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Antimicrobial Resistance Through the Lens of One Health in Ethiopia: A Review of the Literature Among Humans, Animals, and the Environment

Ayako Wendy Fujita[a,**,*], Kaitlyn Werner[b,**], Jesse T. Jacob[a], Rea Tschopp[c,d], Gezahegne Mamo[e], Adane Mihret[c], Alemseged Abdissa[c], Russell Kempker[a,**], Paulina A. Rebolledo[a,**]

[a] Emory University School of Medicine, Department of Medicine, Division of Infectious Diseases, Atlanta, Georgia, United States
[b] Emory University, Rollins School of Public Health, Atlanta, GA, United States
[c] Armauer Hansen Research Institute, Addis Ababa, Ethiopia
[d] Swiss Tropical and Public Health Institute, Basel, Switzerland
[e] Addis Ababa University, College of Veterinary Medicine and Agriculture, Department of Microbiology, Immunology and Veterinary Public Health, Addis Ababa, Ethiopia

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ABSTRACT

Objectives: We aimed to review and describe antimicrobial resistance (AMR) prevalence in humans, animals, and the environment in Ethiopia.
Methods: We conducted a structured review of literature on AMR in humans, animals, and the environment in Ethiopia from 2016–2020. We reported the pooled prevalence of AMR of bacterial pathogens in all 3 sectors.
Results: We included 43 articles in our review. Only 5 studies evaluated AMR across multiple sectors. The most common bacteria in humans were *Escherichia coli, Klebsiella pneumoniae*, and *Staphylococcus aureus*. High prevalence of resistance to third-generation cephalosporins, fluoroquinolones, and sulfamethoxazole-trimethoprim were seen in gram-negative organisms, often with >50% prevalence of resistance. Highest resistance rates were seen in humans, followed by environmental isolates. *Salmonella* spp. exhibited higher rates of resistance than previously reported in the literature. We found methicillin-resistant *S. aureus* (MRSA) in approximately half of *S. aureus* from the environment and a third from human isolates. Few studies evaluated AMR across all 3 sectors.
Conclusion: Our review demonstrated high prevalence of AMR among bacteria in humans, animals, and the environment in Ethiopia. Integrating a One Health approach into AMR surveillance as part of Ethiopia's national surveillance program will inform future implementation of One Health interventions.

Introduction

Antimicrobial resistance (AMR) is widely recognized as a global problem, including in sub-Saharan African countries (Elton et al., 2020, Gebretekle et al., 2020). Increasing rates of AMR render many antibiotics ineffective and result in increased morbidity and mortality due to bacterial infections (Global Action Plan on Antimicrobial Resistance2015a, Report to the Secretary-General of the United Nations IACG, 2019). Antimicrobial misuse and overuse are attributed as drivers of increasing AMR worldwide, compounded by additional challenges in low- and middle-income countries (LMICs). In resource-limited areas, insufficient diagnostic infrastructure and laboratory capacity, inconsistent AMR surveillance, and inadequately resourced infection prevention and control contribute to empiric antibiotic use on the basis of syndromic approaches rather than microbiological data (Escher et al., 2021, Gebretekle et al., 2020, Gebretekle et al., 2018). This has led to high

* Corresponding author. Phone: 404-514-1586.
E-mail address: afujita@emory.edu (A.W. Fujita).
** Contributed equally

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rates of antibiotic consumption in LMICs (Gebretekle et al., 2020), which create high selection pressure for resistant organisms.

In addition to human consumption, antibiotic use in food animals and agricultural crops are recognized as likely drivers of AMR in low-resource settings (Rousham et al., 2018). Globally, >70% of all antimicrobials are used in food animals, not only for treatment of diseases but also for infection prophylaxis and growth promotion (Van Boeckel et al., 2019). Transmission between humans and animals can occur through consumption of contaminated food of animal origin or direct contact with livestock (Rousham et al., 2018, White and Hughes, 2019). Antibiotic resistance genes are now considered an environmental pollutant, with exposure occurring through human and animal waste released into the soil and water, which are then used in agriculture (Manyi-Loh et al., 2018, Zalewska et al., 2021). In LMICs, healthcare waste combined with inadequately disinfected drinking water contribute to water contaminated with drug-resistant bacteria (Rousham et al., 2018, Talukdar et al., 2013). This complex interplay of AMR transmission between humans, animals, and ecosystems underscores the need for a One Health approach to better understand the mechanism of transmission and mitigate its spread.

A One Health approach to AMR, which uses an interdisciplinary approach to surveillance and implementation of programs, policies, and research, is increasingly recognized as a vital component to national and global AMR strategies (One Health Basics, 2018a)). In 2015, the World Health Organization (WHO) launched the Global Antimicrobial Resistance Surveillance System (GLASS), a collaborative effort to standardize AMR surveillance with the aim to inform policies and infection prevention strategies (Global Action Plan on Antimicrobial Resistance, 2015a). In Ethiopia, the Ethiopian Food, Medicines, and Healthcare Administration and Control Authority developed the "Strategy for the Prevention and Containment of Antimicrobial Resistance" plan in 2015 (Strategy for the Prevention and Containment of Antimicrobial Resistance for Ethiopia, 2015b). Then in 2017, they launched the Ethiopian Antimicrobial Resistance Surveillance System, a standardized, laboratory-based surveillance system and one of the first national efforts to combat AMR (Ethiopia Antimicrobial Resistance Surveillance Annual Report, 2020). More recently in December 2020, the Strategic Plan was revised with particular attention to a One Health platform (Ministry of Health MoA, 2020).

Since the implementation of Ethiopia's AMR surveillance system, substantial achievements have been made, including an expanded surveillance network, collation of AMR surveillance data, and increased laboratory capacity (Ethiopia Antimicrobial Resistance Surveillance Annual Report, 2020). However, national AMR surveillance in Ethiopia is currently primarily focused on humans, and there remains a knowledge gap of AMR trends across animals and the environment. Despite extensive interaction between the 3 sectors, few research studies have evaluated AMR through the lens of One Health. Here, we provide a detailed, structured review of the AMR literature published during 2016-2020 in Ethiopia to describe AMR rates across the One Health sectors.

Methods

Search Strategy

A structured literature search was performed using PubMed, CINAHL, Global Health Database, AgriCOLA, Embase, and MEDLINE online databases. We included all articles on AMR in Ethiopia published in English from January 2016–October 2020. The literature search was conducted from October 6th–November 30th, 2020, by 1 author (KW). The search strategy used the following search string: ("antimicrobial resistance" OR "antibiotic resistance" OR "drug resistance" OR "gram-negative" OR "gram-positive") AND ("*Escherichia coli* "OR "*E. coli*" OR "*Salmonella*" OR "*Staphylococcus aureus* "OR "*Enterobacter cloacae*" OR "*Shigella* "OR "Methicillin-resistant *Staphylococcus aureus*" OR "*Klebsiella pneumoniae* "OR "*Acinetobacter baumannii*" OR "*Streptococcus pneumoniae*)" AND ("foodborne infections" OR "healthcare infections") AND ("animal" OR "livestock" OR "cattle" OR "cows" OR "beef" OR "poultry" OR "chickens" OR "pig" OR "swine") OR "human" OR "environment" OR "One Health") AND ("Ethiopia").

Selection Criteria

Articles were reviewed by a single reviewer according to PRISMA guidelines. Full-text articles on AMR prevalence among bacteria isolated from humans, animals, and animal products (cows, pigs, and poultry), or the environment (swabs of surfaces and objects in clinical settings, surfaces in community settings including slaughterhouses, and water sources) in Ethiopia were screened for inclusion. Publications were reviewed and included if they reported AMR prevalence and information about sample collection. Studies evaluating AMR from sources of bacterial colonization (eg, nares swabs and stool samples from asymptomatic individuals) were excluded. Additionally, we excluded environmental samples collected from nonanimal food products (eg, juice and fruit). After our initial literature review, we identified and added 3 additional environmental studies that were discussed and referenced in another study. Publications reporting AMR for *Mycobacterium tuberculosis* or nonbacterial pathogens were excluded from this review.

We assessed AMR in the following clinically relevant pathogenic bacteria identified by the Global Antimicrobial Resistance Surveillance System (GLASS organisms, Additional File 1): *Escherichia coli, Klebsiella pneumoniae, Acinetobacter* spp., *Staphylococcus aureus*/Methicillin-resistant *Staphylococcus aureus* (MRSA), *Streptococcus pneumoniae, Salmonella* spp., and *Shigella* spp. Additionally, we included *Enterobacter* spp., *Serratia* spp., *Proteus* spp., and *Citrobacter* spp. because there is concern of growing resistance among these gram-negative organisms but excluded *Neisseria gonorrhea*, which is limited to humans.

Data Extraction

Data extraction was performed by 1 author (KW) and reviewed and confirmed by a second author (AWF). Data extracted included: (i) article information (first author, year, city/region, and sample source/host), (ii) study design (study approach, sample size, and setting), and (iii) results (clinical syndrome/infection, sample site [humans], sample source [animal and environment], organisms, and rates of resistance).

Statistical analysis

Data were extracted by organism and sector (humans, animals, and environment), and descriptive statistics were used for summarizing frequencies and proportions. For calculating the prevalence of AMR, we focused on resistance to antimicrobials prioritized by GLASS (Additional File 1) (2015a). Confidence intervals for proportions were used to estimate the pooled prevalence of AMR of each organism-antibiotic combination, and this was reported separately for humans, animals, and the environment, as well as overall. We used oxacillin or cefoxitin resistance to determine the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA). In our results and main tables, we report the pooled prevalence of AMR among the bacterial pathogens included. Resistance rates reported by individual studies are reported in Additional Files 2–4.

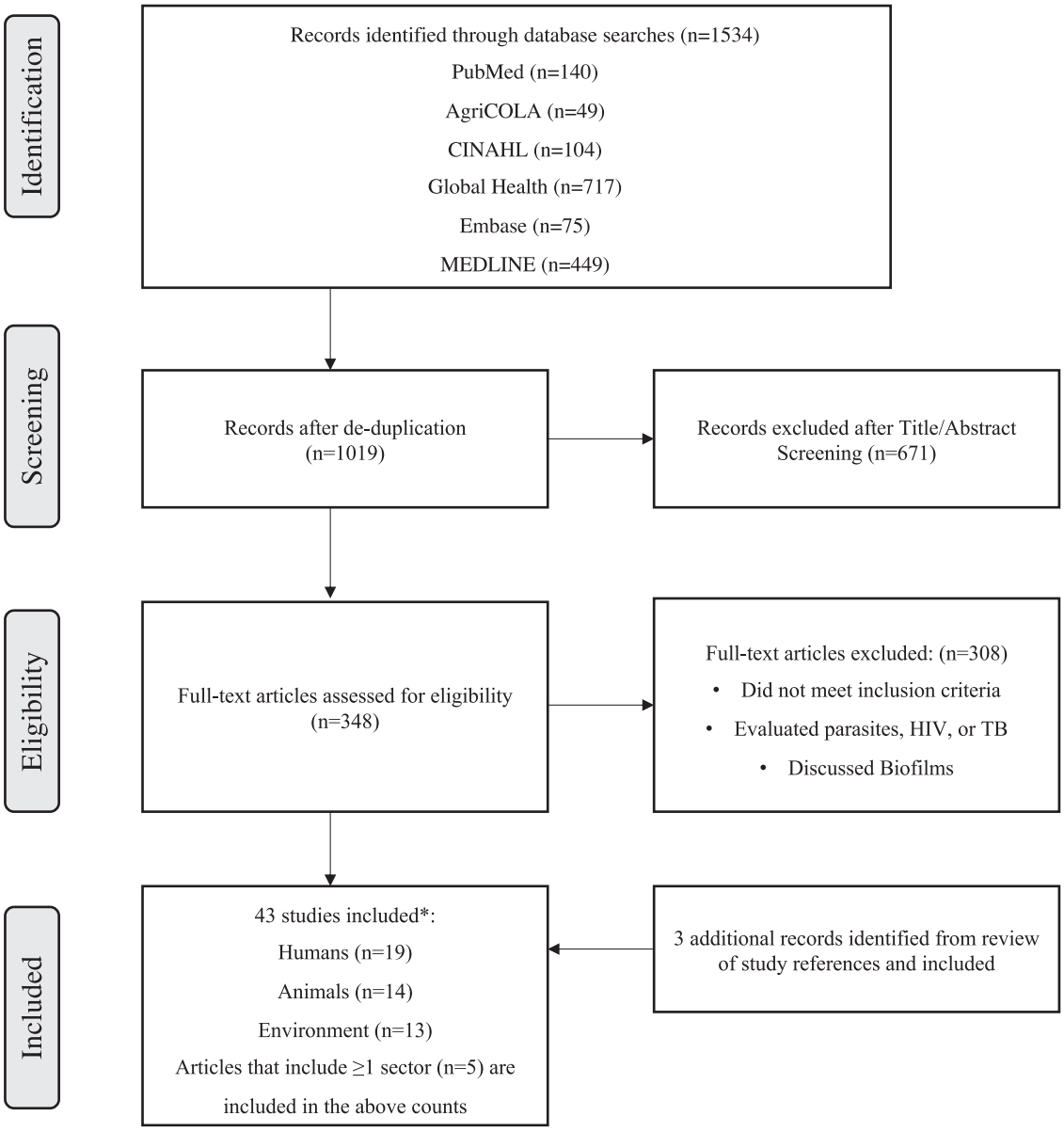


Figure 1. Study selection process for literature review of AMR in humans, animals, and the environment in Ethiopia

Results

Initial literature search yielded a total of 1534 articles. After excluding 515 duplicates and 671 articles by screening titles and abstracts that were not pertinent to AMR, 348 articles were reviewed in full. An additional 308 articles were excluded because they did not meet our selection criteria (Figure 1), leaving 40 articles in the final data extraction. A total of 3 additional studies were later identified after reviewing references from included studies; thus, a total of 43 studies were included in this review.

Study Characteristics

Of the 43 full-text articles included for review, all were cross-sectional, most of which were retrospective. Studies were conducted in 17 cities and 6 regions in Ethiopia, representing urban and periurban areas (Figure 2). A total of 19 studies evaluated AMR in humans, 14 studies in animals, and 13 studies in environmental samples. Only 5 studies evaluated AMR across multiple sectors, all of which were conducted in slaughterhouses or dairy farms (Abdi et al., 2017, Abunna, 2017, Beyene et al., 2017, Garedew et al., 2016, Takele et al., 2018).

Antimicrobial resistance rates in humans

A total of 19 studies evaluated bacterial AMR in humans. Most studies were conducted in urban cities, predominantly in Addis Ababa, Jimma, and Hawassa (Figure 2) and described AMR of bacteria in a single, specific infectious syndrome, such as surgical site infections, urinary tract infections, otitis media, or diarrhea (Additional File 2) (Argaw-Denboba et al., 2016, Bitew Kifilie et al., 2018, Deyno et al., 2017b, Gorems et al., 2018, Hailu, 2018, Lamboro et al., 2016, Mamuye, 2016, Nigussie and Amsalu, 2017, Shimekaw et al., 2020, Tadesse et al., 2018, Terfassa and Jida, 2018, Teshome et al., 2019, Tsige et al., 2020). Only 1 study evaluated AMR specifically in bloodstream infections (Arega et al., 2018). The most frequently sampled sites for culture were urine (n = 1664, 29%), ear swabs (n = 1521, 25%), wounds (n = 1420, 25%), and stool

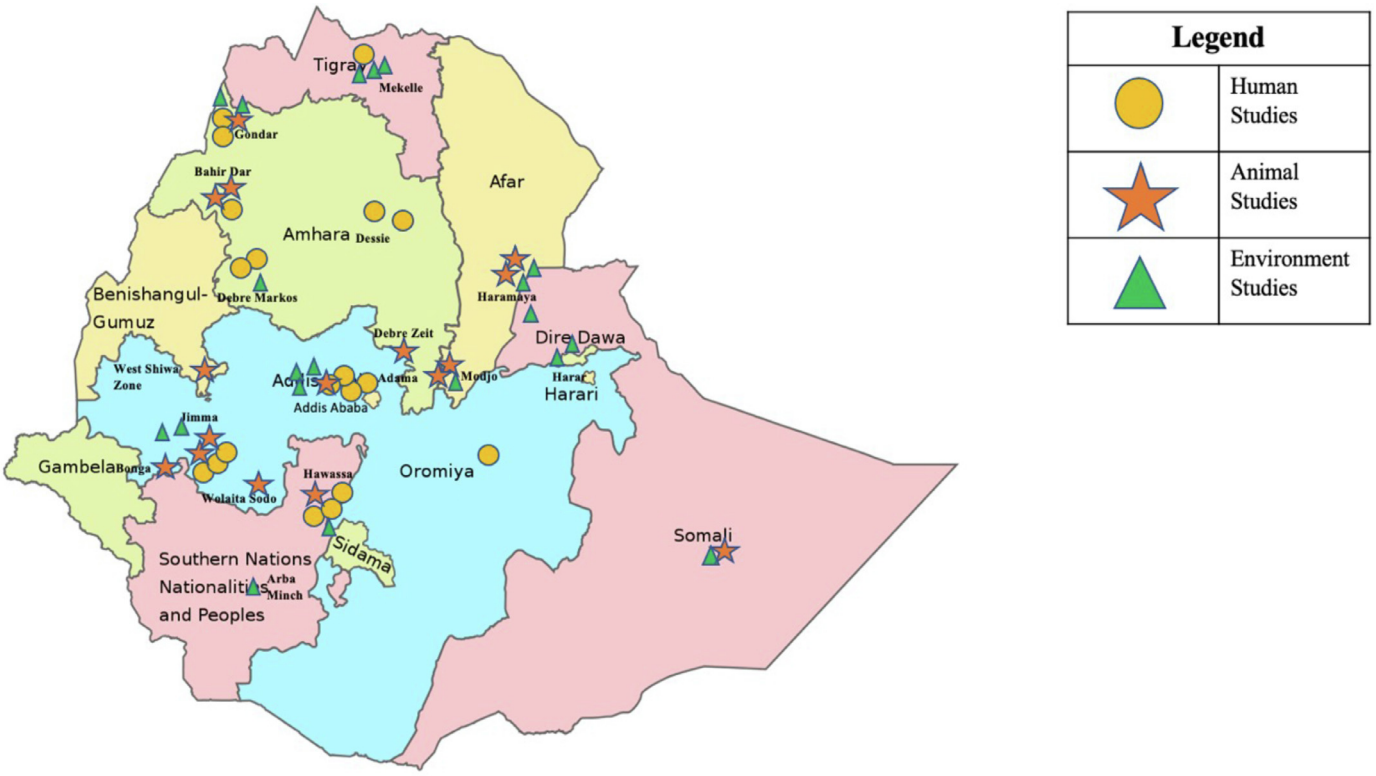


Figure 2. Geographical locations of AMR studies conducted in Ethiopia between January 2016 and October 2020

(n = 752, 13%). Only 305 (5%) of all samples obtained were blood cultures.

Most bacteria isolated were gram-negative organisms (80%), most frequently *E. coli* (n = 676), *Klebsiella* spp. (n = 347), *Proteus* spp. (n = 422), and *Salmonella* spp. (n = 97). Susceptibility against broad-spectrum gram-negative antimicrobial agents such as cefepime, piperacillin/tazobactam, and meropenem were infrequently tested for susceptibility, and only 20% of human samples were tested for carbapenems. However, among the bacteria that were tested, 20% (117/582) were carbapenem-resistant. When carbapenem susceptibility was assessed, resistance was observed in *Serratia* spp. (n = 3, 60%), *Enterobacter* spp. (n = 20, 53%), *Proteus* spp. (n = 3, 43%), *Citrobacter* spp. (n = 19, 38%), *Klebsiella* spp. (n = 30, 18%), and *E. coli* (n = 19, 13%).

E. coli had high pooled prevalence of resistance to ciprofloxacin (77%; 95% CI: 74%–80%), sulfamethoxazole/trimethoprim (SMX/TMP) (54%; 95% CI: 50%–58%), ceftriaxone (46%; 95% CI: 42%–50%), and ceftazidime (29%; 95% CI: 26%–33%) (Table 1). Compared with *E. coli, Klebsiella* spp. had higher rates of resistance to SMX/TMP (74%; 95% CI: 69%–79%), ceftriaxone (66%; 95% CI: 61%–71%), and ceftazidime (52%; 95% CI: 47%–58%) but lower rates of resistance to ciprofloxacin (35%; 95% CI 30%–40%).

Most *Salmonella* species (97%) were obtained from stool specimens, and only 2 were found in blood cultures. Data on serovars were not available in most studies. Pooled estimates of *Salmonella* spp. resistance to ciprofloxacin were 25% (95% CI 16%–34%) and ceftriaxone 17% (95% CI 10%–25%).

Typical hospital-acquired gram-negative organisms, such as *Citrobacter* spp., *Enterobacter* spp., and *Proteus* spp., also demonstrated high rates of AMR, especially to SMX/TMP, ceftriaxone, and aminoglycosides (Table 1).

A total of 15 human studies identified *Staphylococcus aureus* with a total of 1062 isolates, and we determined the pooled prevalence of MRSA to be 34% (95% CI 31%–36%) (Table 2). The pooled prevalence of *S. aureus* resistance to SMX/TMP was 49% (95% CI 46%–52%) and ceftriaxone 28% (95% CI 25%–30%). Overall, few studies tested *S. aureus* against vancomycin, daptomycin, linezolid, doxycycline, or clindamycin.

Animicrobial resistance rates in animals

A total of 14 studies evaluated AMR in animals or food of animal origin, including chickens (n = 5), cattle (n = 8), or both (n = 1). We did not find any studies in Ethiopia assessing AMR in pigs. Most studies evaluated bacteria isolated from food of animal origin, such as milk, raw or cooked meat, and eggs. Animal studies were conducted in 15 urban or periurban cities rather than rural or pastoral regions. From a One Health perspective, 4 studies tested for AMR in pathogens isolated from all 3 sectors (Abdi et al., 2017, Abunna, 2017, Beyene et al., 2017, Garedew et al., 2016), and 1 study evaluated AMR in *Salmonella* isolated from both cattle and human fecal samples (Takele et al., 2018).

In total 5237 samples were collected from animals or animal products, and 700 samples (13%) tested positive for pathogenic bacteria. Fewer types of bacteria were isolated and tested for AMR, focusing primarily on *E. coli/E. coli O157:H7* (n = 297, 42%) and *Salmonella* species (n = 274, 39%). *Staphylococcus aureus* was isolated in 129 (18%) samples. Prevalence of carbapenem-resistant Enterobacterales could not be calculated owing to lack of carbapenem susceptibility testing performed in animal samples.

E. coli was the most common organism isolated from animals and food of animal origin. High rates of resistance to SMX/TMP were observed; however, lower resistance rates to fluoroquinolones and third-generation cephalosporins were seen compared with *E. coli* isolated from human clinical samples. The pooled prevalence of resistance to SMX/TMP was 18% (95% CI 13%–22%), ceftazidime 10% (95% CI 7%–14%), ciprofloxacin 1.4% (95% CI 0%–3%), and ceftriaxone 2% (95% CI 0%–4%) (Table 1).

Table 1
Pooled prevalence of AMR among Enterobacterales from humans, animals, and the environment.

Organism	Sector	Total Number Positive Cultures	Ceftriaxone (%, 95% CI)	Ceftazidime (%, 95% CI)	Cefepime (%, 95% CI)	Meropenem (%, 95% CI)	Ciprofloxacin (%, 95% CI)	SMX/TMP (%, 95% CI)	Gentamicin (%, 95% CI)
E. coli	Humans	676	46 (42-50)	29 (26-33)	1 (0-1)	6 (4-8)	77 (74-80)	54 (50-58)	36 (32-39)
	Animals	297	2 (0.4-4)	10 (7-14)	N/A	N/A	1 (0-3)	18 (13-22)	3 (1-5)
	Environment	254	13 (9-17)	9 (5-12)	31 (25-36)	18 (13-22)	35 (29-41)	38 (32-44)	26 (21-31)
	Total	1227	28 (26-31)	20 (18-23)	7 (5-8)	7 (6-9)	50 (47-53)	42 (39-45)	26 (23-28)
K. pneumoniae	Humans	97	43 (37-49)	44 (38-50)	0	5 (2-8)	38 (32-45)	55 (49-62)	36 (30-42)
	Animals	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Environment	45	41 (27-55)	19 (7-30)	24 (11-36)	9 (1-17)	16 (6-27)	26 (13-39)	12 (3-21)
	Total	142	42 (34-50)	36 (28-44)	7 (3-12)	6 (2-10)	31 (24-39)	46 (38-54)	28 (21-36)
Klebsiella spp. (not K. pneumoniae)	Humans	250	76 (71-81)	57 (51-63)	14 (9-18)	14 (9-18)	34 (28-40)	83 (78-87)	64 (58-70)
	Animals	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Environment	49	26 (14-39)	6 (-0.1-13)	6 (-0.1-13)	2 (-2-6)	14 (4-24)	37 (24-51)	29 (16-42)
	Total	299	67 (61-72)	48 (42-53)	7 (4-10)	12 (8-15)	30 (25-36)	74 (69-79)	57 (52-63)
Proteus spp.	Humans	422	82 (79-86)	3 (1-5)	4 (2-5)	1 (0-1)	11 (8-14)	83 (79-86)	21 (17-25)
	Animals	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Environment	22	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Total	444	82 (79-86)	3 (1-5)	4 (2-5)	1 (0-1)	11 (8-14)	83 (79-86)	21 (17-25)
Salmonella spp.	Humans	103	16 (9-23)	9 (3-14)	N/A	N/A	24 (15-32)	27 (19-36)	8 (3-14)
	Animals	268	12 (8-16)	N/A	N/A	N/A	8 (5-11)	46 (40-52)	8 (4-11)
	Environment	15	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Total	386	9 (6-11)	2 (1-4)	N/A	N/A	10 (7-13)	32 (28-37)	6 (4-9)
Citrobacter spp.	Humans	158	44 (36-52)	19 (13-25)	5 (2-9)	12 (7-17)	16 (10-22)	58 (50-66)	26 (19-33)
	Animals	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Environment	37	19 (6-32)	5 (-2-13)	11 (1-21)	0	27 (13-41)	30 (15-44)	14 (2-25)
	Total	195	39 (32-47)	16 (10-22)	6 (2-10)	10 (5-14)	18 (12-24)	53 (45-60)	23 (17-30)
Enterobacter spp.	Humans	113	57 (48-66)	24 (16-32)	3 (0-6)	18 (11-25)	15 (9-22)	52 (42-61)	34 (25-42)
	Animals	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Environment	13	N/A	N/A	N/A	N/A	N/A	N/A	
	Total	126	53 (45-62)	22 (14-29)	2 (0-5)	16 (10-22)	17 (10-23)	50 (41-58)	31 (23-39)
Shigella spp.	Humans	55	20 (9-31)	22 (11-33)	N/A	N/A	29 (17-41)	37 (25-50)	9 (1-16)
	Animals	10	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Environment	15	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Total	80	23 (14-33)	15 (7-23)	N/A	N/A	20 (11-29)	26 (16-35)	6 (1-11)

The pooled prevalence of AMR and 95% confidence intervals were calculated for each organism and antibiotic by sector and as an aggregated total. Pooled prevalence of AMR was only calculated when the total number of positive cultures from a sector was ≥50. When susceptibility testing was not performed or when the sample size was too small to calculate pooled prevalence, "N/A" was used to designate non-applicability. *Acinetobacter* spp. (n=39), *Serratia* spp. (n=15), and *Streptococcus pneumoniae* (n=38) were excluded from the table, as their aggregated totals were <50. For full details of each study in our review, please see Additional Files 2–4.

Table 2
Pooled prevalence of AMR among *Staphylococcus aureus* isolates from humans, animals, and the environment.

Staphylococcus aureus	Total Number Positive Cultures	Pooled Cefoxitin Resistance (n, %)	95% Confidence Intervals
Humans	1062	357, 34%	31-36%
Animals	120	Not tested	N/A
Environmental	240	128, 53%	47-60%
Community settings	61	21, 34%	22-46%
Hospital settings	179	107, 60%	53-67%
Total	1422	485, 37%*	35-40%

The pooled prevalence of MRSA and 95% confidence intervals were calculated for *S. aureus* isolates from humans, animals, and the environment. Cefoxitin or oxacillin resistance were used as surrogates to determine prevalence of MRSA. Environmental samples were further stratified by samples obtained from the community (e.g., slaughterhouses and dairy farms) versus from hospital settings. We could not determine MRSA rates in animal sectors as these studies did not report susceptibility testing for MRSA. For this reason, only human and environmental samples were used to calculate the total pooled prevalence of MRSA.

Salmonella species were identified in 8 studies with a total of 274 isolates. Pooled prevalence of resistance against SMX/TMP was 34% (95% CI 28%–39%) with lower rates of resistance observed for ceftriaxone 6% (95% CI 3%–9%) and ciprofloxacin 5% (95% CI 3%–8%). However, we noted that susceptibilities against ceftriaxone were only tested in 3 studies despite being a common alternative to fluoroquinolones for the treatment of severe *Salmonella* disease.

Staphylococcus aureus (n = 129) was identified in 2 studies and all samples were collected from milk of dairy cattle. One of these studies found that 62% of *S. aureus* isolates were resistant to cefoxitin (Sileshi and Munees, 2016). However, susceptibility testing against oxacillin or cefoxitin was not consistently performed; thus, pooled estimates of the prevalence of MRSA could not be calculated in animals. The study characteristics and AMR rates for individual studies are shown in Additional File 3.

Antimicrobial resistance rates in the environment

Thirteen studies evaluated AMR in environmental samples. We included water sources, surfaces of clinical settings, and surfaces of community settings and excluded swabs of human hands or nonanimal food products (Additional File 4). Five studies used a One Health approach by assessing AMR among bacteria from both animal and environmental sources (Abdi et al., 2017, Abunna, 2017, Beyene et al., 2017, Garedew et al., 2016, Takele et al., 2018). Four studies included swabs of human hands in abattoir settings, which offered a unique One Health perspective of AMR across the human-animal-ecosystem interface.

A total of 1657 samples were collected, of which 906 (55%) positive cultures yielded 1713 bacterial isolates. The most common pathogens isolated were *E. coli* (n = 254), followed by *S. aureus* (n = 240) and *Klebsiella* spp. (n = 94) (Additional file 4). Susceptibility to carbapenems was tested in fewer than half (44%) of all gram-negative isolates; of these, carbapenem resistance was identified in 38% of gram-negative bacterial isolates. Carbapenem resistance was observed in *Acinetobacter* spp. (n = 29, 74%), *Klebsiella* spp. (n = 5, 50%), *E. coli* (n = 45, 28%), and *Serratia* spp. (n = 1, 25%).

Nearly all 184 samples from water sources had positive cultures, all of which grew gram-negative organisms. A total of 255 bacterial isolates were identified, and 75% were *E. coli*. Water samples were collected from hospital wastewater systems, as well as from abattoirs and downstream rivers in Addis Ababa (Belachew et al., 2018, Takele et al., 2018, Tesfaye et al., 2019, Teshome et al., 2020). Of 478 samples from surfaces in the community, 300 were swabs from handles of city buses, where most positive cultures (54/66) grew *S. aureus*. The remaining samples were obtained from surfaces from abattoirs or dairy farms, and *Shigella* (n = 15), *S. aureus* (n = 7), and *Salmonella* (n = 3) were isolated. From hospital settings, the most common organisms isolated were *S. aureus* (n = 179), *Klebsiell*a spp. (n = 60), and *E. coli* (n = 54), followed by other nosocomial gram-negative organisms such as *Acinetobacter* spp, *Citrobacter* spp, and *Serratia* spp (Table 2).

Among 254 positive cultures with *E. coli,* pooled prevalence of resistance was highest for SMX/TMP (38%; 95% CI: 32%–44%), ciprofloxacin (35%; 95% CI: 29%–41%), and cefepime (31%; 95% CI 25%–36%). For *Klebsiella* spp. (n = 94), the pooled prevalence of resistance for ceftriaxone was 33% (95% CI 24%–43%) and SMX/TMP was 32% (95% CI 22%–41%).

In total, *S. aureus* was isolated from 240 positive cultures, and the pooled prevalence of MRSA was 53% (95% CI 47%–60%) (Table 2). When stratified by community versus hospital settings, MRSA prevalence was 34% among *S. aureus* isolated from the community versus 60% from hospital surfaces.

Salmonella was only identified in 15 bacterial isolates from water sources and a dairy farm. Susceptibility testing to antibiotics were inconsistent and low in frequency; however, when tested, there was no resistance reported to ciprofloxacin or ceftriaxone from these environmental samples.

Discussion

Our review of the AMR literature in Ethiopia revealed high prevalence of resistance to common and clinically important antimicrobials among GLASS priority pathogens (Global Action Plan on Antimicrobial Resistance, 2015a). Our broad overview included studies from diverse regions across Ethiopia and included a wide range of samples obtained from humans, animals, and the environment. We identified a notable gap in the AMR literature of studies with an integrated, One Health approach to surveillance in Ethiopia, with only 5 studies describing AMR across all 3 sectors (Abdi et al., 2017, Abunna, 2017, Beyene et al., 2017, Garedew et al., 2016, Takele et al., 2018). Previous studies in Ethiopia have focused on only a single pathogen, a particular clinical syndrome, or only 1 or 2 One Health sectors. More recently, a systematic review and meta-analysis of AMR was published in Ethiopia through a One Health lens (Gemeda et al., 2021). However, authors focused on bacteria in the animal-source food chain; thus, only food handlers were included for human samples. Our literature review is unique in that it included studies of human clinical samples along with animal and environmental studies in Ethiopia.

Nearly all animal studies were conducted in urban and periurban areas (Figure 2) and included animal husbandry systems, composed mostly of dairy cattle and poultry. The absence of studies in pigs is possibly because pork consumption is less common in Ethiopia. Although intensive dairy cattle constitute only a small portion of the nation's cattle, this sector is important because it represents a population with better access to pharmacies and veterinary care, which may lead to greater exposure and risk to AMR.

For this review, we focused on priority antimicrobials identified by GLASS according to its Access, Watch, Research (AWaRe) classification system (Additional File 1) (Sharland et al., 2018). Antimicrobials classified as "Access" are those used to treat common, susceptible bacteria and are expected to have low rates of resistance. Those in the "Watch" group have higher rates of resistance and are recommended to be prioritized in surveillance and stewardship programs. Finally, the "Reserve" group of antimicrobials are those that should be reserved to treat multidrug-resistant organisms. We found high resistance rates among 5 antibiotics in the AWaRe "Access" group and 8 in the "Watch" group, emphasizing the importance of not only AMR surveillance programs but also of implementation of antibiotic stewardship programs.

Antimicrobial susceptibility testing appeared to be inconsistent and disproportionately low in animal and environmental isolates compared with humans. In many animal and environmental isolates, pooled prevalence of resistance could not be calculated due to lack of susceptibility data, highlighting a gap in AMR data in the animal and environmental sectors. We observed that in many cases, clinically irrelevant antibiotics were tested for susceptibility, whereas other clinically important antibiotics were not. In addition to increased laboratory capacity and support for susceptibility testing, AMR surveillance would benefit from standardized procedures or panels for susceptibility testing for different categories of pathogens.

Susceptibility testing against carbapenems was exceedingly low across all sectors, which is problematic given the growing concerns of carbapenemase-producing bacteria in sub-Saharan Africa (Manenzhe et al., 2015). True rates of carbapenem resistance in this region are difficult to ascertain owing to lack of carabapenem susceptibility testing. However, in isolates where testing was performed, the pooled prevalence of carbapenem resistance was as high as 20%. Increased and consistent susceptibility testing to carbapenems should be performed to identify prevalence and trends of carbapenem-resistant Enterobacterales.

Regarding distribution and types of culture samples, we found low numbers of blood cultures, with only 5% of all cultures consisting of blood. Cultures of sterile sites can offer important microbiological information because these typically represent true infections; whereas, cultures obtained from wounds and urine can represent colonization or contamination and are difficult to interpret in the absence of clinical data.

We found higher rates of MRSA among *S. aureus* isolates in the environment compared with humans (53% vs 34%). However, when environmental samples were stratified by hospital and community settings, we discovered higher rates of MRSA from hospital settings (60% vs 34%), mostly from hospital surfaces and equipment, suggesting a need for improved and thorough cleaning practices

to reduce surface contamination with AMR organisms in healthcare settings. In a One Health study by Beyene, T et al, *S. aureus* was isolated from dairy milk, beef, human hand swabs, and equipment at dairy farms and abattoirs, demonstrating possible transmission of organisms between humans, animals, and the environment (Beyene et al., 2017). Both settings suggest that AMR transmission between One Health sectors may occur owing to inadequate hygiene during points of contact, such as touching hospital surfaces or during milking or slaughtering of animals. Our review found MRSA rates to be comparable with the pooled prevalence of methicillin resistance (47%) noted in a meta-analysis of *S. aureus* resistance in Ethiopia (Deyno et al., 2017a). High MRSA rates are concerning as infections caused by MRSA have limited treatment options and have been shown to have worse clinical outcomes, including longer hospitalizations and higher mortality (Bassetti et al., 2012, Cosgrove et al., 2005). To mitigate the spread of MRSA between the 3 sectors, we recommend improved cleaning protocols of hospital surfaces and increased education about hand hygiene in dairy farms and slaughterhouses.

Although the studies with a true One Health approach were few, they showed the interconnection of the 3 domains, primarily in abattoirs, dairy farms, and butcher shops. In these studies, samples were taken from human hands, animals or animal products, and environmental surfaces and showed similar organisms or resistance (Abdi et al., 2017, Abunna, 2017, Beyene et al., 2017, Garedew et al., 2016, Takele et al., 2018). This suggests the potential circulation of AMR isolates among the human-animal-environment domains, which may have serious impact on human and animal health. Risk factors for AMR organisms in animals varies depending on the type of production system, but prophylactic antibiotics in animal feed and water may contribute to the development of AMR, which could be transmitted to humans through consumption of animal products containing antibiotic residue. However, little research has been done in Ethiopia to assess the impact of prophylactic antibiotics on the development of AMR in farm settings. Additionally, studies that prospectively collect samples from multiple sectors simultaneously are needed to inform future areas for intervention to reduce AMR transmission.

Studies that identified drug-resistant organisms in hospital wastewater systems suggest that healthcare-acquired resistance could be transmitted into the community and environment through wastewater (Belachew et al., 2018, Tesfaye et al., 2019, Teshome et al., 2020). Environmental exposure to antimicrobials has adverse effects on environmental and human health, and a recent global study of pharmaceutical pollution in rivers across 104 countries revealed high concentrations in sub-Saharan Africa, South Asia, and South America (Wilkinson et al., 2022). Rivers with highest rates of pharmaceutical contamination were in LMICs where wastewater management infrastructure is poor (Wilkinson et al., 2022). In fact, Addis Ababa, Ethiopia had the third highest concentration of pharmaceutical pollution in rivers in the world (Wilkinson et al., 2022). Future studies should sample not only wastewater systems within the hospital but also in the community near or around the hospital and from rivers downstream from the hospital, which would substantiate the One Health concept of AMR transmission between humans in the healthcare setting, agricultural crops, and livestock through contaminated water.

E. coli and *Klebsiella* spp. were the most common gram-negative organisms isolated, and both exhibited high rates of AMR to third-generation cephalosporins, fluoroquinolones, and SMX/TMP. A recent One Health review of AMR in Cameroon found similarly high rates of AMR in Enterobacterales isolated from hospital settings (Mouiche et al., 2019). There has been growing attention to drug-resistant gram-negative organisms, including those with extended-spectrum beta-lactamases (Abayneh and Worku, 2020), which render many commonly used antibiotics ineffective. For example, previous evidence showed that using piperacillin-tazobactam to treat patients with *E. coli* or *K. pneumoniae* bacteremia with ceftriaxone resistance had poorer outcomes than those treated with carbapenems (Harris et al., 2018). In LMICs, where broad-spectrum antibiotics such as carbapenems may be unavailable, options to effectively treat resistant gram-negative infections may be limited.

Multidrug-resistant *Salmonella* is an increasing global concern and has been reported in sub-Saharan Africa, including Ethiopia. In our review, *Salmonella* spp. were primarily isolated from fecal specimens, and only 2 of 305 blood cultures grew *Salmonella*. In the most recent Typhoid Fever Surveillance in Africa Program, blood cultures from 847 febrile patients from Butajira, Ethiopia over 2 years revealed only 3 cases of invasive Salmonella disease, all *S. typhi* with no resistance to cephalosporins, fluoroquinolones, or SMX-TMP (Marks et al., 2017). In contrast, our review showed higher pooled prevalence of resistance to antibiotics commonly used to treat Salmonella disease in humans, including ciprofloxacin, ceftriaxone, and SMX-TMP. Lower rates of resistance to ceftriaxone and fluoroquinolones were seen in animals; however, resistance to SMX-TMP remained high at >30% (Figure 3c). This suggests that there may be variance in AMR prevalence in *Salmonella* spp. reported in the literature and to be suspicious of single reports of pansusceptibility of *Salmonella* with small sample sizes per study and a wide range of resistance rates reported in Ethiopia.

Our review has several limitations. A known limitation of One Health AMR research is the lack of studies evaluating all 3 sectors simultaneously. Without integrated AMR data across all 3 sectors, it is difficult to assess the true prevalence of AMR, the directionality of transmission, and how to effectively combat resistance at the human-animal-environment interface (Rousham et al., 2018). Prospective studies sampling human, animal, and environments simultaneously are needed; however, this is resource-intensive and logistically challenging, especially in resource-limited settings.

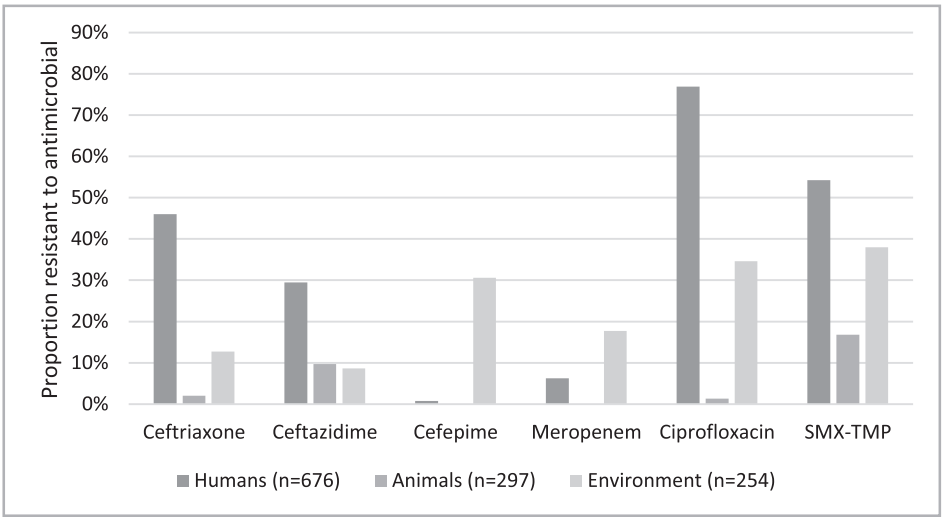
Another limitation is that our initial search did not include small ruminants such as sheep and goats. However, when re-examining the literature for AMR studies in Ethiopia in sheep and goats, only a few studies were carried out during our search period (Abreham et al., 2019, Messele et al., 2017).

Finally, all human samples were obtained from hospitalized patients in clinical settings, which may create bias toward including patients with nosocomial infections. In these settings, cultures may only be obtained after prolonged hospital courses when patients have not improved on empiric antibiotics, thus selecting out for patients with higher rates of drug-resistant organisms. However, this approach is difficult to avoid, as gathering AMR data in humans usually occurs in clinical settings, and we aimed to avoid collecting data from asymptomatic individuals with bacterial colonization.

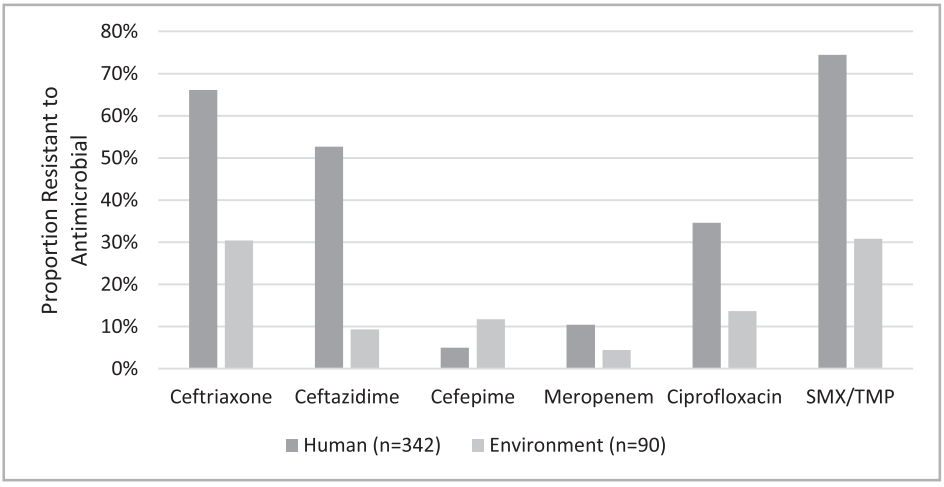
On the basis of our review, there are several opportunities for future AMR research with a One Health approach. First, we need to identify barriers to routine cultures and antibiotic susceptibility testing in not only human clinical settings but also in veterinary medicine and agricultural sectors. Susceptibility testing with appropriate antibiotics should be standardized with protocols and discussed with clinicians to test for the most clinically relevant antibiotics. Second, additional studies from animals and the environment (particularly agriculture, aquaculture, live animal markets, and small ruminants) are needed. These were underrepresented in our review and would offer greater generalizability of the AMR data. Third, prospective studies with a One Health approach—integrating collection of AMR data from all 3 sectors simultaneously—would provide important surveillance information and help us to better understand AMR transmission across sectors.

Fourth, it is imperative that we gain additional knowledge about antibiotic-prescribing practices among physicians and veteri-

A. *Escherichia coli*



B. *Klebsiella* spp.



C. *Salmonella* spp.

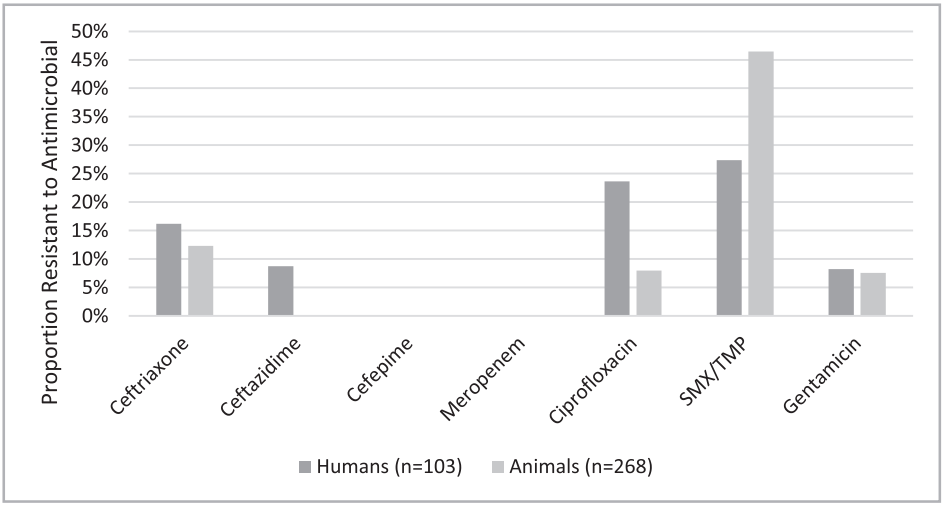


Figure 3. Pooled prevalence of AMR for select gram-negative pathogens from studies of human, animal, and environmental samples. *Escherichia coli* (A), *Klebsiella* spp. (B), and *Salmonella* spp. (C) are included in the graphs. *Klebsiella* spp. were not isolated from animal studies. *Salmonella* spp. were isolated from all 3 sectors; however, the sample size in environmental samples (n=15) was too small to calculate pooled prevalence of resistance.

narians, as well as usage among livestock owners. Despite the limited AMR data in Ethiopia, the existing data show increasing AMR prevalence to commonly used empiric antibiotics. The WHO has published a methodology for conducting point prevalence surveys on antibiotic use in hospitals (WHO methodology for point prevalence survey on antibiotic use in hospitals, 2018b); however, additional information on antibiotic consumption in the animals would inform policies on antimicrobial stewardship across all sectors.

Ethiopia has already established a national surveillance program with increased support and funding for laboratory capacity, and the revised Antimicrobial Resistance Prevention and Containment Strategic Plan prioritizes a One Health approach. Our review is aligned with its second strategic objective, which is to strengthen the knowledge and evidence on antimicrobial use and resistance through surveillance (Ministry of Health MoA, 2020). We found high pooled prevalence of AMR in bacteria from humans, animals, and environmental samples in Ethiopia, but we identified gaps in AMR data from animal and environmental sectors. There is a noticeable lack of studies that use a One Health approach to collecting and reporting AMR data across all 3 sectors. Next steps to optimizing a One Health approach would be to develop standardized protocols for antimicrobial susceptibility testing in not only humans but also animals and environmental samples. This will support future AMR surveillance by making routine cultures and susceptibility testing more efficient and clinically relevant. Future AMR interventions and policies should prioritize representation from all stakeholders, including the environmental sector, which has historically been under-represented (Essack, 2018, Khan et al., 2018). As Ethiopia carries out its "Strategy for the Prevention and Containment of Antimicrobial Resistance," a collaborative effort among all 3 sectors will be crucial to a One Health approach to AMR surveillance. Integrating AMR surveillance from humans, animals, and the environment is key to understanding mechanisms of transmission and will inform future implementation of One Health interventions to combat AMR across all 3 sectors.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Data generated and analyzed during this review are included in this published article in the form of the main tables and additional figures. Additional details of our analysis are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

KW, JJ, RK, and PR conceived and designed the study. KW performed the literature review and extraction of data. AWF and KW analyzed and interpreted the data, created figures and tables, and drafted the manuscript. JJ, RK, and PR offered mentorship and guidance on antimicrobial resistance. RT, GM, AM, and AA offered veterinary expertise and Ethiopian perspective. RK and PR contributed equally as co-senior authors. All authors read, commented, and approved the final manuscript.

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Authors' information (optional)

AWF is currently an infectious diseases clinical fellow at Emory University School of Medicine, Department of Medicine, Division of Infectious Diseases.

Supplementary materials

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