resistance in global, national and local level, including Ethiopia. Internationally, the worst threat comes from the emergence and rapid spread of multi-drug resistant Gram-negative bacteria. Once again, an intercontinental, interdisciplinary and multiple approaches should be taken to combat this problem among worldwide nations with special emphasis in developing countries encompassing Africa and Ethiopia.

Keywords: Antimicrobial Resistance (AMR); Ethiopia; Low- and Middle-Income Countries (LMIC)

Introduction

Antimicrobial resistance (AMR) was accepted as a global health threat in the United Nations General Assembly call for action in 2016. It can complicate the therapy of infections so that leading to increased deaths and health care costs. According to the World Health Organization (WHO) appraisal on AMR held in 2014, an estimated 700,000 people die each year globally due to antimicrobial resistant infections [1]. Over the past 30 years, more than 30 new infectious diseases have emerged. Around 60% of all human infectious diseases known so far and about 75% of emerging ones have arisen from animals. Increasing in contact between habitats of human and wild animals is introducing the risk of our exposure to new bacteria and viruses [2]. This indicates the transfer of resistant pathogens in both directions and the increment of antimicrobial consumption that drives the development of bacterial resistance naturally. Even though surveillance systems have been established in the developed world, disease causing microbes are not restricted by intercontinental borders, and the occurrence of resistance in any nation poses an international threat [3]. According to Hedman and his co-workers there is a leak out of AMR to developing countries with no back history of antimicrobial use in agricultural sector [4]. So that Thakur and Gray from North Carolina reminded that surveillance must be a universal “One Health” effort to resolve one of the today’s most remarkable challenges to human, animal and environmental health [3].

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AMR has attained its end stage, and some are thinking that we are currently in post-antibiotic age. This has been supported by new reports from China, India and USA [5-7]. Active infections kill 4000 people a day worldwide, more than AIDS does. But the notion that a quarter of the global population harbors silent tuberculosis is “a fundamental misunderstanding” [8]. The ability of genome evolution and the spread as well as emergence of new resistance mechanisms have compounded the paucity of new antibiotics while escalating the crises posed by drug-resistant bacteria. It is estimated that annually 10,000,000 human lives will be in danger by the year 2050 if we don’t succeed in halting the rise of resistance to antimicrobials [9]. AMR creates particularly significant trouble to low- and middle-income countries (LMIC) due to the health-care problems these nations face, and a raise in small-scale intensive animal production, worsen by poor sanitation system [10]. According to the first study to quantify the burden of poor quality health systems worldwide, an estimated 5,000,000 deaths per year in LMICs is the result of poor quality care, with a further 3.6 million the result of inadequate access to care [8]. In Ethiopia, reports indicate that there are wide practices of overuse and misuse of antimicrobials by health professionals, animal husbandry operations and drug consumers. These, coupled with the rapid spread of resistant microbes and poor surveillance, have exacerbated the situation [11].

An increase in AMR burden acquaintances with 65% increase in antimicrobial use in humans within 2000-2015 across 76 countries and with a projected 67% increase in consumption by 2030 [12-14]. Globally, the availability and utilization of last resort drug (colistin and carbapenem) to treat Gram-negative bacteria have been increased extraordinarily. In fact, antibiotic use is sharply increased in many LMIC including Africa [15]. At country level, the main drivers of increased antibiotic use are raising incomes, insufficient investment in public health capacity, and a noteworthy background of infectious diseases [16]. Every 10 min, almost two tons of antibiotics are used around the world, all too often with violation of rational drug use [17]. Inappropriate use of these drugs increase AMR; as a result, every ten minutes a patient dies in the Europe or USA [18,19]. Such figures are unknown in other jurisdictions, but they are likely to be substantially higher in Asian and African countries [10]. This meeting report aims to contribute our share to the fight against AMR. It gives an insight on the burden of AMR at global and local level. It may help to fill gaps of information on AMR from Africa and Ethiopia. We tried to present brief concepts regarding causes and drivers of AMR. The report also describes the means of AMR spread by showing its inter-continental and multi-sectorial nature. More importantly, we mention strategies to intervene AMR through one health approach including our suggestions for situations in Ethiopia.

Countries and antimicrobial resistance

Data gaps are largest in nations where health systems are weakest. As a result, drug-resistance burden in LMIC remains poorly described, but appears to be greater in high-income countries [20]. Recently, a systematic review done on AMR in Africa revealed that AMR data was not available for 40% of the countries in the continent [21]. Even if various data are available on AMR in Ethiopia, they are fragmented and not presented in an organized way to address the existing problem of the country [11].

At the global level, the worst threat comes from the emergence and rapid spread of multi drug resistant (MDR) Gram-negative bacteria. It is a common concern in intensive-care units (ICU) in Europe and Latin America. In Arabian Peninsula, the proportion of MDR Gram-negative bacteria exceeds 50% in some hospitals, with constant rising of carbapenem-resistant and extended-spectrum beta-lactamase (ESBL) producing pathogens [22,23]. Despite the national surveillance system have been in place, many hospitals across the world lack the necessary resources for the implementation of successful infection prevention and control measures [24]. They also lack technique to execute antimicrobial stewardship programmes. The prevalence of beta-lactamases, which have the capacity to degrade carbapenems, among healthy population in India has been estimated as 7.4% and its incidence in ICU patients as 27.4% [25]. Other forms of resistance (unrelated to β-lactam antibiotics) by Gram-negative bacteria are also becoming serious in India and in other countries, with resistance rates as high as 73% against fluoroquinolones in *Escherichia coli* [26]. AMR document presented by 22 WHO countries has been revealed that resistance to penicillin was ranged from 0 - 51%. Resistance for ciprofloxacin by *E. coli* in urinary tract infections (UTIs) was ranged
from 8 - 65%. Elevated level of resistance was also existed in bacteria that have been considered as priority pathogens by the WHO (Table 1). Around 75% of Acinetobacter isolates obtained from blood in South Korea were found to be resistant to carbapenem antibiotics [27].

<table>
<thead>
<tr>
<th>Priorities</th>
<th>Antibiotics</th>
<th>Non-susceptible Bacteria</th>
</tr>
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<tbody>
<tr>
<td>Priority 1: Critical</td>
<td>Carbapenem</td>
<td>Acinetobacter baumannii</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pseudomonas aeruginosa</td>
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<tr>
<td></td>
<td></td>
<td>Enterobacteriaceae</td>
</tr>
<tr>
<td></td>
<td>3rd generation cephalosporin</td>
<td>Enterobacteriaceae</td>
</tr>
<tr>
<td>Priority 2: High</td>
<td>Vancomycin</td>
<td>Enterococcus faecium</td>
</tr>
<tr>
<td></td>
<td>Methicillin</td>
<td>Staphylococcus aureus</td>
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<tr>
<td></td>
<td>Clarithromycin</td>
<td>Helicobacter pylori</td>
</tr>
<tr>
<td></td>
<td>Fluoroquinolone</td>
<td>Campylobacter</td>
</tr>
<tr>
<td></td>
<td>3rd generation cephalosporin</td>
<td>Salmonella spp.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neisseria gonorrhoeae</td>
</tr>
<tr>
<td>Priority 3: Medium</td>
<td>Penicillin</td>
<td>Streptococcus pneumoniae,</td>
</tr>
<tr>
<td></td>
<td>Ampicillin</td>
<td>Haemophilus influenzae</td>
</tr>
<tr>
<td></td>
<td>Fluoroquinolone</td>
<td>Shigella spp.</td>
</tr>
</tbody>
</table>

Table 1: WHO priority pathogens list for research and development of new antibiotics [28].

In spite of inadequate laboratory facilities to monitor AMR; available data suggest that the WHO African Region shares the global trend of increasing resistance. Notable resistance has been reported for HIV viruses, Plasmodium species, Shigella species, Salmonella species, Vibrio cholerae, Neisseria meningitides, N. gonorrhoeae and Mycobacterium tuberculosis [29]. The level of resistance to commonly prescribed antibiotics was significant in Africa. Streptococcus pneumoniae was reported as penicillin resistance which is in line with the WHO report. Haemophilus influenza isolates (34.0%) were resistant to amoxicillin. E. coli were found to be resistant to amoxicillin, trimethoprim and gentamycin. Carbapenem resistance was common in Acinetobacter species and Pseudomonas aeruginosa which is consistent with WHO result but unlikely not common in Enterobacteriaceae. Furthermore, gaps were seen in AMR diagnostic standardization and reporting and use of available information to optimize treatment guidelines [21].

In Malawi, approximately 100% of N. gonorrhoeae detected from genital isolates were resistant (non-susceptible) to ceftriaxone and roughly 15% were non-susceptible to azithromycin [27]. High level of AMR among Gram-negative infections for commonly used antibiotics has been reported in East Africa including 20 - 47% to gentamycin, 46 - 69% to ceftriaxone, and 50 - 100% resistance to ampicillin and cotrimoxazole. Much of the resistance reported was by Klebsiella species and E. coli. Among Gram-positive infections, extensive resistance was reported for ampicillin (100%), and gentamicin and ceftriaxone (50 - 100%) with Methicillin-resistant Staphylococcus aureus (MRSA) prevalence ranging from 2.6 - 4% [30].

Recent analysis on E. coli resistance patterns in Ethiopia has been revealed that 45.38% of the study samples were antibiotic resistance. The highest resistance of E. coli was reported for ampicillin (83.81%) and amoxicillin (75.79%), whereas only 13.55% of E. coli isolates showed resistance to nitrofurantoin [31]. A study from surgical site infections at two government hospitals in Addis abeba had

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shown that out of 107 samples, 84.1% were culture positive and 104 organisms were isolated. More than 75% of the Gram-negative isolates were MDR and pan-antibiotic resistance was observed in 34.8% and 12.5% of Acinetobacter species and E. coli, respectively [32]. More recently, a cross-sectional study conducted at Hiwot Fana Specialized University Hospital in Harar has been investigated that E. coli is becoming resistant for 3rd generation cephalosporins, such as ceftriaxone and ceftazidime [33]. A high prevalence of Salmonella species resistant against amoxicillin, ampicillin and chloramphenicol has been observed in Karamara Hospital, Jigjiga, East Ethiopia [34].

**Etiology of antimicrobial resistance**

Nowadays, a lot of factors are played as causes for AMR. This includes insufficient regulations and usage inaccuracy, lack of awareness in best practices which steers unwarranted use of antibacterials, use of antimicrobials as a poultry and farm animal growth promoter and online marketing which promote the availability of unfit antibiotics very accessible. A number of researches have showed that indications, drug choice and treatment duration are improper in 30 - 50% of the cases [35-37]. Overuse of antimicrobials in human, animal and agriculture sector is the main cause of resistance evolution. Antibiotics kill sensitive bacteria but allow resistant microbes to remain and then replicate and flourish through natural selection. Though overuse is badly unsupported, antibiotics remain overprescribed across the world [38,39].

**Drivers of antimicrobial resistance transmission**

Microbes faced with antibiotic selection pressure boost their fitness by gaining or expressing resistance genes, and then share those genes with new bacteria through gene transfer by means of mobile genetic elements such as phages, plasmids, naked DNA or transposons. Hence, use and overuse of antimicrobials are very imperative drivers for the occurrence of resistance. The other major drivers are factors that facilitate or support the dissemination of resistant bacteria and their genes locally and globally [40]. These include:

1. Poor infection prevention and control. For example, at the community level resistant pathogens such as Enterobacteriaceae is transmitted through feco-oral route due to sanitation failure. Community acquired MRSA is usually transmitted due to unhygienic hospital settings. Unprotected sexual contact is a source of transmission for resistant N. gonorrhoeae [41-43].

2. Environmental contamination. If antibiotics are used in anywhere, there will be reservoirs of resistance in water, soil, plants, wildlife, and many other ecological niches due to pollution by sewage, waste of pharmaceutical industry, and manure runoff from farms [44,45]. This is true because antimicrobial residues and their metabolites are constituents of human sewage, livestock manure, and aquaculture, along with fecal bacteria and resistance genes. In the agriculture sector, metals are used as microbicides and may contribute critically to resistance development [41].

3. Geographical movement of infected humans and animals. Bacterial genes and the bacteria itself would travel comparatively easily within and between us, animals, and the environment. Irrational use of antibiotics as growth promoters in farm animals is associated with the transmission of resistance to humans through animal products. The considerable pathogens we acquire from animal products are Salmonella species and Campylobacter species [46-48].

**Antimicrobial resistance and its spread**

Rising of human and animal populations, international travel and trade as well as contact with wild life all contribute to AMR spreading and making it a worldwide health concern. There are many pathways by which drug residues and resistant bacteria can disseminate among humans, animals and the surroundings. Therefore, beyond international collaboration, a “One Health Perspective” is urgently needed as AMR involves a dynamic and complex network of interactions [10]. High concentration of antibiotics and resistant bacteria has been documented in effluents released from hospitals and drug manufacturing sites in developing countries. In some situation, the water
what we drink can also act as a dissemination media, as this was evidenced by carbapenem-resistant Enterobacteriaceae noticed in nine out of nineteen samples of the New Delhi chlorinated water supply in India [49-51]. Food-borne diseases by resistant *Salmonella* and *Campylobacter* bacteria are well recorded in people; hence food chain also has a task in spreading resistance [52,53]. Food-borne *E. coli* associated with critical ESBLs is frequently found in retail meat. For instance, a 2013 survey done in USA revealed a 65% prevalence of *E. coli* in retail chicken products [54]. Some of these were closely resembled *E. coli* isolates found in humans. Overall, both Gram-positive and Gram-negative pathogenic bacteria of human origin have been reported in animals [55]. Furthermore, streptomycin, tetracyclines and some other antibiotics are occasionally used for the treatment and prophylaxis of bacterial infections plant in fruits. As a result, some plant origin bacteria acquire resistance through selective pressure. Consequently, we will be exposed to resistant pathogens as we eat this fruit in horticulture [56].

From the above information, we may conclude that adaptations of micro-organisms within one sector are reproducing in any other sectors which mandate "one health perspectives". "One Health Approach" is defined as: the collaborative effort of various medical professions which works locally, nationally and globally to bring optimal health for humans, domestic animals, wildlife’s, plants and the environment. Given the interdependent human, animal, and environmental dimensions of AMR, it is logical to take a One Health Approach when addressing this problem [57]. A tripartite partnership (collaboration between World Organization for Animal Health (OIE), the WHO and Food and Agriculture Organization of the United Nations (FAO)) reflects the "One Health" nature of the AMR challenge and has been proven as a means of successfully addressing animal and public health risks associated with zoonoses and animal diseases [58].

In Ethiopia, the spreading of AMR is almost in a similar fashion with the global aspects. A study done in Addis Ababa revealed that *Salmonella* serotypes were widely distributed particularly in supermarket meat samples and significant proportion have been developed resistance for routinely prescribed antimicrobial drugs both in veterinary and public health sectors [59]. A cross-sectional study conducted in Ambo town revealed 78.1% MDR *E. coli* isolates from visceral organs of chickens [60]. In another cross-sectional study conducted in Kombolcha town among 150 dairy cows, resistant *S. aureus* was isolated from 11 (73.3%) cows with clinical and 29 (42%) cows with subclinical mastitis [61]. Using similar study design, an investigation performed at Gonder town on 55 of oral, intranasal and locally administered herbal medicines revealed that the products contain important bacterial pathogens, including *Shigella dysentery*, *Salmonella* and *Enterobacter* species. More importantly, 125 isolates were found to be resistant to two or more antibiotics indicating the presence of antimicrobial resistant microbes in the environment such as medicinal herbs that are of public health importance [62].

Ethiopia is an agrarian (agricultural) society with over 80% of the population located in rural areas living in close proximity to domestic and wild animals in a sensitive ecosystem. This intense contact can lead to a serious risk to public health, including emerging and re-emerging zoonoses. Antimicrobials used in both humans and animals are similar and can be over-prescribed for therapeutic and prophylactic purposes, and as feed additives, and can cause resistance. Several published and unpublished research data generated from various health sciences universities in Ethiopia indicate that drug resistant bacteria including MDR are isolated from humans, animals, food, water, and other environmental samples. These need a multidisciplinary intervention through a One Health Approach [11].

**Global and Ethiopian initiatives to fight against AMR**

Few nations developed nationwide strategies and implemented their tactics to diminish this risk as early as 1990s. Little of them fruitfully reduced antibiotic expenditure in animals and humans, and local spread and emergence of antibiotic resistance while majority of nations tackled this crisis only in more recent times [10]. The World Economic Forum held in 2013 affirmed that antimicrobial agents (one of the most efficient and common tools to guard human life) may not be readily obtainable and accessible in the near future [63]. Ministers of science present at the G8 Summit in 2013 identified AMR as the major health insecurity of the 21st centuries [64]. India barred non-prescription sales of antibiotics in March 2014 while the WHO released its first international report on antimicrobial resistance in

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April 2014 [2]. United States publicized a five year plan to battle against AMR locally and internationally in September 2014. Furthermore, USA has established a Presidential Advisory Council on combating resistant bacteria [65].

In 2015, a lot of activities were under gone across the globe. The WHO launched Global AMR Surveillance System (GLASS) to establish a standardized GLASS and so far 40 countries are participating [27]. Once more, the G7 meeting called for rigorous global collaboration in this area, endorsing One Health approach and the WHO's global action plan including strategic objectives [66,67]. In existing condition analysis released in 2015 by the WHO, the imminent international trend is found to be encouraging and there are best achievements and performances that should be shared [68]. This impetus gathers 68 global experts at the 5th biennial World Healthcare-Associated Infections Forum in Annecy, France, June 2015. Experts come together to deal on how to control AMR in LMICs through a “One Health” point of view.

At the OIE’s 83rd General Assembly in 2015, all 180 Member Countries made a commitment to support the WHO Global Action Plan on AMR and the development of National Action Plans. In 2016, the 84th General Assembly of OIE adopted Resolution no. 36, which mandates the organization to move its AMR activities into a strategy. The OIE strategy is aligned with the WHO Global Action Plan and takes the importance of a “One Health Perspectives” into consideration. This same year, the United Nations General Assembly adopted a political declaration aimed at combating the global threat posed by AMR and confirmed the “One Health Approach” in line with the Global Action Plan. Three Directors General of the tripartite partnership (OIE-FAO-WHO) were present and addressed the General Assembly to support the declaration [58].

In 2009, the Ethiopian Drug Administration and Control Authority (DACA) in collaboration with Management Sciences for Health/Strengthening Pharmaceutical System (MSH/SPS) carried out a formal situational analysis to comprehend the status of resistance and trends in the use of antimicrobial agents in Ethiopia. This report concluded that high level of antibacterial resistance was recorded despite data were limited and called for a national approach to prevent further AMR progress and spread in Ethiopia. Subsequent work identified weak microbiology laboratory capacity and the lack of a systematic national AMR surveillance system to be primary limitations to effective AMR response in Ethiopia. In particular, laboratory-based surveillance that detects resistance patterns and monitors their spread was called for. Then, according to the 2014 WHO antimicrobial resistance surveillance report, Ethiopia has committed to join global partners in the detection and prevention of AMR. In 2015, that same year the WHO released its Global Action Plan, the Federal Democratic Republic of Ethiopia released a Strategy for the Prevention and Containment of Antimicrobial Resistance in Ethiopia (Table 2) [1].

<table>
<thead>
<tr>
<th>Objectives</th>
<th>Means</th>
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| Raise awareness and improve education on antimicrobial use, resistance prevention, and containment via communication and training | • Improve awareness, education, and empowerment of clients and the community  
• Support education and training of human and animal health care professionals |
| Strengthen the knowledge and evidence on antimicrobial use and resistance via one-health surveillance and research | • Support surveillance of antimicrobial use and AMR microbes  
• Establish (strengthen) capacity of national, regional, and health facility laboratories  
• Support basic and operational/intervention research |
| Improve infection prevention and contain the spread of resistant microbes in human and animals and health care settings via individual and environmental sanitation and hygiene | • Strengthen infection prevention and control programs  
• Strengthen infection prevention and control practices in health facilities  
• Promote infection prevention and control practices in communities |
| Optimize the use of antimicrobials in human and animal health through effective stewardship practices | • Promote optimal prescribing and dispensing of antimicrobials  
• Promote adherence to treatment and proper use by clients and the public  
• Rational antimicrobial use in animal health and food production |
| Strengthen and establish national alliances and partnerships, management and governance arrangements, and resource mobilizations for the prevention and control of AMR at all levels | • Strengthen (establish) a national alliance for the prevention and containment of AMR  
• Resource mobilization  
• Strengthen national and international networks and collaborations  
• Governance and partnerships |

Table 2: Strategic objectives to prevent and control AMR in Ethiopia [69].

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In 2016, Global Health Security Agenda (GHSA) and Ethiopian FMoH joint external evaluation declared that in Ethiopia both the animal and public health sectors have AMR testing capacity. Based on the joint assessment, Ethiopia has to strengthen AMR surveillance systems, increase AMR laboratory capacity, improve infection prevention and control activities, foster inter-sectorial collaboration and implement an Antimicrobial stewardship program within the animal health and public health sectors. In line with this, a national AMR advisory committee and AMR sub-technical working groups which include individuals from human, animal and environmental sectors have been established [11].

In 2017, the Ethiopian AMR Surveillance Plan was developed and launched by the Ethiopian Public Health Institute (EPHI) under the FMoH with support from the Ethiopian Food, Medicine and Healthcare Control and Authority (EFMHACA) and international partners including the WHO, CDC, American Society for Microbiology (ASM) and Ohio State University (OSU) Global One Health initiative. In July, AMR surveillance was officially launched in at four sentinel surveillance sites whereby submit isolates and data to the national reference laboratory at EPHI. Priority pathogens for surveillance most are gram-negative bacteria are listed in table 3 [1].

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Priority surveillance pathogens</th>
<th>Remark</th>
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<tbody>
<tr>
<td>Urine</td>
<td>Escherichia coli</td>
<td></td>
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<tr>
<td></td>
<td>Klebsiella pneumoniae</td>
<td></td>
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<tr>
<td>Wound (purulent drainage)</td>
<td>Staphylococcus aureus</td>
<td></td>
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<tr>
<td>All specimens</td>
<td>Acinetobacter spp. Carbapenem Resistant Bacteria</td>
<td></td>
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<tr>
<td></td>
<td>Pseudomonas aeruginosa</td>
<td></td>
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<td></td>
<td>Enterobacteriaceae</td>
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Table 3: Priority surveillance pathogens by specimen for reporting to Ethiopia AMR Surveillance.

Annual report by EPHI, the first year of AMR surveillance implementation (July 2017 - August 2018), illustrates the progress made after the establishment of Ethiopia’s Antimicrobial Resistance Surveillance System. The report had mention that more or less 1716 urine specimens and 323 pus (abscess and wound) specimens from a total 184 patients were processed at Tikur Anbessa Specialized Hospital (TASH) during this one year. *E. coli* was the most common pathogen isolated from urine and the second most common pathogen in pus. The percentage of these *E. coli* isolates that showed resistance to antibiotics tested is depicted in figure 1. Most of the isolates demonstrated resistance to broad-spectrum antimicrobials with the peak resistance in ampicillin (98%), amoxicillin-clavulanic acid (90%), and co-trimoxazole (77%). A significant number of isolates were also resistance for 3rd generation and 4th generation cephalosporins including cefazidime (53%) and cefepime (68%), respectively [1].

![Figure 1: Proportion of E. coli isolates (N = 184) from urine and pus showing resistance by antibiotic tested at Tikur Anbessa Specialized Hospital, September 2017 - July 2018.](image-url)
K. pneumoniae detected between September 2017 and July 2018 from a total of 115 patients at TASH was found to be the second most common pathogen isolated from both urine and pus specimens. The proportion of these K. pneumoniae isolates that showed resistance to the antibiotics used for the test is presented in figure 2. The large number of isolates showed resistance to broad-spectrum antibiotics with maximum resistance in amoxicillin-clavulanic acid (92%) and co-trimoxazole (88%). High levels of resistance were also seen among the 3rd and 4th generation cephalosporins, namely ceftazidime (89%), cefepime (87%) and ceftriaxone (85%). A considerable level of resistance against ciprofloxacin (59%) was also revealed. Similar patterns of resistance were found between the E. coli and K. pneumoniae isolates; however resistance to gentamicin appears to be higher in K. pneumoniae (79%) isolates than the E. coli isolates (34%) [1].

**Figure 2:** Proportion of K. pneumoniae isolates (N = 115) from urine and pus showing resistance by antibiotic tested, Tikur Anbessa Specialized Hospital, September 2017 - July 2018.

**Approaches to tackle antimicrobial resistance**

**Education, Training, Surveillance and Research**

We could enhance awareness and understanding of AMR through effective communication, education and training using various opportunities including professional development programs (veterinary medicine, human medicine) and health promotion and health protection programs offered by public and animal health organizations [57]. Continued education of medical students concerning the conventional prescription of antimicrobials is essential [2,70]. Reinforced teaching as well as providing training for nurses, midwives, dentists, pharmacists and animal health professionals is also required as these professionals may be involved in prescribing antimicrobials or influence prescriptions in some conditions [71,72]. The application of modern technologies in education and training was proved to be highly precious. A number of open access Online Courses can reach a broad range of professionals in our globe and smart phones offered very useful platform for antimicrobial stewardship applications [73,74].

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In some European countries, public awareness campaigns targeting antibiotic use have been reduced inappropriate use and consequently bacterial resistance [75,76]. The WHO has recommended the inclusion of antimicrobial use and resistance in school curricula. However, simply creating awareness and improving knowledge has not been known as the best solutions rather promoting behavioral change should be in place in human health, animal health, and agricultural practice [77]. In Ethiopia, a lot of observable irrational practices on antimicrobial use are present in the ground among the local community and health institution which needs intervention. Educating and provide training for the medical, and para-medical professionals particularly health extension workers can be an indispensable act to address AMR and its contributing factors in the public at large. Infoming the population about AMR through the government and public radio and television should be mandatory to retard the progress.

Research and surveillance are fundamental because they discover AMR problems and ways to prevent them [2,67]. AMR surveillance using One Health Approach should include sampling of appropriate microbes from specimens collected in various human, animal, and environmental settings including hospitals, extended-care and community settings, veterinary clinics, farms, food, and the environment [78-80]. Surveillance on antimicrobial use, including antibiotic consumptions, should also be undertaken in human, veterinary, and agricultural sectors [78,80,81].

Antimicrobial Stewardship in Human and Animal Health

Cautious use of antibiotics on hand must be precedence since their utilization is one of the major drivers of AMR. Restriction or prohibition policies have been effective in reducing resistance in some settings [16,82,83]. Regardless of strong evidence about the cost-effectiveness of stewardship interventions, the huge amount of AMR related resources are currently allocated for the development of new antimicrobials. This might not be the most excellent tactic, because if we develop novel drugs and carry out little intervention activities in all other areas, history is likely to repeat itself; any new agent will lose its efficacy as soon as resistance develops in bacterial strains [84].

In hospitals, prophylactic antibiotics should be the first target of stewardship programs. Even though this practice is necessary for certain preoperative and operative procedures, treatment should not extend beyond 24h and commonly a single dose is adequate [85]. Referring to a study done in Jimma University Medical Center (JUMC), the prevalence of antimicrobial use-related problems (mostly dose too low followed by dose to high) may be high in Ethiopia; particularly in surgical antibiotic prophylaxis use compared to therapeutic, which earn rapid action to safeguard those antibiotics in the market. Irrational use resulted in high extra cost as a consequence. An indication of antibiotic use for prophylaxis, a dual indication (prophylaxis and treatment), polypharmacy, greater than 2 antibiotic exposures during a hospital stay and duration of hospital stay for > 21 days were found to be independent predictors for antibiotic use-related problems [86].

According to Gebretekle, et al. (2018), Ethiopian physicians and pharmacists perceived that antimicrobial stewardship is a key strategy to limit AMR and favored an approach based on education, access to local AMR surveillance data, and prospective non-confrontational feedback. However, this study revealed that there were incorrect perceptions from physicians’ that drug resistant Gram-positive infections (especially MRSA) are of greater concern than drug resistant Gram-negative infections, which is likely directly linked to the unnecessary use of vancomycin. It also highlights that guidelines based on literatures originated from high-income countries negatively affect the prescribing behaviors in LMIC and can weaken stewardship efforts. Although most physicians agreed on the importance of diagnostics in stewardship, they focused on the need for institutional empiric treatment guidelines and omitted to comment on improving diagnostic capacity. Thus, implementing microbiological testing and focusing educational efforts on appropriate use of diagnostic tests for infections constitutes a major paradigm shift for LMICs including Ethiopia. Pharmacists were more likely to identify inappropriate combinations, doses or other parameters than physicians, but tended not to communicate their observations to the prescribing physician for the simple reason that these professional groups hardly ever interact. So, including clinical pharmacists within the treating teams and facilitating their participation in clinical rounds for example, could lead to significant improvements in antibiotic prescriptions [87].

Citation: Dejen Nureye, et al. "One Health Approach and Antimicrobial Resistance: From Global to Ethiopian Context". EC Pharmacology and Toxicology 8.9 (2020): 59-75.
In different nations, bans policies have attained inspiring results in decreasing AMR in the veterinary settings [88]. By implementing stewardship programs in the veterinary sector, the quantity of antimicrobials consumed in animal meat was diminished by half from 1994 to 2013 in Denmark [89,90] and by 56% in Netherlands [91]. Thirty months later of withdrawal of ceftiofur (one of the 3rd-generation cephalosporins for veterinary use) in Canada, resistance levels was reduced by 50% in S. enterica from chicken meat and humans and in retail chicken E. coli [92]. In Australia, fluoroquinolones were not approved for livestock use. As a result, its resistance in E. coli, Salmonella species or Campylobacter species is absent in food animals. Quinolone resistance is also absent or only at very low levels in domestically acquired Salmonella or Campylobacter infections in people [93]. Restriction strategy on deployment of medically crucial antimicrobials for growth promotion has also been used in the European Union, Korea and United States [79,94,95].

**Infection Prevention and Control Measures**

Weak infection prevention and control practice is one of the contributing factors to emergence and spread of AMR in the health facility as well as in the community. Hence, applying basic measures such as appropriate use of personal protective apparatus, hand hygiene, disinfection of medical equipment, cleaning of the public and healthcare environment, and control of patient and visitor crowd are necessary to minimize the extension of AMR. A report tells that utilization of wipes or antiseptic baths have a major impact on dropping Acinetobacter incidence [96]. After promotion and deployment of hand hygiene across 179 countries, 50% reduction in hospital-acquired infections has been occurred, this contributed to saving about 8 million lives each year [97]. Practicing hand hygiene in hospitals has played a key role in the turn down of MRSA cases in Australia [98]. Vaccination and hygiene-related rules have made a remarkable improvement in India. The country vowed to become “open defecation free” by 2019, with plans to construct 120,000 toilets in rural India [10]. Coming to Ethiopia, literatures express the presence of gaps regarding knowledge and practice of infection prevention among health care workers [99-101]. As a conclusion, health professional should prevent infections by assuring materials, equipments, hands and environments are hygienic. They should also educate the patients about the methods or ways of preventing infection (vaccination, hand washing, safer sex, covering nose and mouth when sneezing).

**Novel Interventions**

Latest drugs against resistant gram-negative bacteria should join the market in the near future but it is unlikely [102]. Therefore, serious MDR infections necessitate the use of combination treatment (for example, colistin-imipenem-tigecycline combination to treat carbapenem-resistant bacteria) as well as old drugs. Unluckily, evidences present about the effectiveness of these therapies are inadequate [103,104]. On the other hand, resistance to these last-resort groups of antibacterials is also rising in quite a lot of gram negative bacteria which demands immediate large-scale studies in order to decide best choice of treatments [105,106]. There is also urgent requirement for alternative options to circumvent AMR. Nanoparticles can be used in different ways as therapeutic management of infections. They can be coupled with existing antibiotics for augmentation of their physiochemical behavior against drug-resistant pathogens. The colloidal forms of zinc, silver, copper, and titanium can itself be used as antimicrobial drugs [107,108]. Moreover, probiotics, prebiotics, drugs targeting bacterial communication/virulence, antibodies/vaccines, and therapies based on phage/its enzymes are taken as alternatives to antimicrobials. A novel study indicates promising avenues in an innovative approach for developing a vaccine against Plasmodium vivacious, the most prevalent human malaria parasite outside sub-Saharan Africa [8]. Antibiotic resistance is of major community health concern in Ethiopia. For this reason, the idea of using phage should be taken into consideration and health professionals should have to demonstrate preference towards bacteriophage therapy [109]. Besides, substantial academic efforts have to be made in Ethiopia to further optimize preliminary studies done on antimicrobial plants and to integrate traditional medicines with modern health care systems.

**Conclusion**

Although data gaps were exist, the burden of antimicrobial resistance is increasing at global level with creating more threat in developing countries including Africa. It is a problem in human and animal medicine. We reach a stage where multi-drug resistant pathogens
mainly gram negative bacteria are becoming out of control even by the last-resort antibiotics. Our environment is founded to have a great role in holding resistance genes and disseminating of resistant microbes from human to animals and vice versa. Now it is time to involve many sectors to tackle this international health insecurity through one health policy. Developing nations should revise their strategies and polices to stop the progress of antimicrobial resistance. Governments should think about the deployment of new interventions to turn the current situations. Strong surveillance system should be in place in low income countries like Ethiopia.

**Conflict of Interests**

The authors declared there is no any conflict of interests in this work.

**Authors’ Contributions**

Dejen Nureye conceptualized and drafted the manuscript. Mohammed Salahaddin and Workineh W/selassie reviewed the draft and add significant intellectual content. All authors have read and approved the final version of the manuscript.

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