Towards multi-sectoral actions to tackle antimicrobial mis-use and resistance in Tanzania

KEY MESSAGES

- Antimicrobials (including antibiotics) are natural or synthetic agents that kill microorganisms or stop their growth
- Despite usefulness of antimicrobials in the treatment and prevention of infectious diseases in human and animals, the world is now faced with the threats of antimicrobial resistance (AMR)
- The misuse and abuse of antimicrobials in human, animal and crop health practices are the main driving factors to the development and spread of AMR
- The increase and widespread AMR mean that infectious diseases that were once easily treatable can become costly and deadly
- This policy brief provides a summary of the AMR threat associated with human, agriculture and food production systems in Tanzania and suggest steps required to mitigate the situation.

EXECUTIVE SUMMARY

During the past 10 decades, antimicrobials (including antibiotics) have played an essential role in the treatment of infections in humans and animals and have significantly improved population health. However, over the years several antimicrobial agents have become less or completely ineffective against the targeted disease-causing agents. The misuse and abuse of antimicrobials in human, agriculture and food production practices have been described to be the main driving factors to the development and spread of antimicrobial resistance (AMR). AMR may cause complicated, untreatable, and prolonged infections in humans, leading to higher healthcare cost and sometimes death. In Tanzania, the overuse and misuse of antimicrobials in human health, agriculture and food production systems and the subsequent contamination of the environment has been associated with development and spread of AMR.Moreover, antimicrobial use (AMU) in crops and food-producing animals may leave residues in foodstuffs like fruits, meat, milk, and eggs, hence selecting the resistant organisms. This situation is exacerbated by the fact that there is lack of surveillance programmes on AMU in agriculture and food production systems.Tanzania has developed the National Action Plan on Antimicrobial Resistance to address the problem. The success in addressing AMU and AMR will depend on effective implementation of the plan through coordinated one health approach. This policy brief analyses the threat of AMR in human, animals and crops and provides actions to be taken to curb the problem in Tanzania.

THE PROBLEM

Background

Since their discovery, antimicrobials (including antibiotics) have played an essential role in the treatment of infections in humans and animals and have significantly improved population health. However, in recent years, antimicrobial resistance (AMR) has emerged as among the major global threat to public health systems. Resistance means that an antimicrobial agent becomes less effective, up to becoming completely infective, against disease causing microorganisms it targets. The misuse and abuse of antimicrobials in human, animal and crop health practices have been described to be the main driving factors to the evolution and spread of AMR.

Available statistics in Tanzania indicate that the prevalence of multidrug resistant (MDR) bacteria

ranges from 25% to 50% [1-4]. On the other hand, the resistance to ampicillin, sulphonamide, tetracycline, chloramphenicol, nalidixic acid, kanamycin and ciprofloxacin have been mostly detected in the majority of the domestic animals[5]. MDR *Escherichia coli* strains have been detected in different food animals, such as poultry in Tanzania[5-7]. There are reports that resistance rates for trimethoprim-sulfamethoxazole among the common pathogen *Streptococcus pneumoniae* among children had increased rapidly between 2003 and 2012 [3,8].High levels of Campylobacter resistance to commonly used antimicrobials in both humans and animals [9,10] have been reported in the country. Genes that confer resistance in animal, human or environment have been reported in Tanzania[11, 12]. AMR is of great public health concern because the antimicrobial-resistant pathogens may be pathogenic to humans, easily transmitted to humans via food chains, and widely disseminated in the environment via animal wastes.AMR may cause complicated, untreatable, and prolonged infections in humans, leading to higher healthcare cost and sometimes death [13].

Antimicrobial use in humans

Data on antimicrobial use (AMU) humans is very limited in Tanzania [14]. A recent study in northern Tanzania reported an overall prevalence of antibiotic use of 44.0%[15], with ceftriaxone, metronidazole and penicillinsas the most commonly prescribed medicines in hospitals.Moreover, antimicrobial for treatment of infections are usually frequently prescribed empirically without results of laboratory examination to guide treatment [16]. In addition to high use of antibiotics in health care, self-medication is a common practice in the country. Results from studies done in Kilosa and Moshi districts have shown that the guardians/parents practice self-medication and once their children get sick, they prefer to purchase drugs from the pharmacies /drug shops or use left-over medicines from their homes, neighbours, relatives or friends and other sought advice from vendors[17, 18].

In Tanzania, community pharmacies/drug shops are a source of antimicrobials. A study in Dar es Salaam reported that 45% of the dispensed medicines were requested by the client, 32 were recommended by the dispenser and only 23% were on prescriptions [19]. In the same study, of the client who bought antimicrobials, one-fifth bought incomplete doses. In a study in Moshi, it was recently reported that 92.3% of

retailers dispensed antimicrobials without prescriptions. The antibiotics most commonly dispensed without a prescription were ampiclox and azithromycin[20].In another study in Mbeya, Morogoro, Singida and Tanga, 84% of patients with acute respiratory infection were sold one antibiotic on request without a prescription [21].

Antimicrobial use in agriculture and food production systems

Due to the increased demand of crop and animal protein, intensive farming has been the most common strategic path undertaken. Thus, antimicrobial agents are commonly used in crop production for control of pests, and in animal production systems for growth promotion, the treatment of sick animals and the prophylactic and/or metaphylactic treatment of healthy animals. The misuse and overuse of antimicrobials of variable quality and efficacy in crops, humans and animals, improper storage and disposal of antimicrobials and preservatives for food and antibacterial agents in household products are common [22, 23].

Antimicrobials find their way into crops through spray in crops, animal-sourced manure, antimicrobial-laden waters from sources of effluent pollution used for vegetable farming [24]. AMR resistance in food can be a result of contamination with resistant micro-organisms or drug residues during harvesting, transportation, preparation and consumption of raw products [25, 26]. In addition, the use of manure and waste water for irrigation and contamination by handlers during harvesting, transportation and processing are some of the causes of AMR in vegetables and fruits [27, 28]. Studies have indicated a strong link between the use of fungicides in agriculture and clinical development of azole resistance *Aspergillus fumigatus*[29, 30]. *A. fumigatus* is a pathogen most frequently associated with chronic pulmonary and invasive aspergillosis [25, 31].

Antimicrobial use in fish and bee farms

Antimicrobials are also used in fish farms to prevent or treat bacterial infections especially in hatcheries. The increased use of antimicrobial use in fish farms and antimicrobial residues in the aquatic environment have led to an increase in the prevalence of antibiotic resistant bacteria. In a study in Tanzania, integrated fish farming practices using domestic farm and poultry waste along with antimicrobial residues from animal

husbandry were reported to contribute to a pool of resistance genes in the aquaculture systems [32].Bee keeping industry is growing in Tanzania and antimicrobials are commonly applied to eliminate disease among honeybees. Studies have shown that honey and other bee products face problems in the growing use of antibiotics, hence honey may become contaminated with residues of antibiotics and thus affects the human health and environment.

Antimicrobial residues in food

The AMU in food-producing animals may leave residues in foodstuffs like meat, milk, and eggs.Antimicrobial contamination in various foodstuffs has been reported Tanzania [33]. Over one-third of marketed of milk samples in Mwanza and Dar es Salaam have been found to contain antimicrobial residues [34].Oxytetracycline residues have been detected in tissues from cattle in the Kilosa [35]. The occurrence of antimicrobial residues (AR) may be due to a failure to observe the withdrawal periods of each drug, extra-label dosages for animals, contamination of animal feed with the excreta of treated animals, or the use of unlicensed antimicrobials. Antimicrobial residues in foods may be associated with a number of health concerns in humans [36]. In a study in northern Tanzania, though majority of the smallholder dairy farmers were aware of drug residues, but over half of them (57 %) were unaware of human health effects caused by veterinary drug residues in milk[37].

Despite the impact of AMU on AMR, there is limited knowledge concerning the transmission of AMR within agricultural sites and to humans via foods of plant and animal origins in Tanzania. Moreover, there is inadequate knowledge as regards to human health risks posed by the agricultural release of antimicrobial agents, antimicrobial resistance genes, and antimicrobial-resistant bacteria into the environment. There is lack of surveillance programmes on AMU in crop production, including lack of application records, in Tanzania, which these hinder efforts to estimate the real number of antimicrobials being applied for crop protection.In Tanzania, although the agricultural sectors consume a large portion of antimicrobials in animal farming [38], there is no clear regulation controlling antimicrobial contamination of feedstuffs in most countries.

Drivers of antimicrobial resistance

Several factors have been identified to contribute to the increase in AMR in Tanzania. The uncontrolled use of antimicrobials both in humans and animals coupled with environmental contamination are responsible for the development and spread of AMR. Higher proportion of usage of veterinary antimicrobials for prophylactic and therapeutic purposes in animal farmingare common[38].Improper disposal of wastes from households, disposal of human and veterinary drugs, and weak implementation of the legal framework have been identified as the major contributors to the environment contamination with antimicrobials [2, 24, 38]. Other factors include misuse and overuse of antimicrobials of variable quality and efficacy in humans and animals, improper storage and disposal of antimicrobials and preservatives for food and antibacterial agents in household products.

Lack of continuing education on AMU for prescribers and animal health practitioners, agriculture extension officers, tendency for animal owners to stock drugs in their houses and engaging unskilled people to treat animals contribute to mis-use of antimicrobials. High degree of drug abuse by livestock keepers through failure in observing the recommended therapeutic doses, use of wrong routes of administration, non-observance of withdraw periods and unregulated disposal of pharmaceutical wastes have been documented in Tanzania [38-40].Socio-economic factors such as lack of awareness on antimicrobial, illiteracy, poor economic status, and lack of faith in government programmes, influence self-medication and self–veterinary care among farmers [41,42].

POLICY OPTIONS AND RECOMMENDATIONS

The threat from AMR calls for concerted and integrated actions to prevent the spreading and the emergence of new resistant strains. The control of AMU and hence AMR could potentially be addressed through educational and other interventions targeting all key stakeholders including policy makers, manufacturers, distributors, prescribers, and consumers of antimicrobials. The aim is to improve surveillance of AMR organisms among humans, animals and crops, delay emergence, limit transmission, and mitigate harm among patients infected with resistant pathogens.In 2017, Tanzania developed and launched its first National Action Plan on Antimicrobial Resistance to address the AMR threat. Several achievements have been recorded during the past four years. These include (i) the

establishment of a multi-sectoral coordinating committee; (ii) the establishment of human and animal surveillance sites; (iii) creation of AMR awareness in the community and (iv) availability of guidelines at the health facility level to ensure AMR stewardship[42].However, some dimensions of the governance areas, including reporting and feedback mechanisms, accountability, transparency and sustainability of AMR plans, are not effectively implemented. Addressing these challenges should involve strengthening the collaboration of the different sectors involved at different NAP implementation levels by careful planning and coordination, and provision of adequate resources to ensure sustainability. To control and prevent the increase in AMR in Tanzania the following measures need to be undertakenand/or consolidated:

Enforcement of Regulations
The Government needs to enforce the requirements for a prescription in the use of antimicrobials in both human, animal and plant health. This could involve the review and dissemination of standard treatment guidelines. Key policies/regulations for addressing AMU and AMR in agriculture and food production are needed. These should include policies on prescription practices, regulations on animal feed, surveillance of AMR and AMU, antimicrobial disposal, and strengthening the national drug regulatory authorities in the agricultural and environmental sectors.Already the Government of Tanzania has developed Guidelines on the use of antimicrobials in for healthcare staff [43]. Moreover, regulatory authorities with capacity to monitor AMU in agriculture and other food production systems need to be established/strengthened.

To curb mis-use of antimicrobials, emphasis should be given to improved animal husbandry practices, biosecurity measures and animal diseases management.It is equally important that factors such as unregulated drug availability, inadequate antimicrobial drug quality assurance, inadequate surveillance, and cultures of antimicrobial abuse must be addressed to permit a holistic strategy for AMR control. Tanzania should develop and implement washout periods between the use of antimicrobial and animal slaughter, milk, egg and honey consumption.Environmental regulations to monitor and control many of the pathways responsible for the release of antimicrobials should be emphasized in the implementation of the NAP. It is important that the

national multi-sectoral coordinating committee to include a representative from the environmental sector. To reduce unnecessary use of antimicrobials in agriculture and their dissemination into the environment, the Government should introduce bans on the use of antimicrobials for growth promotions. This could be through regulation, taxation, and subsidies of alternatives to lower antimicrobial use as well as increase vaccine coverage in agriculture and aquaculture.

Strengthening of the laboratory diagnostic services
Detection of resistance and monitoring its spread requires appropriate laboratory-based surveillance. Thus, to maintain the useful life of antimicrobial agents in the country there is need to strengthen and promote the use of laboratory to provide confirmatory diagnosis before clinical management is instituted in both humans and animals. There is need for concerted actions and increased investment into laboratory capacity strengthening, including quality assurance, laboratory networks and standardization of methodologies.Rapid point-of-care diagnostic tests are likely to be part of the solution to reduce huge quantities of antimicrobials that are wasted on patients who actually do not need them. Reducing underdiagnosis and overtreatment in primary healthcare facilities through strengthening the diagnostic capacity is crucial. It is time that provision of low-cost rapid diagnostics for the endemic febrile-associated diseases is seriously considered to reduce unnecessary use of antimicrobials.

Infection Prevention and Control
The effective prevention of infectious diseases and the adoption of strict sanitation and hygiene standards may reduce the unnecessary use of antimicrobials and limit the impact of AMR infections, in both the human and animal health sectors.In the health sector, improving infection prevention and control practices, including behaviour change, should be emphasized at both the facility and household levels. Handwashing by clinicians and other facility staff, between contact with patient should be emphasized. On the other hand, it is critical to establish/promote biosecurity principles for food animal production systems. Emphasis should be given to improved animal husbandry practices, biosecurity measures and animal diseases management. Routine vaccination against some of the endemic bacterial diseases in domestic animals may be of great value.In fish farming, it is also possible to

increase productivity through vaccination programmes and sound biosecurity measures.Antimicrobial use in feed additives should be banned.There is need for promoting changes in production practices and animal husbandry systems to improve hygiene, and reorganizing the planning of production sites to reduce disease.

One Health AMR Surveillance and Monitoring

There is need to establish/strengthen a One Health AMR surveillance system to enhance burden estimation for early detection of emerging AMR pathogens. AMR surveillance and monitoring aims to detect and track changes and trends in microbial populations including drug-resistant microorganisms and resistant determinants. The proposed One Health AMR surveillance system is envisaged to integrate findings on drug-resistant microorganisms in animals, humans, plants and the environment. This involves sharing data and information across sectors for a more effective and coordinated response to tackling AMR. It is equally important to strengthen the national monitoring programmes for AMU, AR, and AMR in agriculture and food production systems to assess the effectiveness of AMR control and prevention measures. The surveillance and monitoring systems in agriculture and food production sector should provide timely information on the scale of AMR in animals, plants and the environment, AMU and the levels of antimicrobial residues in food. National monitoring of AR in foods and updating of the maximum permissible limits of these residues should be undertaken.

The implementation of these recommendation should be complemented by relevant research studies to explore the challenges hindering the enforcement of available polices/regulations on AMU in health, agriculture and food production systems.Studies to understand the economic and social factors that are propelling the use of antimicrobials in health and food-animal production are critical.

Training on AMU and AMR

Studies in Tanzania have shown that prescribers and paravets have been rarely exposed to training on AMU and/or AMR. It is important that pre-service and in-service trainings of human and animal health staff on AMU and AMR are introduced/promoted. The government and relevant institutions should develop worker's education and curricula guides on antimicrobial use and resistance. Through education and other means of effective communication we will improve awareness and understanding of AMR.It is equally important that the government, in collaboration with non-governmental organizations and the private sectors, play an important role to train veterinarians, paravets, guide development of regulatory frameworks for antimicrobials, and improve farming practices, and other similar methods of capacity building.

Sustained Public Awareness Campaigns

It is important to create awareness and provide education interventions to improve the understanding of AMU, AR, and AMR in humans, agriculture and food systems and their subsequent effects on public health, environment and economy. Sustained awareness creation campaigns to inform the community to change behaviours and have positive impacts on health outcome are important. Improving animal health practitioners' and farmers awareness of AMR and education around appropriate antimicrobial use will also be critical. The use of relevant channels of communication, to include social media, text messaging, radio, and television adverts, should be explored. In addition, traditional means such as banners, posters and leaflets in healthcare facilities, veterinary centres, pharmacies should be used.The use of Civil Society Organizations, celebrities, sports stars and other high-profile figures in community engagement and advocacy is recommended.

IMPLEMENTATION CONSIDERATIONS

In Tanzania, except for National Health Policy 2020 (still in a draft form), most of the national policies to a great extent do not have provisions which are relevant to the implementation of AMU and AMR. Surprising, despite the comprehensive nature of the *National Livestock Policy 2006*and the *National Environmental Policy 1997,*they do not address issues of pertaining to the AMU and AMR.The Acts that address AMR include Medical Stores Department 1993, Public Health Act 2009, The Pharmacy Act 2011, Drug Control and Enforcement Act 2015 and the Tanzania Medicines & Medical Devices 2019. The Tanzania National Health Policy 2020stipulates that measures to combat antimicrobial resistance will be established; and that water and food safety will be enhanced. Already, the National Action Plan on Antimicrobial Resistance 2017-2022 addresses actions needed to be taken in order to

combat AMR in Tanzania. The Plan covers in details the desire to strengthen AMR knowledge, surveillance and research and establish a national surveillance system for AMR. It also aims to establish and build capacity for a national reference laboratory and designated laboratories for AMR surveillance, developing a national research agenda on AMR and establishing and supporting a coordinated mechanism that will ensure harmonized AMR guidelines, data management and sharing systems in human, animal and plant health settings.

Tanzania recognises the contribution of cross-sectoral collaboration in addressing complex health problems including zoonoses and disease epidemics through one health approach. However, the current *National One Health Strategic Plan 2015-2020* does not address issues related to AMU or AMR. Thus, AMU and AMR being cross-cutting issues, effective interventions must be multi-sectoral in character and require comprehensive and integrated measures that include human and animal health and food production and supply chains; public, private and civil society actors; governmental and non-governmental players. To implement the proposed approaches, there is need to use the available opportunities including the willingness of some sectors to collaborate; and make AMR among the top agenda in all sectoral plans.

There are, however, some critical factors that need to be addressed for a successful implementation of the proposed policy options. Inadequate knowledge and skills on AMU and AMR intersectoral collaboration at all levels is one of the major challenges. The lack of sustainable institutionalisation of intersectoral partnership has been described to be attributed to attitude of the specific disciplines and experts. Unavailability of adequate resources, lack of clarity on the mandates and lack of institutional framework have also been described as challenges to the implementation of inter-sectoral collaboration [44]. Thus, strategic assessment of extent of potential involvement, level of focus on AMR and AMU and source of resources are necessary prior to implementation.

Competing interests

The authors declare that they have no competing interests.

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