

BMJ Open Understanding transmission pathways and integrated digital surveillance potential of antimicrobial resistance in Ethiopia in a One Health approach: a mixed-method study protocol

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ABSTRACT

Introduction Antimicrobial resistance (AMR) has a critical global impact, mostly affecting low- and middle-income countries. A major knowledge gap exists in understanding the transmission pathway of the gut colonisation with AMR bacteria between healthy humans and their animals in addition to the presence of those AMR bacteria in the surrounding environment. A One Health (OH) approach is necessary to address this multisectoral problem.

Methods and analysis This cross-sectional, mixed-method OH study design will use both quantitative and qualitative methods of data collection. Quantitative methods will be carried out to assess the prevalence and risk factors associated with multidrug resistant Gram-negative bacteria and vancomycin-resistant enterococci in humans, animals (cattle) and the environment. The focus will be on cattle rearing as an exposure risk for AMR among humans. The assessment of AMR in the population of Jimma, Ethiopia with or without exposure to cattle will reinforce the importance of OH research to identify the impending exchange of resistance profile between humans and animals as well as its ultimate dissemination in the surrounding environment.

The targeted semistructured key stakeholder interviews will aid to strengthen the OH-AMR surveillance in Ethiopia by understanding the acceptability of an integrated AMR surveillance platform based on the District Health Information Software-2 and the feasibility of its context-specific establishment.

Ethics and dissemination The study has been approved by the Regional Ethics Committee, Norway, and the Institutional Review Board of Jimma University, Ethiopia. The study's data will be stored on a secure server known as Services for Sensitive Data hosted by the University of Oslo. In addition, the new European Union Global Data Protection Guidelines for data sharing, storage and protection will be followed. We will publish the results in peer-reviewed journals and present the findings at national and international conferences.

INTRODUCTION

Antimicrobial resistance (AMR) is a global public health challenge without geographical restrictions. Inappropriate use of

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ We present an integrated One Health (OH) antimicrobial resistance (AMR) surveillance in Ethiopia focused on human, animals (cattle) and the environment, which will address the potential transmission of AMR between the OH sectors and will aid to strengthen the local surveillance capacity.
- ⇒ Spatial mapping of the environmental resistant pathogens and physiochemical properties of the aquatic environments will aid to identify possible hotspots.
- ⇒ The cattle-rearing practice, biosecurity system and antibiotic dispensing in the study site may not represent those of other regions in Ethiopia or the whole country.
- ⇒ Sample size is comparatively small to conclude cattle rearing as an occupational risk. Therefore, any findings from analyses of the questionnaire data administered to selected household members will be exploratory, and can be considered pilot data for further research.
- ⇒ All routes of exposure to AMR in both cattle rearing or non-rearing population may not be identified in this study such as exposure to other animals/livestock, behaviours related to antibiotic dispensing and use in the selected site and specific household practices that may be related to either exposure or transmission.

antimicrobials, absence of microbiological diagnostic services, poor sanitation (personal and environmental), shortage of clean water and interpersonal spread are key factors in the development and dissemination of resistant bacterial strains in low/middle-income countries (LMICs).¹ Studies have documented a high prevalence of AMR in LMICs, whereas the epidemiological situation in the WHO African region is largely unknown.^{2–4} In a recent review article, it was demonstrated that reliable AMR data were not

available from a significant number (42.6%) of African countries, and some of the susceptibility results were dubious as the resistance patterns were highly unusual.⁵ WHO has also identified Africa and South-East Asia as the regions without established AMR surveillance systems.⁶ Therefore, surveillance of AMR and proper use of antimicrobials are difficult to implement in LMICs.⁷ An interdisciplinary surveillance system for optimising the use of antimicrobials in human and animal health and in agricultural practices is needed for improved and successful national and global containment of drug resistance. We aim to focus on these issues in the resource-constrained setting of Ethiopia.

In many LMICs, antibiotic use in veterinary medicine, aquatic and terrestrial agriculture is weakly regulated or regulations are not put in practice, along with frequent disposal of animal manure and waste to the environment or used as agricultural fertiliser.^{8,9} With irrational antibiotic use in agriculture and livestock farming, there are concerns about the spread of resistant bacteria from animals to humans and the environment, contributing to the reservoir of antibiotic resistance genes, the so-called resistomes.¹⁰ The lack of well-regulated farm waste disposal systems and excessive and unregulated use of antibiotics as prophylactics and growth promoters in food production and animal farming act as the major contributors in this perspective.¹¹ Resistant bacteria have been observed in the environment to a large extent including water, soil, wildlife and fresh produce.¹² Therefore, it is important to quantify and identify the source of environmental reservoirs of resistant pathogens and to establish environmental interventions to prevent the transmission to humans and animals.¹¹ The transmission of these bacteria to humans, specifically their role in infectious diseases and the potential consequences of the reduced susceptibility to antimicrobials on the outcome of infections, is largely unknown.

In addition to environmental contamination, livestock workers are one of the occupational groups at risk of becoming colonised with resistant bacteria. However, the rate of colonisation between occupational groups in food chain may differ based on the farm types and working hours.¹³ A high proportion of fresh meat samples (20%) intended for human consumption in Ethiopia has been documented to contain *Escherichia coli*, and 46% of the tested bacterial strains were multidrug resistant.¹⁴ Another study conducted among cattle farm workers in Egypt revealed that the workers' hands and nasal pathways were heavily contaminated with similar resistant bacteria detected in the air of the farming environment.¹⁵ Unfortunately, we could not find any research conducting concurrent sampling of humans, food animals and the surrounding environment, nor human resistance data based on occupational exposure to rearing of food animals like cattle/poultry in sub-Saharan countries. Therefore, in our current study, we aim to develop a One Health (OH) surveillance approach in Ethiopia, through screening humans, animals (cattle) and the environment

for Multidrug-resistant Gram-negative bacteria (MDRGN) and vancomycin-resistant enterococci (VRE) to understand the transmission dynamics between these different sectors in a multidisciplinary way.

We argue that an integrated and user-friendly surveillance platform to collect and use the AMR data is equally important as the OH surveillance approach itself. Without a uniform, open-access and global platform for AMR data archiving, analysing and sharing, the interdisciplinary surveillance approach will not be effective.¹⁶ As per WHO recommendations, the National AMR Surveillance Plan in Ethiopia was approved in 2017 and aimed for a nationwide laboratory-based sentinel surveillance system by 2020.¹⁷ However, the national action plan did not include animal health and environmental surveillance for AMR. In addition, the Ethiopian authorities mentioned the challenges of real-time data entry and transfer with resource management and communication among the microbiology laboratories at the implementation phase.¹⁸ Like many other LMICs, the ongoing research studies in the different regions of the country also collect and disseminate their AMR data independently, and lack any sort of linkage with national databases. To address these challenges, we want to explore the acceptability and feasibility of the usage of an integrated AMR surveillance platform based on the District Health Information Software-2 (DHIS2).

DHIS2 is an open-source, web-based health management information system platform managed by the Department of Informatics at the University of Oslo (UiO). Most solutions work offline, enabling improved reach in locations with poor connectivity.¹⁹ If the national AMR action plan in Ethiopia adopts DHIS2 as the general data platform, it will be linked with all research and routine data on drug resistance in the country. This platform is currently being used in 47 countries including Ethiopia especially for reporting, analysis and dissemination of data from different national disease control and immunisation programmes, and regular reporting from subdistrict level to national health system.²⁰ However, it has never been used as a surveillance platform for AMR in the African region. Therefore, in addition to the quantification of the resistant pathogens, we will also conduct a qualitative key informants' survey on the OH approach to understand the context-specific acceptability and feasibility of the DHIS2 platform among relevant stakeholders in Jimma, Ethiopia.

To our knowledge, our protocol describes the first study in the sub-Saharan Africa region collecting samples from healthy humans and cattle along with the adjacent environment to develop an integrated AMR profiling in a geographical area. The faecal carriage of resistant bacteria in humans and animals coupled with geospatial mapping of sampling and analysis of spatial distribution of AMR will provide a link of occupational risk exposure and baseline data to initiate an OH-AMR surveillance at the local level. Furthermore, the qualitative feedback of local AMR stakeholders on the feasibility of using DHIS2

as a digital AMR surveillance platform would be the basis of DHIS2 customisation to make it fully functional for this purpose. We believe that our study will be an important step forward to strengthen the local AMR surveillance applying a multisectoral OH approach.

The specific objectives of our study are as follows:

1. To determine the prevalence of colonisation with MDRGN and VRE in people, animals (cattle) and the environment, comparing cattle-rearing and non-cattle-rearing households (HHs), in the Jimma region of Ethiopia.
2. To evaluate possible transmission pathways of MDRGN and VRE through linking the resistance pattern obtained from the three different sectors, that is, human, animal and the environment within the Jimma region of Ethiopia.
3. To evaluate potential predictors/risk factors for colonisation with MDRGN and VRE in people, comparing cattle-rearing and non-cattle-rearing HHs, from the Jimma region of Ethiopia.
4. To observe the spatial variation of the occurrence of MDRGN and VRE in different settings (cattle rearing and non-cattle rearing) and environmental compartments from the Jimma region of Ethiopia.
5. To conduct targeted interviews for understanding the acceptability of an integrated digital AMR surveillance platform based on DHIS2 and the feasibility of its context-specific establishment.

Thus, this project will contribute to capacity building and evidence generation for implementation of a continuous, systematic OH-AMR surveillance system in Ethiopia, which is an important prerequisite for appropriate policy

generation at national and local levels for both AMR and antibiotic stewardship.

METHODOLOGY AND WORK PLAN

Study site and duration

This ongoing study will be 3 years in duration and it will take place in Jimma, at the Oromia Region of Ethiopia (figure 1).²¹ Jimma is a special zone of the Oromia Region as well as the largest city in South-Western Ethiopia where livestock, especially cattle and sheep, are a major component of agricultural economy. We have already collected qualitative data.

Study design

This study will use a mixed-method OH study design, including cross-sectional quantitative data collection in humans, animals and the environment and key informant interviews (qualitative data collection) in order to test the potential for the establishment of digital AMR surveillance platform such as DHIS2 (figure 2). The study design will be adopted to suit our main research outcomes, that is, to establish the prevalence of and risk factors for MDRGN and VRE in humans, animals and the environment, and at the same time, the potential for using a OH digital surveillance platform in the study area.

This project consists of five work packages (WPs).

WP 1: recruitment of human participants and animals

After obtaining the list of HHs rearing cattle from the local Livestock Office, the required HHs (n=55; for sample size calculation, see below) will be randomly selected from the list. Following information about the study, the person

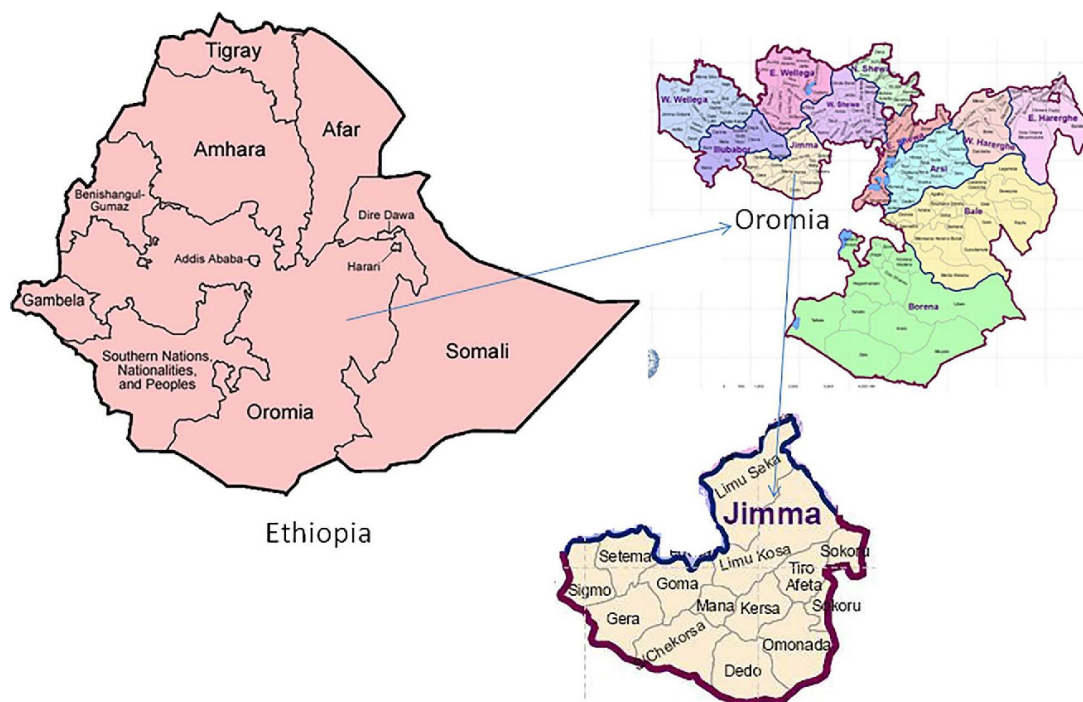


Figure 1 Map of study area (Jimma).²¹

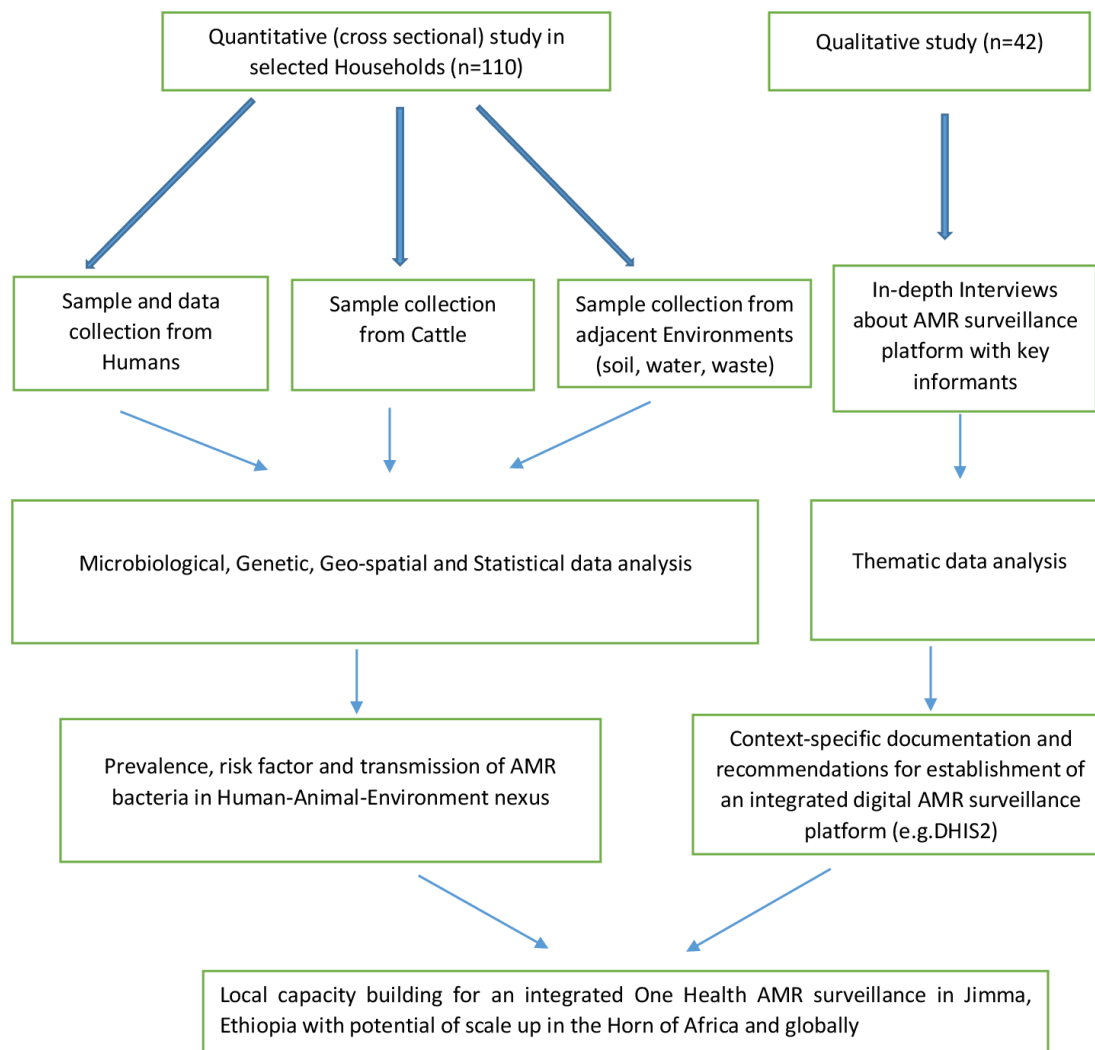


Figure 2 Schematic description of the study components and expected outcomes. AMR, antimicrobial resistance.

taking care of the cattle such as cleaning, feeding and giving medication will be requested to participate. Only volunteers who are willing to provide written consent will be recruited. The matched (age and sex) control from the neighbouring non-cattle-rearing HH (n=55) will then be asked to take part in the study to ensure that both cattle-rearing and non-cattle-rearing HHs (n=110) share the same environment. Structured interviews and the collection of stool samples from single individuals in each selected HH and two cattle from each cattle-rearing HH will be conducted by the field team, including an experienced veterinarian. This process will be led by an expert OH researcher (MA).

WP 2: sample collection, processing and laboratory analysis

Human and cattle faecal samples

The study participants will be provided a stool sample container the day before the interview and approximately 10g fresh stool sample will be collected the next day by field staff. The stool sample must have been collected within 2 hours by the field staff. For cattle, faecal samples (approximately 30g) will be collected by a trained veterinarian directly from the rectum of the selected cattle on

the date of interview and will be transported to the local laboratory along with other samples.

Environmental samples

The environmental samples (soil, drinking water both at the point of source and at the point of use, solid waste/waste water, pond and river water) will be collected and processed as per standard precautions and procedures. Soil samples (n=110; n=55 for cattle-rearing and non-cattle-rearing HHs each) will be taken by an autoclaved spoon (20g), at maximum depth of about 0.5 inch (from the surface) at an area of all selected HHs where movement of people is more frequent (eg, near the kitchen or in front of the main door). Drinking water samples will be collected from two sources: from the point of use at HH jars/pitchers (n=110) and from the point of source (n=110) from a nearby well or supply tank. Each sample will be 500 mL of drinking water. The wastewater/solid waste samples, which are available (n=110), will be collected as pooled samples (500 mL/20g) from the waste dumping areas at three different locations surrounding the HHs and their kitchens.

The ponds and rivers (surface water) are usually assumed common for the selected HHs. We assume to collect samples from ponds and rivers at different points based on the proximity of the selected sampling units. A sterile bottle (500 mL) will be plunged about 30 cm below the water surface to allow the bottle to fill completely.

A new pair of gloves will be used before collection of each type of sample and the bottles will be kept in the cool box after collection for transportation to the laboratory analysis.

Sample processing

All samples will be transferred to the Microbiology Laboratory at Jimma University (JU) in appropriate cooled containers and marked with identification codes. For isolation of bacteria, human stool, faeces of cattle and environmental samples will be processed locally.

Laboratory analysis

Conventional phenotypical analyses and antibiograms from human, animal and environmental samples will be conducted at the Microbiology Laboratory at JU. MDRGN and VRE will be identified using selective media. DNA/RNA from these strains will be isolated, stored frozen (-80°C) and will be sent to Norway for genetic analyses, for example, whole-genome sequencing (WGS). WGS of approximately 40 isolates (five from each sample type), will be performed in collaboration with the Department of Microbiology, Oslo University Hospital (OUS) and the Turning the Tide of AMR network at OUS. We will use Qiagen DNA extraction kits for environmental samples particularly DNeasy PowerSoil kit for soil samples and DNeasy PowerWater for water samples. Stool (both human and animal faeces) will be processed by QIAmp DNA Stool Mini Kit. For bacterial isolates, heat-lysis DNA extraction methods will be followed. Antibiotic susceptibility tests (ASTs) for all selected isolates by disk diffusion method will be performed according to EUCAST (www.eucast.org). Bio-Rad CFX96 PCR platform (using TaqMan) will be used for the detection of resistant genes. To further explore genetic determinants, WGS will be carried out in Illumina MiSeq platform. The laboratory techniques such as DNA extraction, qPCR, culture and AST will follow standard procedures as described in Rousham *et al.*¹¹

WP 3: geospatial mapping

We will collect global positioning system coordinates of every place of sample collection and will plot the presence of AMR bacteria and their resistance gene profile in the different environmental compartments in each location with geographical information system software named as ArcGIS. Through this analysis, the extent of environmental contamination with AMR bacteria from anthropogenic activities will be assessed. The spatial variation in the prevalence and concentration of MDRGN and VRE in soil, drinking water, wastewater, ponds and river samples will be compared using quantitative microbiological and

geospatial mapping. We consider the soil and drinking water sources as ‘upstream’ and the wastewater outlets adjacent to individual HH and surface water sources (pond and river water) nearby as downstream locations. The ultimate goal of this approach is to identify the ‘hotspots’ of environmental AMR from upstream to downstream and a greater understanding of sources of contamination for future containment of AMR.

WP 4: qualitative study to understand the acceptability and feasibility of DHIS2 in Jimma, Ethiopia

The study participants will be purposefully selected by relevant key informants for AMR surveillance such as clinicians, veterinarians, environmental professionals, laboratory personnel, hospital administrators and data management people.

Data collection tool

The current status of AMR surveillance with a OH approach (human, animal and environment) in Jimma will be evaluated. A semistructured interview among key informants will be performed using a theme-based interview guide (online supplemental file). The key informant participants will answer questions based on their experience and knowledge.

WP 5: integration and statistical analysis

After obtaining the interview and laboratory data from Ethiopia, we will generate an integrated database. Both descriptive and inferential statistics will be used for data analysis, particularly for comparing between cattle-rearing and non-cattle-rearing HHs. In addition to phenotypical characterisation, the identification of resistant bacteria in humans, cattle and the environment with their clonal relationship at genetic level will be analysed. This will yield more in-depth information regarding the transmission pattern. The quantitative data from the HH survey questionnaires will be analysed using STATA (StataCorp College Station, Texas, USA). Finally, we will try to identify significant predictors/risk factors for AMR in the population of Jimma, using relevant statistical analysis including logistic regression or linear models to provide evidence-based information for AMR surveillance policy.

The semistructured key informant interviews will be recorded via an audio instrument. The audio will be transferred to transcripts, coded and categorised into potential themes and then imported into the qualitative NVIVO/ATLAS-Ti software. The NVIVO/ATLAS-Ti software will be used as an organising tool, which is suitable to gather qualitative data in a meaningful manner. Furthermore, in order to find connections between themes and to establish a thematic framework, a thematic analysis will be adopted. The analysis will elaborate on the text that refers to the relevant interview themes but also observe the absence of comments to specific themes.

Sample size justification

Data on the prevalence of MDRGN and VRE in the environment, humans and livestock in Jimma, Ethiopia,

are scarce. We will include HHs as a sampling unit and we will select one person per HH. Based on the last national census (<http://www.csa.gov.et>) in Ethiopia, the number of HHs in Jimma area is 32 191. Though several important OH studies^{22 23} have been carried out in similar settings without any prior assumption of prevalence or expected difference between groups, we have calculated our sample size with a conservative estimation. Assuming 50% as the most conservative estimate of the prevalence of MDRGN and VRE colonisation in people at HH level, a precision of 12% and a confidence level of 95%, we arrive at a total sample size of 67 HHs using the Win Episcope V.2.0 (<http://www.winepi.net/uk/index.htm>). However, we require a statistically significant sample size for each arm (cattle and non-cattle rearing). Therefore, considering parameters as $\alpha=0.05$, $\text{power}=0.80$, probability of exposure in non-cattle rearing arm=0.25 and odds of being more colonised in cattle-rearing HH=3, we reached a sample size of 110 HHs to include equal number of HHs ($n=55$) in each arm (cattle rearing and non-cattle rearing). The list of HHs with and without cattle will be taken from the local authority and the study subjects from non-cattle-rearing HHs will be matched with those having exposure to cattle. A proportional stratified sampling method will be adopted to select the 110 HHs with each stratum representing a group of 10–11 HHs based on their geographical location. Assuming sampling of one member per HH, we arrive at 110 people to be sampled and 2 cattle from each cattle-rearing HH (to address the diversity among the herd) will be included for faecal sampling. Therefore, the human and animal sample size will be equal ($n=110$).

In addition to human and animal faecal samples, environmental samples (soil, drinking water both at point of source and point of use, solid waste/waste water, pond and river water) will also be collected from the adjacent areas of all selected HHs. We will collect 110 samples for each type. Therefore, the total number of collected samples will be 880 (approximate).

For the qualitative interviews, we aimed to include 35–40 key informants based on expected data saturation. However, we interviewed 42 key informants for this component.

Patient and public involvement

No patient will be involved. However, in preparation and before the fieldwork, investigators visited the study site to meet and discuss activities with the local community, especially with cattle owners (farmers), staff members at the JU Hospital, veterinary faculty members at JU and government's livestock officers. Communication with these contacts helped gather an overall idea of the study context and judge the appropriateness of our intended methods and approaches. Feedback from the different stakeholders on the research has been incorporated in the implementation plan of this study. The stakeholders as well as the local communities including local government

and non-governmental organisations will be included as part of the planned dissemination activities.

Hypotheses

H1: exposure to cattle rearing and the use of antibiotics in cattle farming pose risks to carriage of drug-resistant pathogens in humans.

H2: drug-resistant pathogens and their genes prevalent in cattle are major source of the environmental resistome especially in the adjacent aquatic environment.

H3: spatial variation in the occurrence of the environmental resistomes is present due to physiochemical properties of water bodies and various sources of human and animal origin pollution.

H4: there is an unmet need of an integrated digital AMR surveillance platform in resource-constrained settings like Ethiopia.

ETHICS AND DISSEMINATION

This study protocol was submitted to the Regional Ethics Committee in Norway and was approved (reference number 28914/2019). It has also been approved by the JU Institutional Review Board (reference number IHRPGD 785/20).

The study data will be secured and stored according to national guidelines on local secure servers, for example, Services for Sensitive Data at the UiO. In addition, the new European Union Global Data Protection Guidelines for data sharing, storage and protection that came into effect in April 2018 will be followed. The study findings will be published in peer-reviewed journals and presented at national and international conferences.

Written informed consent will be sought from all individuals taking part in the study and participation will be of their own free will. Informed consent in local language (Amharic and Afan Oromo) will be obtained from the participants to ensure understanding of the study objectives. People-related data will be de-identified and eventually anonymised according to study needs and overall ethical consideration.

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Contributors MA, EKR, ZM and ASW all contributed to the design of the study and the development of this study protocol. MA, EKR and ZM contributed to the field methods and laboratory protocols. MA wrote the first manuscript draft. EKR, ZM, ASW and CG gave critical input to revise the manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

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