


High Burden of Antibiotic-Resistant Bacteria from Wastewater in Ethiopia: A Systematic Review

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Background: Currently, antibiotic-resistant bacteria (ARB) have become a serious global problem and considered as One Health challenge. Despite, wastewater contains a wide range of microbial pathogens and plays a significant role in the dissemination of ARB in the environment. However, it is the most overlooked in developing countries, particularly in Ethiopia.

Methods: Different article searching devices like PubMed, Web of Science, Scopus, and Google Scholar were used to select research article by using the key terms. Hand search using a reference list is also used to retrieve the article. Preferred reporting items for systematic review and meta-analysis (PRISMA) guideline was used for literature search strategy, selection of publications, data extractions, and reporting result for the review process.

Results: A total of seven original research articles were included from a total of 35,999 research articles obtained from the different searching techniques. The selected articles were used, the same study design and laboratory methods to isolate different types of resistant bacteria. All studies isolate pathogenic bacteria and highlighted the presence of resistant bacteria for multiple antibiotics.

Conclusion: Multidrug resistance (MDR) bacteria were isolated from wastewater. This is an indication for the possible presence of pathogenic organisms that are discharged into the receiving environment probably waterbodies (lake and rivers) posing risk to public health, animal, and environment. In Ethiopia the coverage of safe water supply is poor. This obligated the society to use untreated water from rivers, lakes and others. The outlet of most urban sewage from hospital, hotels, and industries are directly running to those water bodies due to lack of proper wastewater management system. Therefore ARB is a direct threat to those people that use those water bodies.

Keywords: antibiotic resistance, antibiotic-resistant bacteria, wastewater, Ethiopia

Introduction

During the last century, detection of microorganisms as causes of infections and findings of antibiotics as effective therapeutic agents have promoted to safeguard the wellbeing of the people and animals.¹ Despite the innovation of many antibiotics, the emergence of antibiotic-resistant bacterial (ARB) strains becomes the highest global public health agenda. Tackling the spread and emergence of antibiotic resistance are a high priority for the World Health Organization (WHO). Antimicrobial Resistance (AMR) is a global threat to the effectiveness of antimicrobials, challenging their value for both the prevention and treatment of infections.² Antimicrobial resistance is a result of complex interacting factors or resistance network;³ that links clinical factors (animal and human health) and

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environmental factors (antimicrobial drug and AMR organism in the soil and waterbodies).⁴ Aside from unselective use of antibiotics in human medicine, farming and agriculture, inappropriate wastewater disposal disrupts the microbial balance in favor of resistant bacteria by selective pressure.⁵ Different literature across the world indicates that wastewater is the potential source of resistant pathogens. Wastewater contains some contaminants that result from the mixing of various sources, discharged by domestic residences, commercial properties, industry, agriculture, pharmaceuticals, and hospitals.⁶ The presence of ARB and ARGs within the environment is selected for and enriched by antibiotics found in sewage and agriculture runoff results from indiscriminate and increased use.^{5,6} Wastewater constitutes a way of dissemination of ARB and ARG among human and animal populations and introduced in natural bacterial ecosystems,⁷ where non-pathogenic bacteria serve as a reservoir of resistance gene.⁸ Moreover, if the resistant genes are transmissible, it causes the wide distribution of ARB and their genes. Infections caused by ARB are usually difficult to treat, prolong hospitalization, and increase the cost of treatment.⁹ These conditions become major public health problems especially in developing country including Ethiopia. To limit its public health impact critical evaluation, treatment and periodic assessment of wastewater released to the receiving environment is mandatory. Therefore, this study aims to review research from Ethiopia, done on the resistance pattern of bacteria isolated from wastewater and the environment. The finding obtained from this study is hoped to provide baseline data for policymakers, healthcare workers and local authorities so that these responsible bodies would recognize the need for a wastewater management system, and proper antibiotic usage.

Study Methods

Research Question

This literature review was guided by the questions “What is the burden of antibiotic resistance pathogens in wastewater released to the environment?”

Data Source and Searching Strategies

The First search was done on June 21, 2020, in PubMed, Web of Science, Embase, Scopus, Directory of Open Access Journal (DOAJ), and Google Scholars. Hand search using a reference list is also used to retrieve the

article. The key terms “Antimicrobial-Resistance”, OR “Drug-Resistance” AND “Bacteria” OR “Pathogens” AND “Wastewater” OR “Sewage” were used.

Selection and Eligibility Criteria

A stepwise relevance selection/screening was done. First, all articles not done in Ethiopia are removed. Then, titles and abstracts were considered for screening and to remove duplication. All article seems relevant went through of the full text article observation and review. Studies were eligible for inclusions if they were original article which addresses ARB in wastewater and environment and written in English. The reference lists of all included articles were hand-searched for another relevant article. Finally, the eligible articles were independently screened and reviewed by each author.

Data Quality

The quality of the data was checked by each of the authors for the similarity of study design and inclusion and exclusion criteria.

Summarizing, Analysis and Reporting

A systematic review was performed according to the PRISMA protocol. A data abstraction tool was used to construct data from each article selected for review and presented in a table. A total of 35,999 articles were identified through database searching and hand searching. Twenty-seven (27) research articles were obtained in the initial literature search done in Ethiopia after removing the 5 duplicate articles; the first screening removed 9 articles through observing titles and abstracts. Finally, 13 full-text articles were assessed for eligibility and a total of seven research articles were qualified for inclusion in the review analysis (Figure 1). All research articles were summarized in the table clearly with the key information and findings (Tables 1 and 2). All seven included articles are used the same pathogens and antimicrobials resistance detection methods (culture plus disk diffusion methods and interpreted according to CLSI).

Result

Overview of the Included Research Studies

Based on the selection criteria, a total of seven original research articles were included and all are conducted using a cross-sectional study design. Among the article, two

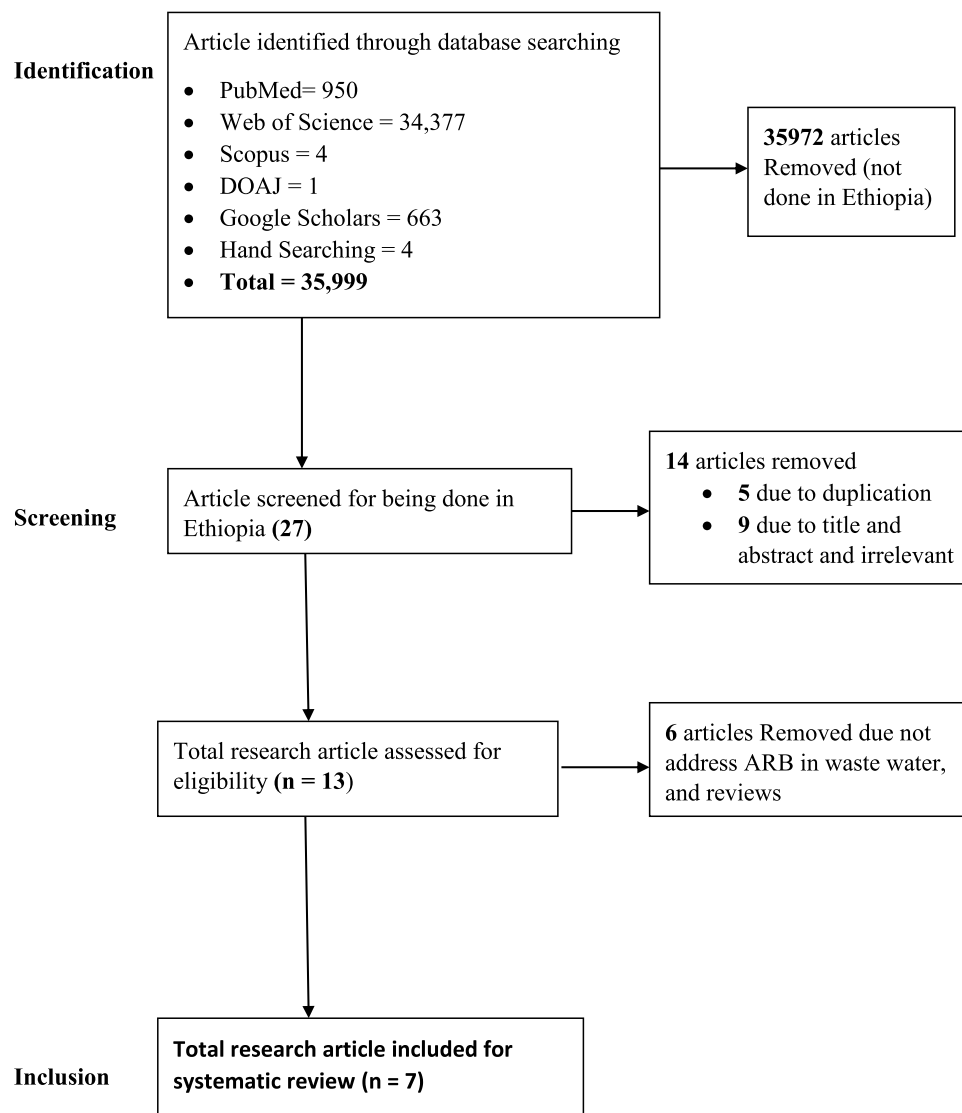


Figure 1 Flow chart of selections of studies that assessed ARB in wastewater released to the environment in Ethiopia.

were done in Southern, Ethiopia,^{10,11} two were done in Gondar, Northwest Ethiopia,^{12,13} two were done in Addis Ababa, Ethiopia^{1,15} and one was from Mekelle North Ethiopia.¹⁶ The included articles were assessed hospital wastewater from the inlet and outlet of oxidation pond,^{11,16} temporary septic tank,^{10,11} Superficial wastewater and different outlet from a different section of hospital,¹² sewage polluted downstream rivers,^{14,15} superficial wastewater from different nonhospital institutions,¹² the surface of bed frames, bedside tables, door handles, floor sinks, chairs and walls of different wards, hospital sewerage system,¹³ hospital sewerage system^{13,15} and Wastewater Treatment Plant (WWTP).¹⁵ Four of the included articles were assessed both gram-negative and gram-positive bacteria,^{10–12,16} the other research assessed

gram negative-bacteria,¹⁴ *Enterobacteriaceae*¹⁵ and Extended Resistant Beta-lactam Antibiotics (ESBL) producing *Enterobacteriaceae*¹³ (Table 1).

Bacterial Isolates

All included studies used different sample sizes to meet their objective (40 composite samples,¹⁰ 24 composite samples,¹¹ 60 grab samples,¹² 384 grab samples,¹³ 90 grab samples,¹⁴ 24 duplicate samples¹⁵ and 40 composite samples¹⁶). Some of the included studies obtained a large volume of indicator organisms from treated hospital wastewater.^{10,11,16} All studies isolate a wide range of bacterial pathogens. The most frequently isolated bacteria were *E. coli*, *Staphylococcal* spp., and *Klebsiella* spp., respectively, from treated final wastewater,¹⁰

Table 1 Description of Relevant Studies Included in Systematic Review

ID	Reference	Study Area	Source of Sample and Year of Sampling	Sampling Point	Study Objective	Key Findings	Recommendation
1	S. dieres et al 2018 ¹⁰	Hawassa University, Southern Ethiopia	Hospital Wastewater (2017)	Inlet and Outlets of temporary collection tank	Effectiveness in the removal of ARB from hospital wastewater	Indicator organism, ARB and MDR bacteria in treated wastewater	Constructed wetland Could be promoted
2	Fekadu et al 2015 ¹¹	Yirgalem and Hawassa, Southern Ethiopia	Hospital wastewater (Dec,2010 - Feb, 2011)	Inlet and Outlets of Pretreated septic tank (Yirgalem) Oxidation pond system (Hawassa)	Assessment of antibiotic and disinfectant resistant bacteria	Indicator organism, Pathogenic and ARB bacteria in the final effluent of wastewater	Proper wastewater treatment before released to receiving environment
3	Moges et al 2014 ¹²	Gondar, Northwest Ethiopia	Hospital wastewater and Nonhospital Environment (2012)	Superficial wastewater and a different outlet from different section of the hospital and Superficial wastewater from different nonhospital institutions	Isolate and characterize public health important bacteria	MDR bacteria in wastewater and high prevalence in hospital wastewater	Proper wastewater treatment plant should be established and improved sanitary measure should be practice.
4	Engda et al 2018 ¹³	Gondar, Northwest Ethiopia	Hospital Environment and Wastewater (2014)	Surface of bed frames, bedside tables, door handle, floors, sinks, waiting chairs and walls of different wards and hospital sewerage system	Magnitude, distribution, and antimicrobial susceptibility of ESBL producing <i>Enterobacteriaceae</i>	High prevalence of MDR bacteria to the commonly used Antibiotics	Hospital should install proper hygiene and rational use of antimicrobials.
5	Belachew et al 2018 ¹⁴	Addis Ababa, Ethiopia	Sewage Polluted Urban Rivers,2017	Downstream of Rivers	Determine the level of drug resistance of gram-negative bacteria	Medically important gram-negative bacteria with a high degree of MDR	Not stated or No recommendations
6	Tesfaye et al 2019 ¹⁵	Addis Ababa, Ethiopia	Health facilities, abattoir, Rivers and WWTP:2017	Hospital sewerage system, Downstream rivers and WWTP	Antimicrobial susceptibility of <i>Enterobacteriaceae</i>	ARB and MDR bacteria in Hospital wastewater, Downstream rivers and WWTP	Hospitals and abattoir Wastewater should be treated. Further studies should be conducted.
7	T. Asfaw et al 2017 ¹⁶	Mekelle, North Ethiopia	Hospital Wastewater (2015)	Inlet and Outlets of Oxidation pond system	Prevalence and drug resistance of bacterial pathogen	Indicator organism, ARB and MDR bacteria in treated wastewater	Liquid waste treatment system (Chlorination) should be developed

Table 2 Type of Bacteria Isolated, Antibiotic Used and Drug Resistance Patterns for Studies Included in Systematic Review

ID	Reference	Type of Bacteria Isolated	Antibiotic Tested Against Isolates	Drug Resistance Pattern
1	S. Dires et al 2018 ¹⁰	<i>E. coli</i> , <i>Shigella</i> spp., <i>Pseudomonas</i> spp., <i>Staphylococcus</i> spp., <i>Klebsiella</i> spp., <i>Salmonella</i> spp., and <i>Citrobacter</i> spp.,	Ciprofloxacin, Ceftriaxone, Ceftazidime, Cotrimoxazole, Erythromycin, Nalidixic Acid, Doxycycline, Amoxicillin-clavulanic, Cefoxitin, Gentamicin and Chloramphenicol	The overall MDR prevalence in the final wastewater was 34.2%, where <i>E. coli</i> and <i>Klebsiella</i> spp. were dominated with 47% and 46.1% respectively
2	Fekadu et al 2015 ¹¹	<i>Staphylococcus</i> spp., <i>Klebsiella</i> spp., <i>E. coli</i> , <i>Bacillus</i> spp., <i>Proteus</i> spp., <i>Enterococci</i> spp., <i>Salmonella</i> spp., <i>Shigella</i> spp., <i>Citrobacter</i> spp.	Gentamycin, Erythromycin, Penicillin, Amoxicillin, Ampicillin, Ciprofloxacin, Erythromycin, Tetracycline, Ceftriaxone and	<i>E. coli</i> , <i>Salmonella</i> and <i>S. aureus</i> were found to be MDR pathogens from final wastewater effluents
3	Moges et al 2014 ¹²	<i>E. coli</i> , <i>Klebsiella</i> spp., <i>Shigella</i> spp., <i>Pseudomonas</i> spp., <i>Staphylococcus</i> spp., <i>Enterococci</i> , <i>Citrobacter</i> spp., <i>Enterobacter</i> spp., <i>Providencia</i> , <i>Morganella</i> spp., <i>Proteus</i> spp., <i>Serratia</i> and <i>Edwardsiella</i> spp	Ampicillin, Chloramphenicol, Ciprofloxacin, Clindamycin, Erythromycin, Gentamicin, Methicillin, Vancomycin, Streptomycin, Trimethoprim-Sulfamethoxazole, Tetracycline, Nalidixic Acid, Cephalothin, Cefotaxime, Kanamycin	The overall MDR prevalence was 69.9% where 54.2% in the non-hospital environment and 81.5% from the hospital environment. <i>Enterobacter</i> spp., <i>Klebsiella</i> spp. and <i>Pseudomonas</i> were most MDR gram-negative bacteria while <i>S. aureus</i> was resistant to all antibiotics except Vancomycin
4	Engda et al 2018 ¹³	<i>E. coli</i> , <i>K. pneumoniae</i> , <i>K. ozenae</i> , <i>P. Mirabilis</i> , <i>E. cloacae</i> , <i>E. aerogens</i> , <i>Citrobacter</i> spp., and <i>P. stuartii</i>	Beta-lactam and non-beta-lactam antimicrobials	56% of ESBL producing <i>Enterobacteriaceae</i> were MDR for non-beta-lactam antibiotics. All ESBL producing <i>Enterobacteriaceae</i> were found to be 100% resistant to ceftiofime, cefpodoxime, ceftazidime, Ceftriaxone and amoxicillin with clavulanic acid.
5	Belachew et al 2018 ¹⁴	<i>E. coli</i> , <i>K. pneumoniae</i> , <i>K. oxytoca</i> , <i>P. alcalifaciens</i> , <i>C. freundii</i> , <i>P. rettgeri</i> , and <i>M. morganii</i>	Ampicillin, Cefazolin, Amoxicillin/Clavulanic acid, Piperacillin/Tazobactam, Cephalothin, Cefuroxime, Cefuroxime, Cefoxitin, Cefpodoxime, Ceftazidime, Ceftriaxone, Cefepime, Gentamicin, Tobramycin, Ciprofloxacin, Levofloxacin, Tetracycline, Nitrofurantoin, Trimethoprim/sulfamethoxazole	The overall MDR prevalence was 64%. <i>P. rettgeri</i> was 100% MDR followed by <i>P. alcalifaciens</i> (90%), <i>E. coli</i> (78%) and <i>C. freundii</i> (60%)
6	Tesfaye et al 2019 ¹⁵	<i>E. coli</i> , <i>Salmonella</i> spp., <i>Klebsiella</i> spp., <i>Klebsiella oxytoca</i> , <i>Enterobacter cloacae</i> , and <i>Enterobacter aerogens</i>	Amoxicillin + Clavulanic acid, Ciprofloxacin, Gentamicin, Sulfamethoxazole + Trimethoprim, Trimethoprim, Tetracycline, Ampicillin, Cephalothin, Cefoxitin, Sulfisoxazole,	23% isolates produce ESBL. The isolates include <i>Klebsiella pneumoniae</i> , <i>E. coli</i> and <i>Enterobacter cloacae</i>
7	T. Asfaw et al 2017 ¹⁶	<i>S. aureus</i> , Coagulase-negative staphylococci, <i>Klebsiella</i> spp., <i>P. aeruginosa</i> , <i>E. coli</i> , <i>Salmonella</i> spp., <i>Shigella</i> spp., <i>Citrobacter</i> spp., <i>Enterobacter</i> spp., <i>Serratia</i> spp. and <i>Proteus</i> spp.	Erythromycin, Gentamycin, Amikacin, Amoxicillin-Clavulanic acid, Ceftriaxone, Ciprofloxacin, Tetracycline, Cotrimoxazole, Ampicillin, Penicillin, Chloramphenicol, Doxycycline and Cefoxitin	Overall MDR prevalence from final effluents was 84%. Among isolates, 28.6% were resistant to for six and more antibiotics. One isolates of <i>Citrobacter</i> spp. was resistant for 9 antibiotics.

Staphylococcus aureus, *E. coli*, *Salmonella* spp. and *Shigella* spp. were also frequently isolated from final effluent,¹¹ *Klebsiella* spp., *Pseudomonas* spp., *E. coli*, *Citrobacter* spp. and *S. aureus* were detected from the hospital and the non-hospital environment from a study done in Gondar, Northwest Ethiopia,¹² from ESBL producing *Enterobacteriaceae*, *K. pneumoniae*, *E. coli*, and *Proteus mirabilis* were predominantly isolated in Addis Ababa,¹³ from gram-negative bacteria *E. coli*, *K. pneumoniae*, and *K. oxytoca* were predominant isolates from study done in Addis Ababa,¹⁴ from a study done by Tesfaye et al *E. coli*, *Salmonella* spp., *K. pneumoniae*, and *E. aerogens* were the dominant isolates,¹⁵ finally, in the study done in Mekelle, North Ethiopia from treated hospital wastewater, *Klebsiella* spp., *P. aeruginosa* and *S. aureus* were frequently detected bacteria (Table 2).

Antibiotic Resistance Patterns of Bacterial Isolates

Among isolates, from a study done in Southern Ethiopia, the frequency of resistance from treated wastewater is high for ampicillin, cotrimoxazole, doxycycline, and chloramphenicol¹⁰ and a higher resistance was obtained for *Pseudomonas* spp., *Salmonella* spp., *Klebsiella* spp., *E. coli*, and *Shigella* spp.¹⁰ Similarly, *E. coli*, *Salmonella* spp., *Shigella* spp. and *S. aureus* were resistant for different antibiotics tested from Hawassa and Yirgalem hospital final effluents.¹¹ From a study done in Gondar, Ethiopia, most isolates of gram-positive and gram-negative bacteria were resistant for many antibiotics tested¹², and at the same time another study revealed that all ESBL producing *Enterobacteriaceae* showed 100% resistance to beta-lactam drugs and 19.3% to 70.18% resistance for non-beta-lactam drugs.¹³ A study done in Addis Ababa from sewage polluted urban rivers showed a high level of resistance by gram-negative bacteria for different antibiotics tested.^{14,15} A study was done in Mekelle; North Ethiopia also showed 100% penicillin-resistant isolates of *S. aureus* and Coagulase-negative staphylococci, and 100% ampicillin-resistant *E. coli*, *Klebsiella* spp. and *Citrobacter* spp.¹⁶ Penicillin was 100% resistant followed by ampicillin 83% and Ceftriaxone 59% for isolates from treated hospital wastewater in Mekelle, north Ethiopia.¹⁶

Multidrug Resistance (MDR) Patterns of Isolates

Among isolates from treated and final effluents in Southern Ethiopia, the overall MDR prevalence was 34.2%¹⁰ and pathogenic MDR bacteria also detected.¹² A study done in Gondar showed the overall prevalence of MDR (two or more drugs) was 69.9% where 81.5% in the hospital environment and 54.2% in the nonhospital environment.¹² According to this study, MDR was common for both gram-positive and gram-negative isolates.¹² Another study done from Gondar also showed a high burden of MDR bacteria.¹³ A study was done in Addis Ababa, Ethiopia also showed medically important gram-negative bacteria with a high degree of MDR.^{14,15} A study was done in Mekelle; North Ethiopia also showed a high degree of MDR bacteria isolates with a total prevalence of 84%.¹⁶

Discussion

This review summarized the results from seven studies investigating pathogenic ARB for multiple antibiotics from wastewater in Ethiopia. Increasing knowledge on the dissemination of pathogenic ARB through surveillance and research was a key strategic plan for WHO.¹⁷ Therefore, this summarized study highlighted the role of wastewater as a major source of pathogenic bacteria with MDR to the environment which is a global problem with a serious implication on public health.

From this review, three studies obtained indicator organisms from hospital wastewater which exceed WHO for restricted and unrestricted irrigation,^{18,19} Health Protection Agency,²⁰ Environmental Protection Agency²¹ and Food and Agriculture Organization²² standard permissible and tolerable level which indicates that microbial contamination and fecal pollution of the environment.^{10,11,16} The number of coliforms released from hospital mostly depends on the number of patients served, hospital capacity, and the type of case-managed.²³ During the diagnosis and treatment of disease, the hospital releases large amounts of pathogenic bacteria.²³ At the same time hospital could be a storm house of ARB due to the large use of antibiotics to treat bacterial infections.²⁴

Almost all studies showed the presence of pathogenic bacterial isolates such as *klebsiella* spp., *E. coli*, *P. aeruginosa*, *S. aureus*, and *Salmonella* spp. in the final wastewater and environment. Those isolates are among the lists of WHO that identified bacterial species and their

complementary antibiotic-resistance profile that pose the greatest threat to human health.²⁵ The bacterium in wastewater is a public health problem with risk factors in all parts of the world. Waterborne pathogens can occur in all types of water sources particularly in improperly treated wastewater. Therefore, if wastewater is improperly treated large amounts of infectious agents and ARB are shed into communities causing waterborne disease.²⁶

All studies reported MDR bacteria in the wastewater released to the environment. The use of antibiotics and the dissemination of ARB in the clinical setting are studied well across the world but overlooked in the environment.^{27–29} This is one of the challenges to attain one health approach that aims to achieve an optimum health approach for people, animals, and the environment.³⁰ Currently in Ethiopia, the use of natural compost having human and animal feces as fertilizer is encouraged. This can be one way for the spread of ARB within the environment since water and soil contaminated by slurry, fermentation residue, sewage sludge, municipal wastewater, particularly wastewater with indirect entry from healthcare facilities, are generally contaminated directly with ARB through excretions from people and animals.³¹

Human and animal treatments are the main routes where antibiotics are introduced to the environment. Antibiotics are excreted through feces and urine of patients and reached to the environment and act as a selective pressure on naturally susceptible microflora to develop ARB and ARGs.³² Moreover, if the resistant genes are transmissible and these bacteria reach community bacterial strains, it causes the wide dissemination of resistance gene and resistance bacteria in the receiving environment.³³ Especially, hospital bacteria could increase the number of resistant bacteria in the recipient sewers due to large concentrations of antibiotics and biocide.^{5,6} Infections caused by ARB are usually difficult to treat, prolong hospitalization, and increase the cost of treatment. This can be even worse in the developing countries since more than half of the population does not have access to proper sanitation and more than 80% of the wastewater generated is directly discharged into the open field and surface waterbodies.³⁴ In Ethiopia, the sanitation facility coverage is very low, and a large number of populations use open defecations.³⁵ The habit of open field disposal of wastewater is one of the main causes of soil and water contaminations and the cause of many communicable diseases.³⁶

Multiple drug resistance bacteria undergo wide-ranging genetic exchange in the environment where opportunistic (commonly found in free-living communities) may become resistant upon acquiring resistance mechanisms. The growing distribution of ARB among environmental bacteria has led to consider ARB as emerging pollutants^{37–39} and have unique property compared to contaminants due to their ability to amplify, spread, and persisting in the environment for a long period.³⁹ The presence of MDR in the environment is a major public health threat since it can infect humans and animals through contaminated food and drinking water or directly from the environment.⁴⁰ Antibiotic resistance presents in bacteria which are not primary pathogens also, a threat to public health due to possibilities of transmittance of resistance to other microorganisms.⁴¹ Therefore, the reduction of selective pressure by regulating the use of antibiotics is a key step to reduce the dissemination of resistance in wastewater in order to not favor resistant strains.⁴²

Conclusion and Recommendations

Large numbers of bacteria were isolated from wastewater. This is an indication of the possible presence of pathogenic organisms in the receiving environment. The absence of wastewater treatment and low habit of disinfection before releasing into the sewerage system contribute to the dissemination of MDR bacteria to the environment possibly waterbodies for example, lakes, rivers, posing risk to public health, animals and environment. Especially in Ethiopia were those waterbodies used as public consumption the problem even become worse. This study showed wastewater isolates with significantly higher antibiotic resistance rates. Therefore, wastewater should be treated by an appropriate wastewater treatment system before released into the environment. Moreover, there should be regular assessments and evaluations of the final quality of the wastewater before discharging into the receiving environment. Large-scale microbiological, epidemiological, and social science studies should be conducted across the one-health spectrum in order to decrease the gaps of knowledge about ARB and to increase the wastewater management system.

Limitation of the Study

This study is not assessed possible occupational health risks of wastewater and management practices. The included research articles were not designed at molecular

levels so that this review did not assess the presence of resistance genes and other associated factors.

Data Sharing Statement

Not applicable to this article as no datasets were generated.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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The authors declare that they have no potential conflicts of interest for this work.

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