Combating Global Antibiotic Resistance: Emerging One Health Concerns in Lower- and Middle-Income Countries

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Antibiotic misuse in lower- and middle-income countries (LMICs) contributes to the development of antibiotic resistance that can disseminate globally. Strategies specific to LMICs that seek to reduce antibiotic misuse by humans, but simultaneously improve antibiotic access, have been proposed. However, most approaches to date have not considered the growing impact of animal and environmental reservoirs of antibiotic resistance, which threaten to exacerbate the antibiotic resistance crisis in LMICs. In particular, current strategies do not prioritize the impacts of increased antibiotic use for terrestrial food-animal and aquaculture production, inadequate food safety, and widespread environmental pollution. Here, we propose new approaches that address emerging, One Health challenges.

Keywords. antibiotic resistance; One Health; lower- and middle-income countries; animal agriculture; environmental pollution.

Antibiotic resistance is a global public health issue. The need for higher-income countries to support lower- and middle-income countries (LMICs) in identifying actionable strategies has been recognized by major global public health institutions, including the US Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) [1, 2]. Because of unique structural, cultural, and socioeconomic factors contributing to the development of antibiotic resistance, it is widely acknowledged that LMICs require different approaches com- pared with higher-income countries [3–5]. Specifically, LMICs are challenged to improve antibiotic access for therapeutic uses while minimizing antibiotic misuse that causes population-level resistance [6]. Balancing these issues is critical; more children in LMICs countries die from inadequate access to antibiotics each year than drug-resistant infections [3], yet resistance threatens the long-term viability of these drugs. Most LMIC-specific strategies to date have focused on reducing antibiotic misuse in the human health sector [3, 6]. These include antimicrobial stewardship education, strengthened hospital infection control, and increased surveillance of antibiotic use and resistance, as outlined in the WHO's recent Global Antimicrobial Resistance Surveillance System initiative [2, 4].

Fewer strategies have been proposed to address the contributions of animal and environmental reservoirs to the dissemination of antibiotic resistance in LMICs. Terrestrial food-animal and aquaculture production have intensified in LMICs to meet protein demands from an expanding middle class and an urbanizing population [7]. The amount of antibiotics used to grow livestock, poultry, and aquatic animals such as fish and shrimp is rapidly growing, and may already double the volume prescribed annually in humans [7, 8]. The livestock industry in China, where half the world's pigs currently live, is expected to consume 30% of all veterinary antibiotics sold in 2030 [7]. Antibiotic use in food animals selects for antibiotic-resistant bacteria that may spread to humans via contact with animals [9], direct and indirect contact with waste [9–11], and food consumption [8] (Figure 1). Antibiotic misuse in animal agriculture in LMICs may disproportionately impact health due to lack of surveillance, frameworks for training farmers, biosecurity, and food safety regulation (Figure 2) [12–14]. The unregulated use of colistin to grow food animals in China, for example, has been linked to the emergence of novel colistin resistance mechanisms (mcr-1 and mcr-3) [15]; mcr-1 has now been detected worldwide among human colonization and infection isolates [16].

Simultaneously, humans in LMICs continue to be exposed to other environmental sources of antibiotics, resistance genes, and antibiotic-resistant bacteria. Anthropogenic waste streams such as municipal, hospital, and pharmaceutical waste greatly increase environmental reservoirs of resistance when discharged without sufficient treatment [17]. Humans can be directly exposed through consumption of unsafe food and water, poor domestic and personal hygiene, and animal contact [8, 9, 13]. Resulting symptoms of infection may be treated with antibiotics, which are in turn excreted into the environment. A cycle thus persists in which humans both contribute and are exposed to environmental reservoirs of resistance (Figure 1).

To address these evolving contributions to the antibiotic resistance crisis in LMICs, "One Health" approaches should be considered. One Health refers to the concept that human, animal, and ecosystem health are inextricably linked. Efforts to improve public health from a One Health perspective seek to minimize risks that arise from the interface between humans, animals, and the environment. Because of inadequate public health protections (eg, access to clean water, farm biosecurity), humans living in LMICs may be more exposed to animal and environmental reservoirs of antibiotic resistance than humans living in higher-income countries (Figures 1 and 2). Thus, One Health strategies are uniquely needed. Implementing One Health strategies in LMICs will require multidisciplinary collaboration, adequate surveillance systems, and strong laboratory capacity, many of which are challenges for LMICs [2]. However, the World Organization for Animal Health (OIE), Food and Agriculture Organization of the United Nations (FAO), WHO, and other organizations are actively working with LMICs to develop these capacities [2, 18, 19]. Here, we examine the need to work toward One Health strategies that specifically address increasing antibiotic misuse in animal agriculture and growing environmental reservoirs of resistance in LMICs.

ONE HEALTH STRATEGIES TO REDUCE ANTIBIOTIC MISUSE IN LOWER- AND MIDDLE-INCOME COUNTRIES

Manage Antibiotic Use in Livestock Production and Aquaculture

The world population is expected to increase by >2 billion by 2050 [20], with the most accelerated growth in LMICs. Animal- based protein consumption in LMICs is rapidly increasing due to economic development, and intensive animal production systems are proliferating to meet these demands [7]. In addition to using antibiotics for disease treatment, industrial animal production systems routinely feed antibiotics to healthy animals to prevent disease and promote growth [9]. As LMICs convert to this production model, the associated rise in antibiotic use will set back efforts to reduce overall antibiotic misuse in LMICs [7]. Indeed, among countries that currently consume the most veterinary antibiotics, the 5 estimated to have the greatest percentage increases by 2030 are all LMICs: Myanmar (205%), Indonesia (202%), Nigeria (163%), Peru (160%), and Vietnam (157%) [7]. Moderating veterinary antibiotic use will require major changes in LMIC governments' interactions with the agricultural sector (Figure 2).

First, antibiotic use in the livestock and aquaculture industries should be evaluated. Little is known about the quantity, frequency of administration, or types of antibiotics used in animal production in LMICs [8, 9]. Survey results can be used to identify which types or aspects of animal production are most in need of oversight, and once identified, comprehensive monitoring programs could be designed to address them. Many LMICs currently lack the financial capacity and technical expertise needed to design and maintain animal agriculture monitoring programs [2, 18, 19]. Thus, international resources should be directed toward this goal. Since 2015, the WHO, FAO, and OIE have collectively pledged support. Specifically, these organizations pledged to improve awareness about antimicrobial resistance; develop the capacity for surveillance and monitoring in human, food, and agricultural systems; strengthen governance; and promote good practices and implementation of international standards [2, 18, 19]. LMICs receiving tripartite support report their progress each year; the most recent reports are available online.

Once collected, survey data can be used to identify how government regulation could reduce animal antibiotic misuse and protect human health, and how to prioritize next steps. A recent example of this strategy in action was the reporting of mcr-1 disseminating from Chinese farms, followed by the rapid banning of colistin as a growth promoter in China [16] and, more recently, in Thailand. First, if antibiotics are being used to treat common vaccine-preventable illnesses (for example, Escherichia coli–induced diarrhea in piglets), then vaccines against these diseases should be mandated and made broadly available to farmers [9]. Vaccinating sows against E. coli, for example, could be economically advantageous even if piglet mortality among unvaccinated sows is as low as <1%, not accounting for the public health benefits of reduced antimicrobial use [21]. Second, administration practices that result in veterinary drug residues at slaughter must be curbed; >80% of animal-origin foods sampled from some African countries contain drug residues (eg, Senegal, Algeria), compared to <1% from European countries [14]. Third, any antibiotic classes that are of critical importance to human health (eg, polymyxins) should be banned for animal use [9]. Enforcing such bans may require a 2-pronged approach. First, countries that are major producers of animal feeds containing banned antibiotics may need to be discouraged from manufacturing and exporting these products, which will require international cooperation. Second, LMIC governments will need to devise mechanisms to prevent farmers' acquisition of such animal feeds. Importantly, successful enforcement will rely heavily on effective monitoring programs. Otherwise, farmers may acquire antibiotics or counterfeit drugs through informal markets, with unpredictable consequences for animal and human health [8].

Farmer education is also necessary to reduce animal anti- biotic misuse. Low doses of antibiotics to promote growth are often used to compensate for poor farm hygiene and crowded conditions [9] (Figure 2). In Western Europe, banning non- therapeutic antibiotic use was economically and technically feasible because farmers had the information necessary to re- place antibiotic use with improved management practices, as well as financial and technical support from their governments [9, 22]. Without extensive, government-supported training for LMIC farmers, banning nontherapeutic animal antibiotic use could have negative consequences for animal health and the industry [8, 9]. In India, for example, projected financial losses for a proposed ban on subtherapeutic antibiotic use were 1%–3% of annual meat production, with the greatest losses by poultry farmers; this proposal has not been implemented [23].

Finally, the disposal of untreated waste from intensive fish and livestock farms should be addressed (Figure 1). Up to

80% of antibiotics consumed by farm-raised fish and 90% of antibiotics consumed by terrestrial farm animals are excreted with their activity intact [10, 24]. Fish farmers in LMICs typically use ponds, raceways, or net pens, in which residual antibiotics can freely enter the surrounding environment [25]. Reduced antibiotic use is the only way to limit contamination from these types of aquaculture systems. The use of fluoroquinolones in aquaculture, for example, was banned by many high-income countries after its use was linked to an increase in quinolone-resistant human infections; a ban on veterinary fluoroquinolone use should be considered in LMICs as well [24]. More vaccines are also needed for the types of animals raised in LMIC operations [9]. In aquaculture, for example, bacterial vaccines have been developed for high-value fish (eg, Atlantic salmon) but less frequently for low-value fish such as tilapia and pangasius, which are often farmed in LMICs [26]. To reduce the direct contamination of food with antibiotic-laden waste from intensive animal farms, countries may need to develop rules that discourage farmers from applying antibiotic-rich manure to crops intended for human consumption, particularly crops that are consumed raw (eg, leafy vegetables) [9].
Because antibiotic-intensive food-animal production is relatively new and largely unmonitored in many LMICs, few interventions to reduce the selection and transmission of antibiotic resistance associated with this production model have been implemented. However, in collaboration with the FAO, several LMICs are currently developing action plans that focus specifically on antibiotic use in intensive food-animal production. Development of these national action plans is ongoing and new tools are currently being piloted to assess their effectiveness in engaging with One Health [27].

Improve Safety of Food Supply Chains

Meat and produce can also be contaminated with antibiotic-resistant bacteria, resistance genes, and antibiotic residues through the food supply chain [13, 28] (Figure 3). Food supply chains in LMICs tend to be poorly organized, comprising large enterprises, small-scale actors, and a significant informal sector [13]. In response to growing demand, supply chains for meat and other perishable foods are lengthening and becoming more complex [13], and therefore more susceptible to contamination. A 2012 study of a pork sup- ply chain in Thailand, for example, found that Salmonella species prevalence was higher among market samples (96%) compared with live pigs (3%), indicating substantial contamination along the supply chain [29]. LMICs bear the greatest global burden of foodborne disease, particularly LMICs in Africa and Southeast Asia [28]. Antibiotics are often used to treat foodborne diarrheal disease, even if not bacterial in origin [30]. Thus, reduced foodborne disease through improved food safety could also help reduce anti- biotic consumption in LMICs.

First, studies are needed to determine which points in a food supply chain pose the highest risk of contamination with anti- biotic-resistant bacteria from either human or animal sources. A 2016 study of a broiler chicken supply chain in China, for example, revealed abattoirs to be the most important source of contamination with multidrug-resistant Salmonella, thus identifying where improved handling and hygiene practices could have the highest impact [31]. Food supply network studies are commonly used to identify “hot spots” for transmission of zoonotic diseases, such as high-contact animal holding pens and live markets in the case of avian influenza [32]. Where available, LMICs could exploit ongoing surveillance frameworks to survey antibiotic resistance [33]. Additional data collection may be necessary to identify important yet understudied sources of contamination in the food supply chain; for example, raw milk vendors in Ethiopia were found to add antibiotics directly to their products with the goal of extending shelf life [34].

Second, in areas of the world where intraregional food trade is common, LMICs may need to approach food safety from a regional policy perspective. Poorly monitored food supply chains can cross borders [33], which may result in the regional or international spread of antibiotic-resistant foodborne pathogens. In Southeast Asia, for example, regional trading hubs have been identified as “mixing bowls” for zoonotic agents [33]. As Southeast Asia has the second highest rate of foodborne disease in the world, the WHO has specifically recommended that “there is need for coordinated, cross-border action across the entire food supply chain” [35]. Regional food safety policies have previously been proposed in Southeast Asia and other areas with a high level of intraregional food trade, although with the primary goal of improving regional food security [36, 37]. Reduced cross-border dissemination of antibiotic-resistant pathogens may be an additional benefit.

Treat Highly Contaminated Waste Effluent Before Disposal

Drug manufacturing sites and hospitals are the most important point sources of antibiotics and antibiotic resistance genes into LMIC environments [9, 38] (Figure 1). Because antibiotics present in pharmaceutical wastewater have not been metabolized, their concentrations may be many-fold higher than in human waste [39]. Hospitals additionally discharge antibiotic-resistant bacteria, which propagate in the hospital setting due to poor infection control [17]. Untreated waste streams from drug manufacturers and hospitals are often discharged directly into the environment, as wastewater treatment plants are not common in LMICs [17, 30]. Even if present, wastewater treatment plants are not designed to remove antibiotics or antibiotic resistance genes [38]. A 2007 study of a wastewater treatment plant treating discharge from 90 pharmaceutical companies in India, for example, found that the amount of ciprofloxacin released in 1 day was equivalent to the amount prescribed to humans in Sweden over 5 days [39].

To most drastically reduce contributions to environmental reservoirs of antibiotic resistance in LMICs, minimum treatment levels for drug manufacturing and hospital waste should be mandated following best available guidelines prior to discharge to wastewater treatment plants or the environment [40]. Noncompliance penalties, such as fines or revocation of operation permits, may be necessary for enforcement. Pharmaceutical companies may be able to reduce antibiotic discharge by improving manufacturing practices [17]. In addition, on-site industrial waste treatment systems can be used, but these are expensive (eg, membrane bioreactors, oxidation of active substances with UV or O_3) [38]. More cost-effective solutions should be identified.

Improve Drinking Water and Sanitation

Improving access to safe drinking water and sanitation are policy priorities in many LMICs. These public health measures significantly reduce diarrheal disease, the second-largest cause of mortality among children in LMICs [17]. However, these measures are also important in the context of reducing antimicrobial resistance. Although 70% of diarrheal disease in LMICs is caused by viruses, antibiotics are often used for treatment [17]. Thus, improved water and sanitation can drastically reduce antibiotic consumption. A report presented to the UK Review on Antimicrobial Resistance found that improving sanitation infrastructure in India, for example, could result in 590 million fewer diarrhea cases treated with antibiotics by 2030 [30]. Reduced antibiotic consumption may relieve selection pressure among Enterobacteriaceae, which are primary inhabitants of both animal and human fecal flora, and for which the development of pan-antimicrobial resistance is a global clinical concern. Further, improved sanitation will reduce inputs of antibiotics, antibiotic-resistant bacteria, and antibiotic resistance genes into the environment via human waste. Thus, we suggest that global funding mechanisms that seek to reduce antibiotic resistance in LMICs be inclusive of water and sanitation initiatives.

CONCLUSIONS: PRIORITIZING STRATEGIES

Traditional efforts to constrain the dissemination of antibiotic resistance in LMICs have focused on human antibiotic use. However, LMICs must also consider the growing contribution of animal and environmental exposures to the antibiotic resistance crisis (Figures 1 and 2). Here, we have proposed strategies to reduce antibiotic misuse in LMICs that consider human, environmental, and animal health (Table 1), including reducing antibiotic misuse in livestock and aquaculture production through increased surveillance, regulation, and education; improving food safety; mandating minimum treatment of hospital and pharmaceutical manufacturing waste; and improving drinking water and sanitation. Many of these strategies complement ongoing initiatives to improve LMIC health, which could facilitate their implementation.

Curbing global antibiotic resistance will require integrated approaches that involve both LMICs and higher-income countries, such as the strategies outlined here. However, only LMICs can identify which strategies to prioritize and the timelines in which to achieve them based on their own national contexts. The contribution of human, animal, and environmental sources to the dissemination of antibiotic resistance can vary greatly among countries, and consequently which strategies merit immediate prioritization will also vary [27]. In India, for example, regulation of wastewater discharge from antibiotic-manufacturing companies is urgently needed to reduce the selection and mobilization of resistance elements into human pathogens [39], whereas in Cambodia, unmonitored food sup- ply chains may pose a greater risk [35]. Higher-income countries can help LMICs identify which strategies to prioritize in national action plans based on costs, benefits, and situational context [27], as well as how to implement them by providing frameworks for multidisciplinary collaboration, financial sup- port, and technical expertise, particularly with regard to survey data collection, analysis, and laboratory training [17]. In 2016, funding from the Fleming Fund was used by the FAO to help 4 LMICs (Zimbabwe, Kenya, Ghana, Cambodia) develop national action plans to reduce the threat of antibiotic resistance from agriculture, livestock production, fisheries, and food, and the FAO is currently expanding its efforts to several LMICs in sub-Saharan Africa and southeast Asia. In addition to supporting national action plans, we believe donor countries should support the development of regional antibiotic resistance action plans to improve food safety and security in areas where cross-border food supply chains are specifically implicated in a high prevalence of foodborne disease, such as Southeast Asia [35]. Continued philanthropic support toward the mitigation of antibiotic misuse by humans and animals will benefit LMIC health and may ultimately result in global cost savings [17].

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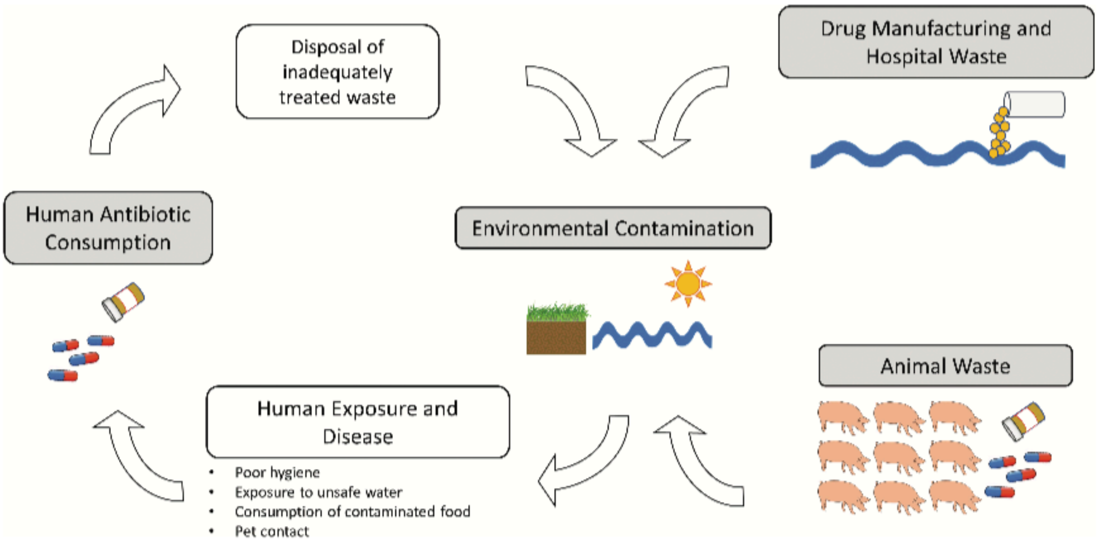

Figure 1. Concurrent human exposures and contributions to environmental reservoirs of antibiotic-resistant bacteria, antibiotic residues, and resistance genes in lower- and middle-income countries.

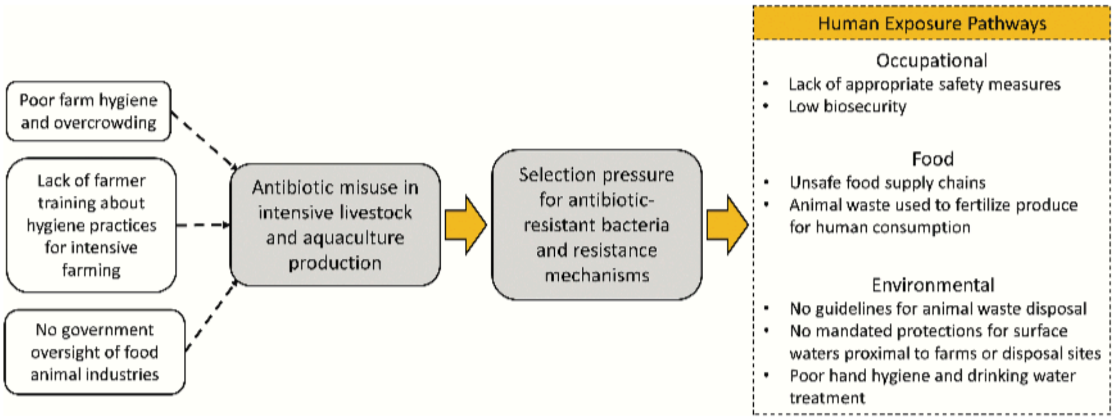

Figure 2. Factors specific to lower- and middle-income countries that contribute to the potential public health impacts of intensive food-animal production.

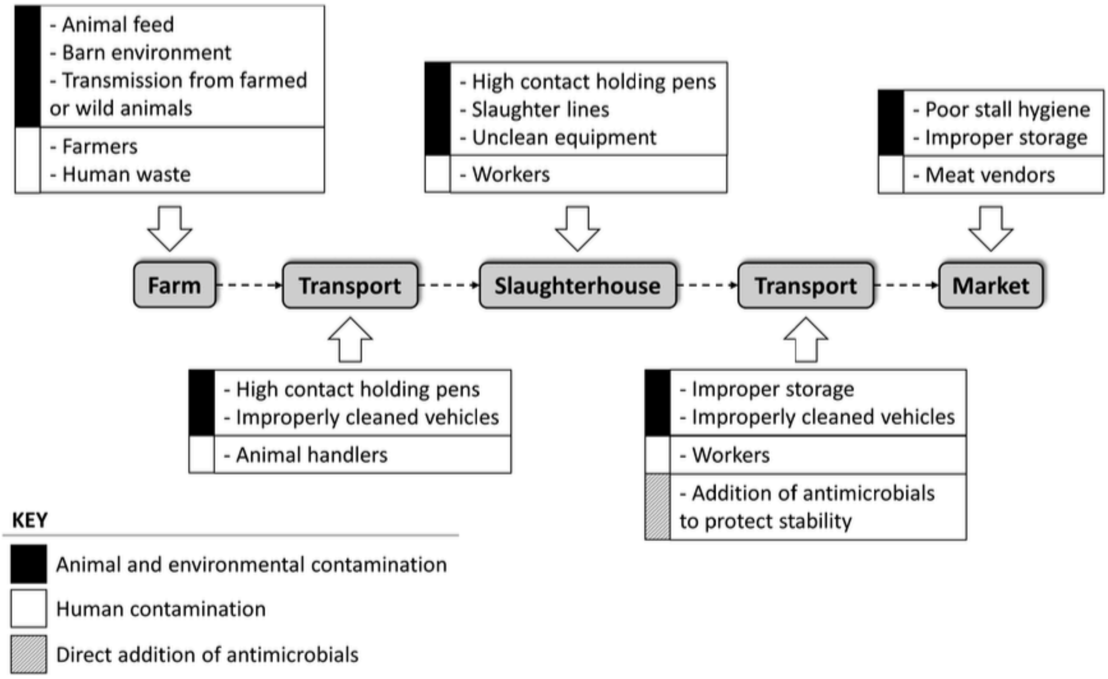

Figure 3. Schematic of possible sources of contamination with antibiotics, antibiotic resistance genes, and antibiotic-resistant bacteria in a meat supply chain in a lower- or middle-income country.

Table 1. Proposed Strategies to Address One Health Challenges Related to Antibiotic Misuse in Lower- and Middle-Income Countries

Strategy	Specific Actions
1. Manage antibiotic use in animal agriculture	• Survey antibiotic use in livestock and aquaculture production
	• Leverage technical and financial input from international organizations to create antibiotic resistance action plans that address antibiotic use in agriculture
	• Improve farmer education about best practices in animal agriculture, including vaccine use and antibiotic withdrawal periods before slaughter
	• Improve waste disposal from farms
	• Ban use of antibiotics that are critically important to human health
2. Improve food supply chain safety	• Determine where risk for contamination is highest in food supply chain (eg, transport, slaughterhouses)
	• Implement targeted hygiene strategies
	• Consider food safety at a regional level in areas where cross-border food supply chains are common and the burden of foodborne disease is high
3. Treat highly contaminated waste effluent before disposal	• Enforce minimum treatment levels for hospital and drug manufacturer waste
4. Improve access to clean water and sanitation	• Encourage funding mechanisms that seek to improve antibiotic use in lower- and middle-income countries to consider water and sanitation initiatives, and vice versa