Urban informal settlements as hotspots of antimicrobial resistance and the need to curb environmental transmission

Maya L. Nadimpalli^{1,2}, Sara J. Marks³, Maria Camila Montealegre³, Robert H. Gilman^{4,5}, Monica J. Pajuelo^{4,6}, Mayuko Saito⁶, Pablo Tsukayama^{5,7}, Sammy M. Njenga⁸, John Kiiru⁸, Jenna Swarthout¹, Mohammad Aminul Islam^{9,10}, Timothy R. Julian^{3,11,12}, Amy J. Pickering^{1,2#}

¹Department of Civil and Environmental Engineering, Tufts University, Medford, MA, USA

²Center for Integrated Management of Antimicrobial Resistance (CIMAR), Tufts University, Boston, MA, USA

³Eawag, Swiss Federal Institute of Aquatic Science and Technology, Dübendorf, Switzerland

⁴Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA

⁵Facultad de Ciencias y Filosofía, Universidad Peruana Cayetano Heredia, Lima, Peru

⁶Department of Virology, Tohoku University Graduate School of Medicine, Sendai, Japan

⁷Instituto de Medicina Tropical ‘Alexander von Humboldt’, Universidad Peruana Cayetano Heredia, Lima, Peru

⁸Kenya Medical Research Institute, Nairobi, Kenya

⁹Paul G. Allen School for Global Animal Health, Washington State University, Pullman, WA, USA

¹⁰International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b), Dhaka, Bangladesh

¹¹Swiss Tropical and Public Health Institute, Basel, Switzerland

¹²University of Basel, Basel, Switzerland

#Corresponding author: Dr. Amy Pickering, Science & Engineering Complex, Anderson Hall, Room 219B, 200 College Avenue, Medford, MA, USA. Email: amy.pickering@tufts.edu

Keywords: antimicrobial resistance, slum, shantytown, lower- and middle-income countries, One Health, child health, water and sanitation, wastewater

Abstract

Antimicrobial resistance is a growing public health challenge that is expected to disproportionately burden lower- and middle-income countries (LMICs) in the coming decades. Although the contributions of human and veterinary antibiotic misuse to this crisis are well-recognized, environmental transmission (via water, soil, or food contaminated with human and animal feces) has been given less attention as a global driver of antimicrobial resistance (AMR), especially in urban informal settlements in LMICs, commonly known as “shantytowns” or “slums.” These settlements may be unique hotspots for environmental AMR transmission given: 1) the high density of humans, livestock, and vermin living in close proximity; 2) frequent antibiotic misuse; and 3) insufficient drinking water, drainage, and sanitation infrastructure. Here, we highlight the need for strategies to disrupt environmental AMR transmission in urban informal settlements. We propose that water and waste infrastructure improvements tailored to these settings should be evaluated for their effectiveness in limiting environmental AMR dissemination, lowering the community-level burden of antimicrobial-resistant infections, and preventing antibiotic misuse. We also suggest that additional research is directed towards developing economic and legal incentives for evaluating and implementing water and waste infrastructure in these settings. Given that almost 90% of urban population growth will occur in regions predicted to be most burdened by the AMR crisis, there is an urgent need to build effective, evidence-based policies that could influence massive investments in the built urban environment in LMICs over the next few decades.

Urban informal settlements are densely populated residential areas characterized by insufficient access to improved water and sanitation services, households constructed of non-durable material, insufficient living area, insecure residential status, and high participation in the informal economy^{1–3}. Four of the five largest slums in the world are in Asian and African LMICs, and in some countries, over 50% of the urban population resides in these types of settlements (e.g., Bangladesh, Kenya, Ethiopia)¹. Population densities are difficult to measure in urban informal settlements but they are estimated to exceed 125,000 persons/square km in multiple major LMIC cities, including Hyderabad

(India)⁴, Mumbai (India)⁵, Nairobi (Kenya)⁶, and Dhaka (Bangladesh)⁷. In comparison, the population density of Manhattan (United States) was less than 30,000 persons/square km in 2010⁸. The populations of urban informal settlements will continue to grow as rural migration escalates in LMICs over the coming decades^{2,9}, and are expected to double from 1 to 2 billion by 2050¹⁰. Worryingly, almost 90% of urban population growth will occur in regions where most deaths attributable to drug-resistant bacteria are predicted to occur, namely Asia and Africa^{9,11}. Given increasing international travel, it is critical to recognize that practices in urban informal settlements (and in LMICs in general) that encourage preferential survival and proliferation of resistant bacteria can have global public health consequences. In particular, resistant enteric bacteria and resistance genes that become established in local gut colonization reservoirs are more likely to be acquired by travelers¹². This concern has been exemplified by the rapid global dissemination of the carbapenemase gene *bla*_{NDM-1} through personal travel and medical tourism to South Asia¹³, as well as growing risks of ESBL-*Enterobacteriaceae* infection among travelers to endemic LMICs¹⁴.

Factors facilitating the spread of antimicrobial resistance in urban informal settlements

Human antibiotic use

Frequent antibiotic use in urban informal settlements, particularly among children (**Table 1**), creates sustained within-host selection pressure. Residents of urban informal settlements have similar access to drug vendors as wealthier urban communities¹⁵. However, higher prevalence of infectious disease coupled with a limited capacity to access essential health information needed to make appropriate health decisions is thought to lead to greater antibiotic demand^{3,16,17}. Previous work has documented exceptionally high antibiotic use among children living in informal urban settlements in Peru, Kenya, India, and Bangladesh (**Table 1**), at rates often exceeding those reported in rural and broader urban areas (formal and informal neighborhoods combined) in these same countries. For example, 49% of children under 5 years old (n=120) living in urban slums of Nairobi, Kenya were recently found to have consumed antibiotics in the

prior two weeks. In comparison, less than 20% of similarly-aged children (n=6,532) living in the greater urban area of Nairobi consumed antibiotics during the same time frame in 2015¹⁸.

Self-medication practices may accelerate the selection and dissemination of antimicrobial-resistant bacteria among residents of urban informal settlements¹⁹. In most LMICs, antibiotics can be purchased at drug stores without a prescription²⁰ and are used both for treatment and prophylaxis^{21,22}. Primary healthcare providers in urban informal settlements (e.g., drug sellers and unqualified practitioners) tend to have less medical training and lower competence than healthcare providers in wealthier neighborhoods¹⁵. These individuals are less likely to refer patients who require medical care to seek treatment²³. Instead, when a resident's infection does not respond to an initial round of antibiotics, healthcare providers often simply provide different types of antibiotics at escalating prices²⁴. Such antibiotics may be consumed or sold as incomplete courses and a substantial portion may be counterfeit or of substandard quality^{23,25}, which also accelerates the selection of AMR. Only when an infection becomes complicated is treatment at a private clinic or tertiary care hospital finally sought, usually at substantial cost³. This cycle of antibiotic self-medication worsens poverty and may also perpetuate AMR in these settings. Specifically, residents' antimicrobial use can negatively impact their gut, skin, and other body site microbiotas, which normally provide protection against the establishment and proliferation of exogenous and potentially pathogenic bacteria, a phenomenon called colonization resistance²⁶. Residents' antimicrobial use can thereby indirectly increase their susceptibility to colonization with antimicrobial-resistant organisms already circulating in the community, or, among those already colonized with resistant organisms, increase the relative abundance of these organisms¹⁹. Overall, the impacts of slum residents' inappropriate antibiotic consumption practices on community-level antimicrobial resistance may explain why a higher proportion of enteric and bloodstream infections among children living in urban informal settlements are resistant to first-line antibiotics, compared to children living in rural areas^{27–29}.

Overcrowding and proximity to livestock

Overcrowding and high population densities in urban informal settlements likely exacerbates the spread of antimicrobial-resistant bacteria from residents' guts or other body sites. Although household crowding (often defined as more than 3 persons per habitable room) is common in many LMIC settings^{30,31}, it is thought to be intensifying in informal settlements as urban populations grow^{2,9,32}. In Nairobi, Kenya for example, the average number of habitable rooms/person decreased from approximately 0.8 in 1999 to 0.6 in 2009 among rented dwellings located in slums, while it remained constant among rented dwellings located in wealthier neighborhoods³². Compared to formal neighborhoods located a similar distance from the center of Nairobi, urban informal settlements were also approximately 10 times as dense by 2009³². Overcrowding and high population density result in a high user demand for water and sanitation services that often far outstrips supply^{33,34}, with the resultant stress to water sources and distribution networks often leading to their poor functionality and non-continuity of services.³⁵ Distribution systems providing intermittent services are highly prone to microbial contamination throughout the network due to loss of pressure in pipes and difficulties maintaining disinfection residual³⁶. Under intermittent supply conditions households' daily water supply may also be insufficient and they can be forced to reduce the frequency of daily handwashing³⁷ or augment supply with untreated surface sources. Such coping strategies may further contribute to the environmental transmission of antimicrobial-resistant bacteria. Overcrowding and poor housing conditions can also increase residents' susceptibility to other diseases that spread through direct person-to-person contact or via droplets, including skin lesions, skin superinfections (*i.e.*, secondary infections caused by organisms that are resistant to treatment used for initial infection), and tuberculosis³⁸, and antibiotics used to treat these infections can further contribute to AMR. For example, overcrowding coupled with unhygienic conditions is thought to contribute to year-round cholera outbreaks in urban informal settlements of Dhaka, while other settings in Bangladesh only experience seasonal outbreaks^{39,40}.

The close proximity of humans and livestock animals in urban informal settlements may also contribute to the spread of resistance. Poultry in particular are

increasingly being raised by households in these settings as sources of nutrition and income⁴¹. Sick animals are typically treated without veterinary consultation and with antibiotics that have been purchased without a prescription from veterinary shops, or from the same pharmacies that residents frequent for their own medical needs⁴¹. In urban areas of Nairobi, Kenya, for example, residents have reported feeding penicillin, sulfonamides, macrolides, and colistin to chickens they owned for treatment of caregiver-diagnosed disease.⁴² Antibiotic use in animals selects for resistant bacteria that can be excreted in animal waste and can contaminate animal products during slaughter⁴³; failure to respect antibiotic withdrawal times can lead to deposition of antibiotic residues in meat, eggs, and milk intended for human consumption⁴⁴. A recent review documented increasing trends in the proportion of antimicrobial-resistant bacteria (such as *E. coli*, *Campylobacter* spp., nontyphoidal *Salmonella* spp.) isolated from animals in LMICs; for example, the proportion of antimicrobial compounds to which more than 50% of isolates from chickens were phenotypically resistant increased from 0.15 to 0.41 from 2000 to 2018⁴⁵.

Insufficient drinking water, drainage and sanitation infrastructure

The environment of urban informal settlements can be contaminated with antimicrobial-resistant bacteria, resistance genes, and antibiotic residues from multiple sources (**Figure 1**). First, due to insufficient sanitation services and animal waste management, antimicrobial-resistant bacteria that are selected through human and animal antibiotic use and misuse can be excreted into the same environments in which residents eat, work, and play⁴⁶. In addition, drinking water, food, soil, and household environments can be contaminated by excreta and grey water from nearby city-dwellers⁴⁷; by untreated waste from hospitals; and by untreated industrial waste, including from pharmaceutical companies^{48–50}. Raw sewage may contain antibiotic residues (originating from human waste, animal waste, or drug manufacturing effluent) at concentrations that can support the horizontal transfer of resistance genes among human pathogens, or theoretically, the mobilization of antibiotic resistance genes from environmental bacteria to human pathogens (directly or via gut commensals)^{51–53}.

Resistance gene transfer and mobilization is thought to be more likely among bacteria that are able to replicate in sewage, rather than merely survive⁵¹. Fecal bacteria – including antimicrobial-resistant *E. coli* – that have been excreted into moist soil or pooled sewage may persist and grow when temperatures are maintained between 30-37°C^{54–56}, which is common in many sub-tropical countries. Thus, in addition to receiving antimicrobial-resistant bacteria, slum environments could also potentially propagate their dissemination. However, to our knowledge, whether antibiotic concentrations in soil and drainage ditches of urban informal settlements are sufficiently high to support resistance gene exchange has not been explored.

Residents of urban informal settlements may be frequently exposed to antimicrobial-resistant bacteria present in their environments (**Figure 1**). Characterization of the resistome – or the collection of all antimicrobial resistance genes from bacteria – in humans, animals, and sewage in a shantytown in Lima, Peru, demonstrated that that AMR genes harbored by pathogenic and non-pathogenic bacteria are diverse and shared between humans and their environment⁵². Individuals may be colonized or infected through direct contact with contaminated water, food, soil, or surfaces; via contact with domestic animals and their feces, particularly when animals are permitted to pass freely into the home⁵⁷; and through vermin such as rats and flies, which can transfer *E. coli* and other enteric pathogens^{58,59}. Insufficient drainage infrastructure, which is common to urban informal settlements, can allow human and animal sewage to pool in low-lying locations resulting in a short dispersal route between environmental reservoirs of resistance and the surrounding population, making dissemination more likely⁵¹. Because of their propensity to play in soil and near open drains, children in particular are thought to be at significantly higher risk of colonization and infection with fecal pathogens compared to other residents⁶⁰. Currently, children living in urban informal settlements in several LMICs have significantly higher diarrhea prevalence than their wealthier urban counterparts²⁹; in at least half of LMICs surveyed in a recent analysis, slum-dwelling children had 1.18 - 1.28 times higher diarrhea prevalence than rural children⁶¹. More frequent exposure to enteric pathogens could explain higher odds of diarrhea among children living in urban informal settlements

compared to both rural children and children living in wealthier urban neighborhoods^{29,61,62}.

Poor drainage in urban informal settlements also results in higher susceptibility to flooding, which is associated with more acute human exposure risks⁶³. These settlements are more likely to be located in low-lying, flood-prone areas than higher income neighborhoods of the same cities^{64–66}. A recent mapping-based study in Ho Chi Minh City, Vietnam, estimated that 83% of urban informal settlement areas were exposed to floods (for a 1000-year return period) compared to 68% of the city as a whole⁶⁵, not considering the impacts of flood protections such as drainage systems that are unlikely to be equitably distributed between urban informal settlements and wealthier neighborhoods⁶³. Floodwaters have been demonstrated to contain elevated levels of antimicrobial resistance genes (*e.g.*, *sul1*) and elevated levels of several fecal pathogen markers, including of *Aeromonas* spp., *E. coli*, *Enterococcus*, *Klebsiella pneumoniae*, and *Clostridium perfringens*^{67–69}. In Vellore, India, children living in parts of urban informal settlements that were susceptible to flooding were recently shown to have increased odds of enteric infection during rainfall events⁷⁰. Flood events are expected to become more frequent and intense with climate change, and could continue to overwhelm existing drainage and sanitation infrastructure^{65,71}.

Most studies comparing the health of slum residents to residents of wealthier neighborhoods have focused on diarrhea as an outcome^{29,61,62}. However, enteric bacteria can also cause invasive infections that typically require antibiotics to resolve, including sepsis, typhoid fever, pneumoniae, urinary tract infections (UTIs), and meningitis. Rising bacterial resistance among bloodstream^{72–74} and typhoid⁷⁵ infections has been documented in some LMICs and is typically associated with poorer clinical outcomes,⁷⁶ though few data specific to urban informal settlements are available. A 2018 study found that the poorest women in India were most likely to be infected by UTIs caused by ESBL-producing strains; differential exposure to an environmental reservoir of antimicrobial resistance was proposed to underlie this ESBL-income gradient⁷⁷. Overall, the role of urban informal settings as sources of exposure to antibiotic-resistant bacteria of clinical concern merits greater attention.

Interrupting Environmental Transmission of Antimicrobial Resistance using Water and Waste Infrastructure

Addressing causes of antimicrobial resistance in urban informal settlements and LMIC cities will likely require multiple approaches, including provider and consumer education, revised antibiotic market regulations and enforcement among pharmacies and veterinary clinics, and investment in antimicrobial resistance surveillance⁷⁸. Herein we focus on how improvements in water treatment and waste management infrastructure could indirectly but substantially reduce the burden of AMR in urban informal settlements. Achieving safe water and sanitation access for all is already a major developmental goal towards which significant progress has been made over the past 20 years⁷⁹. This has the potential to improve urban informal settlements residents' wealth and dignity^{34,80}, and protect health by introducing barriers to pathogen transmission. Existing services in these settings rarely meet current user demand and are often poorly maintained due to high costs, political disinterest, and lack of willpower from landlords³⁴. As a result, open defecation, untreated sewage discharged directly into the environment, inadequate drainage, and poor water quality are common to many urban informal settlements^{31,81}. These pressures will only increase with projected urbanization rates, which continue to outpace the expansion of services to residents of urban informal settlements worldwide⁹. If water and sanitation infrastructure improvements reduce selection for and transmission of antimicrobial resistance, the benefits for urban informal settlements could thus be substantial.

Water and sanitation infrastructure interventions can theoretically reduce the burden of antimicrobial resistance in LMIC settings in two ways. First, improved drinking water quality and safely managed sanitation could reduce the demand for antibiotics⁸² (**Figure 2**, Pathway 1). Government investments are typically motivated by human rights reasons and anticipated reductions in diarrhea, which remains a leading cause of under-five deaths in LMICs⁸³. Antibiotics are often used to treat diarrheal disease in LMICs, even though 80% of diarrheal disease among children under five is caused by viruses such as rotavirus, against which antibiotics are ineffective¹¹. By greatly reducing enteric pathogen transmission and accompanying antibiotic use, improved water and sanitation infrastructure could thereby indirectly reduce the population-level antibiotic

selection mechanisms that support the propagation of resistant strains among slum residents¹⁹. A report commissioned by the UK Review on Antimicrobial Resistance found that improving sanitation infrastructure in Nigeria, for example, could result in 105 million fewer diarrhea cases treated with antibiotics by 2030, compared to a do-nothing scenario⁸². Similar trends were predicted for improved water and sanitation scenarios in LMICs in Asia and South America⁸². A recent drinking water chlorination intervention in Dhaka both reduced child diarrhea prevalence by 23% and reduced under-five child consumption of antibiotics by 7%⁸⁴. Reducing the number of child diarrhea cases treated with antibiotics is of critical importance, as many fecal pathogens are rapidly becoming pan-resistant, including to last resort antibiotics (e.g., carbapenems)⁸⁵.

Further, improvements in sanitation services would substantially limit the load of antimicrobial-resistant bacteria and resistance genes entering the environment, while simultaneously reducing residents' exposure to them (**Figure 2**, Pathway 2). Currently, more than 70% of sewage produced in LMICs is estimated to flow into the environment untreated^{86,87}. Recent metagenomic surveys have shown that human fecal pollution increases the abundance of antimicrobial resistance genes in the environment⁸⁸, and that sewage microbial communities contain a diversity of AMR genes and resistant gut commensals that can potentially be reintroduced into human populations^{52,89,90}. In addition, antimicrobial-resistant pathogens (e.g., expanded-spectrum β -lactamase (ESBL)-producing *E. coli*) have been widely documented in drinking water supplies in urban informal settlements^{91–93}, where piped water supplies are often contaminated with sewage^{94,95}. Thus, improving sanitation services and drinking water quality could reduce the prevalence of resistant organisms and antibiotic residues in the environment, thereby disrupting the cycle of contamination and human exposure illustrated in **Figure 1**.

Despite the pressing need to identify strategies for disrupting environmental transmission of AMR in urban informal settlements, evidence is lacking about whether improved water and sanitation services could actually achieve this goal. This lack of quantitative data is an important limitation to the World Bank's recent suggestion that LMICs account for the indirect public health benefits of reduced AMR when considering future investments in water and sanitation infrastructure⁹⁶. One constraint (for which a

thorough discussion is outside the scope of this viewpoint, but available elsewhere)³⁴ is the lack of water and sanitation technologies and interventions appropriate for urban informal settlements. Networked sewers, wastewater treatment plants, and centralized drinking water treatment facilities are not viable options for settings that have unreliable electricity, intermittent water supplies, inadequate drainage infrastructure, and resource-limited municipalities. Further, such centralized systems may be impossible to implement in urban informal settlements that local municipalities consider to be illegal. Below, we recommend future research directions and social initiatives that could complement ongoing efforts to identify inclusive water and sanitation infrastructure suitable for these settings⁹⁷.

1) Investigate if LMIC urban-appropriate water and wastewater treatment technologies can limit AMR dissemination into the environment

Recently, there has been great interest in identifying how centralized water and wastewater treatment plant processes could be improved to reduce the discharge of antimicrobial-resistant bacteria, resistance genes, and antibiotic residues into the environment in high-income countries^{98,99}. However, almost no studies have evaluated if water and sanitation options more suitable for urban informal settlements in LMICs could do the same^{100,101}. Some of the lowest cost water disinfection options, such as chlorination and UV radiation, are effective at inactivating organisms that typically encode resistance (*e.g.*, *E. coli*, *Salmonella* spp., *Shigella sonnei*) as well as degrading antimicrobial resistance genes^{102,103}. However, these technologies are rarely assessed in terms of their effectiveness to reduce antimicrobial-resistant pathogens and resistance genes in drinking water, wastewater, or soil and water receiving sewage discharge in low-income settings.

Appropriate water and wastewater treatment technologies need to be evaluated to determine whether their implementation could limit environmental dissemination of AMR in terms of both efficacy and effectiveness, which includes user uptake. For example, although drinking water chlorination is an effective method for reducing pathogen exposure, poor compliance with household-level chlorination in field studies suggests that passive point-of-collection chlorination of community taps might be an

effective method to explore¹⁰⁴. Some field studies suggest that pit latrines, which are the most typical type of sanitation infrastructure in urban informal settlements, may be less likely to contaminate underlying groundwater when they are lined, particularly in rainy conditions¹⁰⁵. New approaches to increase access to hygienic toilets in urban informal settlements also present opportunities for reducing environmental transmission of AMR, such as container-based sanitation (in which human waste is collected in sealed containers and transported to treatment facilities) and non-sewered sanitation (e.g., waterless toilets that compost or incinerate waste)^{106–109}, although their cultural acceptability remains unclear. Identifying effective water and sanitation technologies will likely require that field experiments, which can be logistically challenging and expensive to implement in urban informal settlements, are complemented by laboratory experiments. For example, laboratory-based experiments could be used to ensure that sanitation technologies appropriate for slum settings are effective at preventing the dissemination of antibiotic residues, resistance genes, and antimicrobial-resistant bacteria into the surrounding environment. We suggest that global funding mechanisms seeking to combat AMR (e.g., the European Union's Joint Programming Initiative on Antimicrobial Resistance, JPIAMR) are supportive of both field- and lab-based investigations on this topic. Currently, less than 4% of JPIAMR funding is allocated towards research that quantifies environmental pollution with antimicrobial-resistant organisms and antibiotic residues, which is needed to inform strategies for minimizing environmental transmission of AMR through water and sanitation improvements⁹⁶.

2) Determine the impact of water and sanitation infrastructure on the community-level burden of AMR

In addition to assessing the ability of context-appropriate water and waste infrastructure to reduce environmental AMR contamination, these services could also be evaluated for their effectiveness in reducing community-level gut colonization with antimicrobial-resistant bacteria and resistance genes. Previous water treatment and sanitation intervention trials conducted in urban informal settlements or peri-urban settings have typically only based effectiveness on demonstrated reductions in child diarrhea and/or improvements in child growth^{110,112–114}. While these are undoubtedly important outcomes

to assess, these trials are also well set up to simultaneously evaluate the effectiveness of their intervention(s) in reducing residents' gut colonization with antimicrobial-resistant bacteria and resistance genes, which are important outcomes in themselves.

One approach for gauging the impacts of water and sanitation interventions on community-level burden of AMR is the analysis of fecal samples from control and treatment groups (e.g., in the case of randomized control trials). Fecal samples could be cultured in local clinical laboratories for a variety of antimicrobial-resistant bacteria of clinical concern, such as ESBL-producing *E. coli*. The WHO has focused their global AMR surveillance efforts on ESBL-producing *E. coli* given its clinical significance, ubiquitous presence in humans, animals and the environment, and its ability to be easily transmitted between these compartments, therefore serving as a potential indicator organism for global AMR surveillance¹¹⁵. Alternatively, environmental surveillance of feces-impacted sites has recently been proposed as a method for assessing community-level prevalence of AMR¹¹⁶. One benefit of examining the resistance patterns of bacteria from environmental sources is that these microbial populations reflect information about the microbiomes and resistomes of multiple individuals. With appropriate validation, paired environmental sampling both before and after a water or sanitation intervention could potentially yield important insights into the impacts of the intervention on community-level burden of AMR. Feces-impacted environmental sampling sites would have to be located within or as close to urban informal settlements as possible in order to best estimate these associations^{52,116}.

3) Quantify the impacts of improved water quality and safely managed sanitation on residents' antibiotic use

Improved water quality and safely managed waste could indirectly decrease antibiotic use (**Figure 2**), yet few studies have investigated this association⁸⁴. We suggest that researchers measure participants' antibiotic use as an outcome in future water treatment and sanitation infrastructure trials. Recommendations for surveying antibiotic use through vendor sales or participant survey data have recently been published by the WHO's Advisory Group on Integrated Surveillance of Antimicrobial Resistance¹¹⁷. Objective measurements are preferred since residents may not recall the types of

antibiotics they have recently consumed or the frequency with which they have consumed them when self-reporting¹¹⁸. One approach is to infer usage from antibiotic sales in geographic areas, although these data are not available in many LMICs. If these data are available, they may not accurately reflect consumption if antibiotics are not fully consumed or are purchased from unmonitored sources (e.g., online vendors). Testing participants' feces and/or urine for the presence of antibiotic residues and/or metabolites has the potential to be an objective marker of current drug consumption; recent studies of urinary antibiotic residues among children demonstrate a correlation with self-reported antibiotic use¹¹⁹. Testing environmental samples that are impacted by human feces and urine, such as sewage or latrine pits, may be another approach for objectively inferring antibiotic use among a population¹¹⁶. However, measuring antibiotics and/or their metabolites can be expensive, the technology required may not be available in some LMICs, and antibiotics that are less stable (e.g., β -lactams) may not be detectable using current methods¹¹⁹. For estimates of population-level antibiotic use based on environmental samples, the partitioning of antibiotic residues between solid and aqueous phases would also have to be accounted for and this parameter may be difficult to estimate¹¹⁶.

4) Develop stakeholder support for evaluating and implementing water and sanitation infrastructure in urban informal settlements to combat AMR

There is a growing recognition that technical solutions alone will not be sufficient to combat AMR in LMICs, and that social and cultural interventions must be explored as well⁹⁶. In urban informal settlements, the reluctance of government officials and landlords to evaluate or implement water and sanitation infrastructure is a major impediment to leveraging these services for reducing environmental transmission of AMR³⁴. Thus, efforts must be made to engage relevant stakeholders (e.g., government, landlords, national media, health-, and water- sectors, medical doctors, regulatory agencies and local NGOs) in order to raise awareness of AMR and its predicted health and economic consequences, and how stakeholder activities could make a difference¹²⁰. Additionally, economic counterincentives to evaluating and implementing water and sanitation infrastructure will need to be addressed, both for landlords, who

may not be motivated to invest in upgrading rental properties, and for renters, who have the split incentive of experiencing the benefits of such upgrades but not controlling decisions on their capital investments. Thus, we suggest that additional research efforts are directed towards creating new economic and legal incentives for evaluating and implementing these services in urban informal settlements¹²⁰.

Conclusion

There are undoubtedly significant challenges to improving water and sanitation infrastructure in urban informal settlements^{34,75}. Nevertheless, given that most urban population growth will occur in regions where the AMR crisis is projected to be the most severe, it is essential to identify sustainable solutions to curb enteric pathogen transmission, and thereby, environmental transmission of AMR. Millions of urban residences are expected to be built in LMICs in the coming decades to accommodate growing populations. Although multiple strategies may be needed to reduce colonization and infections with antimicrobial-resistant pathogens in these settings (e.g., regulation of drug vendors, provider and patient education), anticipated investments in urban infrastructure present a unique opportunity to simultaneously improve community-wide water, waste, and drainage infrastructure to limit the environmental transmission of AMR⁹⁶. Empirical evidence informing best practices, which will in turn be needed to inform policy, is currently lacking. Here, we have outlined research directions that could help build the evidence base for effective policy making, with a special focus on urban informal settlements as a critical hot spot of environmental transmission of AMR. We encourage governments, urban planners, civil and environmental engineers, and AMR experts to work collaboratively to address this emerging issue.

Funding

No funding was required.

Correspondence

Correspondence should be addressed to Dr. Amy J. Pickering.

The authors declare no competing interests

Author Contributions

A.J.P., S.J.M., T.R.J., and M.L.N. developed the concept. R.H.G., M.J.P., M.S., S.M.N., J.S., and A.J.P. collected the data. A.J.P., S.J.M., T.R.J., and M.L.N. wrote the first draft. A.J.P., T.R.J., J.S., and M.L.N. designed the figures. All authors contributed to the literature search and reviewed the manuscript at all stages.

References

1. The World Bank. Population living in slums (% of urban population).
2. Program, U. N. H. S. *World Cities Report 2016 Urbanization and Development: Emerging Futures*. (2016).
3. Riley, L. W., Ko, A. I., Unger, A. & Reis, M. G. Slum health: diseases of neglected populations. *BMC Int. Health Hum. Rights* **7**, 2 (2007).
4. Kit, O., Lüdeke, M. & Reckien, D. Defining the Bull's Eye: Satellite Imagery-Assisted Slum Population Assessment in Hyderabad, India. *Urban Geogr.* **34**, 413–424 (2013).
5. Dyson, P. Slum Tourism: Representing and Interpreting 'Reality' in Dharavi, Mumbai. *Tour. Geogr.* **14**, 254–274 (2012).
6. Veljanovski, T., Kanjir, U., Pehani, P., Otir, K. & Kovai, P. Object-Based Image Analysis of VHR Satellite Imagery for Population Estimation in Informal Settlement Kibera-Nairobi, Kenya. in *Remote Sensing - Applications* (InTech, 2012). doi:10.5772/37869.
7. Angeles, G. *et al.* The 2005 census and mapping of slums in Bangladesh: design, select results and application. *Int. J. Health Geogr.* **8**, 32 (2009).
8. Bureau, U. S. C. 2010 Demographic Profile Data: Manhattan borough, New York County, New York.
<https://factfinder.census.gov/faces/tableservices/jsf/pages/productview.xhtml?src=CF>
(2010).
9. United Nations Population Fund (UNFPA). *State of World Population 2007: Unleashing the Potential of Urban Growth*. (2007).
10. Prasad, A., Gray, C. B., Ross, A. & Kano, M. Metrics in Urban Health: Current Developments and Future Prospects. *Annu. Rev. Public Health* **37**, 113–133 (2016).
11. Jim O'Neill. *Tackling Drug-Resistant Infections Globally: Final Report and Recommendations*. (2016).

- 489 12. Woerther, P.-L., Andremont, A. & Kantele, A. Travel-acquired ESBL-producing
490 Enterobacteriaceae: impact of colonization at individual and community level. *J. Travel*
491 *Med.* **24**, S29–S34 (2017).
- 492 13. Wilson, M. E. & Chen, L. H. NDM-1 and the role of travel in its dissemination. *Curr. Infect.*
493 *Dis. Rep.* **14**, 213–226 (2012).
- 494 14. Ruppé, E., Andremont, A. & Armand-Lefèvre, L. Digestive tract colonization by multidrug-
495 resistant Enterobacteriaceae in travellers: An update. *Travel Medicine and Infectious*
496 *Disease* vol. 21 28–35 (2018).
- 497 15. Das, J. & Hammer, J. Location, Location, Location: Residence, Wealth, And The Quality Of
498 Medical Care In Delhi, India. *Health Aff. (Millwood)* **26**, w338–w351 (2007).
- 499 16. Institute of Medicine (US) Committee on Health Literacy. What Is Health Literacy? in
500 *Health Literacy: A Prescription to End Confusion* (eds. Nielsen-Bohlman, L., Panzer, A. &
501 Kindig, D.) (National Academies Press, 2004).
- 502 17. Kehinde, O. O. & Ogunnowo, B. E. The pattern of antibiotic use in an urban slum in Lagos
503 State, Nigeria. *West Afr. J. Pharm.* **24**, 49–57 (2013).
- 504 18. General Directorate of Statistics [Kenya], Ministry of Finance [Kenya], and ICF. *Kenya*
505 *Demographic and Health Survey 2015 [Dataset]. KEKR72FL.DTA.* (2015).
- 506 19. Lipsitch, M. & Samore, M. H. Antimicrobial Use and Antimicrobial Resistance: A Population
507 Perspective. *Emerg. Infect. Dis.* **8**, 347–354 (2002).
- 508 20. Morgan, D. J., Okeke, I. N., Laxminarayan, R., Perencevich, E. N. & Weisenberg, S. Non-
509 prescription antimicrobial use worldwide: a systematic review. *Lancet Infect. Dis.* **11**, 692–
510 701 (2011).
- 511 21. Shehadeh, M. *et al.* Knowledge, attitudes and behavior regarding antibiotics use and
512 misuse among adults in the community of Jordan. A pilot study. *Saudi Pharm. J.* **20**, 125–
513 133 (2012).

- 514 22. Nepal, A., Hendrie, D., Robinson, S. & Selvey, L. A. Knowledge, attitudes and practices
515 relating to antibiotic use among community members of the Rupandehi District in Nepal.
516 *BMC Public Health* **19**, 1558 (2019).
- 517 23. Miller, R. & Goodman, C. Performance of retail pharmacies in low- and middle-income
518 Asian settings: a systematic review. *Health Policy Plan.* **31**, 940 (2016).
- 519 24. Nair, M. *et al.* "Without antibiotics, I cannot treat": A qualitative study of antibiotic use in
520 Paschim Bardhaman district of West Bengal, India. *PLOS ONE* **14**, e0219002 (2019).
- 521 25. Ozawa, S. *et al.* Prevalence and Estimated Economic Burden of Substandard and Falsified
522 Medicines in Low- and Middle-Income Countries: A Systematic Review and Meta-analysis.
523 *JAMA Netw. Open* **1**, e181662 (2018).
- 524 26. Lawley, T. D. & Walker, A. W. Intestinal colonization resistance. *Immunology* **138**, 1–11
525 (2013).
- 526 27. Chandel, D. S. *et al.* Extended-spectrum beta-lactamase-producing Gram-negative
527 bacteria causing neonatal sepsis in India in rural and urban settings. *J. Med. Microbiol.* **60**,
528 500–7 (2011).
- 529 28. Breiman, R. F. *et al.* Population-Based Incidence of Typhoid Fever in an Urban Informal
530 Settlement and a Rural Area in Kenya: Implications for Typhoid Vaccine Use in Africa.
531 *PLOS ONE* **7**, e29119 (2012).
- 532 29. Souza, T. B. *et al.* High prevalence of antimicrobial drug-resistant diarrheagenic
533 *Escherichia coli* in asymptomatic children living in an urban slum. *J. Infect.* **59**, 247–251
534 (2009).
- 535 30. Ferraro, C. F. *et al.* Household Crowding, Social Mixing Patterns and Respiratory
536 Symptoms in Seven Countries of the African Meningitis Belt. *PLoS ONE* **9**, e101129
537 (2014).
- 538 31. Akinwale, O. P. *et al.* Living conditions and public health status in three urban slums of
539 Lagos, Nigeria. *South East Asia J. Public Health* **3**, (2014).

- 540 32. Bird, J., Montebruno, P. & Regan, T. Life in a slum: understanding living conditions in
541 Nairobi's slums across time and space. *Oxf. Rev. Econ. Policy* **33**, 496–520 (2017).
- 542 33. Mitlin, D., Beard, V. A., Satterthwaite, D. & Du, J. *Unaffordable and Undrinkable:
543 Rethinking Urban Water Access in the Global South*. (2019).
- 544 34. Katukiza, A. Y. *et al.* Sustainable sanitation technology options for urban slums.
545 *Biotechnol. Adv.* **30**, 964–978 (2012).
- 546 35. Kumpel, E. & Nelson, K. L. Intermittent Water Supply: Prevalence, Practice, and Microbial
547 Water Quality. *Environ. Sci. Technol.* **50**, 542–553 (2016).
- 548 36. Kumpel, E. & Nelson, K. L. Comparing microbial water quality in an intermittent and
549 continuous piped water supply. *Water Res.* **47**, 5176–5188 (2013).
- 550 37. Howard, G. & Bartram, J. *Domestic Water Quantity, Service Level and Health*.
551 https://www.who.int/water_sanitation_health/diseases/WSH03.02.pdf (2003).
- 552 38. Unger, A. & Riley, L. W. Slum health: from understanding to action. *PLoS Med.* **4**, 1561–
553 1566 (2007).
- 554 39. Ross, A. G. P., Zaman, K. & Clemens, J. D. Health Concerns in Urban Slums: A Glimpse
555 of Things to Come? *JAMA* **321**, 1973–1974 (2019).
- 556 40. Longini, I. M., Jr. *et al.* Epidemic and Endemic Cholera Trends over a 33-Year Period in
557 Bangladesh. *J. Infect. Dis.* **186**, 246–251 (2002).
- 558 41. Graham, J. P., Eisenberg, J. N. S., Trueba, G., Zhang, L. & Johnson, T. J. Small-scale
559 food animal production and antimicrobial resistance: mountain, molehill, or something in-
560 between? *Environ. Health Perspect.* **125**, (2017).
- 561 42. Muloi, D. *et al.* A cross-sectional survey of practices and knowledge among antibiotic
562 retailers in Nairobi, Kenya. *J. Glob. Health* **9**, 010412 (2019).
- 563 43. Food and Agriculture Organization of the United Nations (FAO). *Drivers, Dynamics, and
564 Epidemiology of Antimicrobial Resistance in Animal Production*. 1–68
565 <http://www.fao.org/3/a-i6209e.pdf> (2016).

- 566 44. Nisha, A. Antibiotic Residues - A Global Health Hazard. *Vet. World* **2**, 375 (2008).
- 567 45. Van Boeckel, T. P. *et al.* Global trends in antimicrobial resistance in animals in low- and
568 middle-income countries. *Science* **365**, eaaw1944 (2019).
- 569 46. Okeke, I. N. *et al.* Antimicrobial resistance in developing countries. Part I: recent trends
570 and current status. *Lancet Infect. Dis.* **5**, 481–493 (2005).
- 571 47. Kimani-Murage, E. W. & Ngindu, A. M. Quality of water the slum dwellers use: the case of
572 a Kenyan slum. *J. Urban Health Bull. N. Y. Acad. Med.* **84**, 829–38 (2007).
- 573 48. O'Neill, J. *Antimicrobials in Agriculture and the Environment: Reducing Unnecessary Use*
574 *and Waste.* (2015).
- 575 49. Pruden, A. *et al.* Management options for reducing the release of antibiotics and antibiotic
576 resistance genes to the environment. *Environ. Health Perspect.* **121**, 878–85 (2013).
- 577 50. Larsson, D. G. J. Pollution from drug manufacturing: review and perspectives. *Philos.*
578 *Trans. R. Soc. Lond. B. Biol. Sci.* **369**, (2014).
- 579 51. Bengtsson-Palme, J., Kristiansson, E. & Larsson, D. G. J. Environmental factors
580 influencing the development and spread of antibiotic resistance. *FEMS Microbiol. Rev.* **42**,
581 (2018).
- 582 52. Pehrsson, E. C. *et al.* Interconnected microbiomes and resistomes in low-income human
583 habitats. *Nature* **533**, 212–216 (2016).
- 584 53. Lundborg, C. S. & Tamhankar, A. J. Antibiotic residues in the environment of South East
585 Asia. *BMJ* **358**, j2440 (2017).
- 586 54. Ishii, S. *et al.* Factors Controlling Long-Term Survival and Growth of Naturalized
587 *Escherichia coli* Populations in Temperate Field Soils. *Microbes Environ.* **25**, 8–14 (2010).
- 588 55. Naganandhini, S., Kennedy, Z. J., Uyttendaele, M. & Balachandar, D. Persistence of
589 Pathogenic and Non-Pathogenic *Escherichia coli* Strains in Various Tropical Agricultural
590 Soils of India. *PLOS ONE* **10**, e0130038 (2015).

56. Montealegre, M. C. *et al.* Risk Factors for Detection, Survival, and Growth of Antibiotic-Resistant and Pathogenic *Escherichia coli* in Household Soils in Rural Bangladesh. *Appl. Environ. Microbiol.* **84**, e01978-18 (2018).
57. Penakalapati, G. *et al.* Exposure to Animal Feces and Human Health: A Systematic Review and Proposed Research Priorities. *Environ. Sci. Technol.* **51**, 11537–11552 (2017).
58. Barreiro, C., Albano, H., Silva, J. & Teixeira, P. Role of flies as vectors of foodborne pathogens in rural areas. *ISRN Microbiol.* **2013**, 718780 (2013).
59. Lindeberg, Y. L. *et al.* Can *Escherichia coli* fly? The role of flies as transmitters of *E. coli* to food in an urban slum in Bangladesh. *Trop. Med. Int. Health* **23**, 2–9 (2018).
60. Fuhrmann, S. *et al.* Disease burden due to gastrointestinal pathogens in a wastewater system in Kampala, Uganda. *Microb. Risk Anal.* **4**, 16–28 (2016).
61. Mberu, B. U., Haregu, T. N., Kyobutungi, C. & Ezech, A. C. Health and health-related indicators in slum, rural, and urban communities: a comparative analysis. *Glob. Health Action* **9**, 33163 (2016).
62. Fink, G., Günther, I. & Hill, K. Slum Residence and Child Health in Developing Countries. *Demography* **51**, 1175–1197 (2014).
63. Rashid, H., Hunt, L. M. & Haider, W. Urban Flood Problems in Dhaka, Bangladesh: Slum Residents' Choices for Relocation to Flood-Free Areas. *Environ. Manage.* **40**, 95–104 (2007).
64. Cissé, A. & Mendy, P. Spatial Relationship between Floods and Poverty: The Case of Region of Dakar. *Theor. Econ. Lett.* **8**, (2018).
65. Bangalore, M., Smith, A. & Veldkamp, T. Exposure to Floods, Climate Change, and Poverty in Vietnam. *Econ. Disasters Clim. Change* **3**, 79–99 (2019).
66. Douglas, I. *et al.* Unjust waters: climate change, flooding and the urban poor in Africa. *Environ. Urban.* **20**, 187–205 (2008).

67. Yu, P. *et al.* Elevated Levels of Pathogenic Indicator Bacteria and Antibiotic Resistance Genes after Hurricane Harvey's Flooding in Houston. *Environ. Sci. Technol. Lett.* **5**, 481–486 (2018).
68. Kapoor, V., Gupta, I., Pasha, A. B. M. T. & Phan, D. Real-Time Quantitative PCR Measurements of Fecal Indicator Bacteria and Human-Associated Source Tracking Markers in a Texas River following Hurricane Harvey. *Environ. Sci. Technol. Lett.* **5**, 322–328 (2018).
69. Steven M. Presley, *,† *et al.* Assessment of Pathogens and Toxicants in New Orleans, LA Following Hurricane Katrina. (2005) doi:10.1021/ES052219P.
70. Berendes, D. M. *et al.* Associations between open drain flooding and pediatric enteric infections in the MAL-ED cohort in a low-income, urban neighborhood in Vellore, India. *BMC Public Health* **19**, 926 (2019).
71. Fowler, A. M. & Hennessy, K. J. Potential impacts of global warming on the frequency and magnitude of heavy precipitation. *Nat. Hazards* **11**, 283–303 (1995).
72. Saleem, A. F., Qamar, F. N., Shahzad, H., Qadir, M. & Zaidi, A. K. M. Trends in antibiotic susceptibility and incidence of late-onset *Klebsiella pneumoniae* neonatal sepsis over a six-year period in a neonatal intensive care unit in Karachi, Pakistan. *Int. J. Infect. Dis.* **17**, e961–e965 (2013).
73. Musicha, P. *et al.* Trends in antimicrobial resistance in bloodstream infection isolates at a large urban hospital in Malawi (1998-2016): a surveillance study. *Lancet Infect. Dis.* **17**, 1042–1052 (2017).
74. Roy, M. P. *et al.* Changing trend in bacterial etiology and antibiotic resistance in sepsis of intramural neonates at a tertiary care hospital. *J. Postgrad. Med.* **63**, 162–168 (2017).
75. Luby, S. P. Urban Slums: A Supportive Ecosystem for Typhoidal *Salmonellae*. *J. Infect. Dis.* **218**, S250–S254 (2018).

76. Eliopoulos, G. M., Cosgrove, S. E. & Carmeli, Y. The Impact of Antimicrobial Resistance on Health and Economic Outcomes. *Clin. Infect. Dis.* **36**, 1433–1437 (2003).
77. Alsan, M. *et al.* Poverty and Community-Acquired Antimicrobial Resistance with Extended-Spectrum β -Lactamase-Producing Organisms, Hyderabad, India. *Emerg. Infect. Dis.* **24**, 1490–1496 (2018).
78. Gelband, H. & Delahoy, M. *Policies to Address Antibiotic Resistance in Low-and Middle-Income Countries.* (2014).
79. UN General Assembly. *Transforming our world : the 2030 Agenda for Sustainable Development.* (2015).
80. Subbaraman, R. *et al.* The social ecology of water in a Mumbai slum: Failures in water quality, quantity, and reliability. *BMC Public Health* **13**, (2013).
81. Desai, R., McFarlane, C. & Graham, S. The Politics of Open Defecation: Informality, Body, and Infrastructure in Mumbai. *Antipode* **47**, 98–120 (2015).
82. Araya, P., Hug, J., Joy, G., Oschmann, F. & Rubinstein, S. *The impact of water and sanitation on diarrhoeal disease burden and over-consumption of antibiotics.* (2016).
83. UN Inter-agency Group for Child Mortality Estimation. *Levels & Trends in Child Mortality: Report 2018.* 1–48 (2018).
84. Pickering, A. J. *et al.* Effect of in-line drinking water chlorination at the point of collection on child diarrhoea in urban Bangladesh: a double-blind, cluster-randomised controlled trial. *Lancet Glob. Health* **7**, e1247–e1256 (2019).
85. Manohar, P. *et al.* The distribution of carbapenem-and colistin-resistance in Gram-negative bacteria from the Tamil Nadu region in India. *J. Med. Microbiol.* **66**, 874–883 (2017).
86. WWAP (United Nations World Water Assessment Programme). *The United Nations World Water Development Report 2017. Wastewater: The Untapped Resource.* (2017).
87. Fuhrmeister, E. R., Schwab, K. J. & Julian, T. R. Estimates of Nitrogen, Phosphorus, Biochemical Oxygen Demand, and Fecal Coliforms Entering the Environment Due to

Inadequate Sanitation Treatment Technologies in 108 Low and Middle Income Countries.

Environ. Sci. Technol. **49**, 11604–11611 (2015).

88. Karkman, A., Pärnänen, K. & Larsson, D. G. J. Fecal pollution can explain antibiotic resistance gene abundances in anthropogenically impacted environments. *Nat. Commun.* **10**, 80 (2019).

89. Newton, R. J. *et al.* Sewage Reflects the Microbiomes of Human Populations. *mBio* **6**, e02574-14 (2015).

90. Hendriksen, R. S. *et al.* Global monitoring of antimicrobial resistance based on metagenomics analyses of urban sewage. *Nat. Commun.* **10**, 1124 (2019).

91. De Boeck, H. *et al.* ESBL-positive Enterobacteria isolates in drinking water. *Emerg. Infect. Dis.* **18**, 1019–20 (2012).

92. Muhonja, C., Christabel, M., Budambula, N., Kiiru, J. & Kariuki, S. Characterization of antibiotic resistance in environmental enteric pathogens from Kibera slum in Nairobi-Kenya. *J. Bacteriol. Res.* **4**, 46–54 (2012).

93. Talukdar, P. K. *et al.* Antimicrobial Resistance, Virulence Factors and Genetic Diversity of Escherichia coli Isolates from Household Water Supply in Dhaka, Bangladesh. *PLOS ONE* **8**, e61090 (2013).

94. Ercumen, A. *et al.* Upgrading a Piped Water Supply from Intermittent to Continuous Delivery and Association with Waterborne Illness: A Matched Cohort Study in Urban India. *PLOS Med.* **12**, e1001892 (2015).

95. Adane, M., Mengistie, B., Medhin, G., Kloos, H. & Mulat, W. Piped water supply interruptions and acute diarrhea among under-five children in Addis Ababa slums, Ethiopia: A matched case-control study. *PLOS ONE* **12**, e0181516 (2017).

96. World Bank Group. *Pulling Together to Beat Superbugs: Knowledge and Implementation Gaps in Addressing Antimicrobial Resistance.* (2019).

97. The Bill & Melinda Gates Foundation *et al.* *Citywide Inclusive Sanitation: A Call to Action*. (2016).
98. Sanganyado, E. & Gwenzi, W. Antibiotic resistance in drinking water systems: Occurrence, removal, and human health risks. *Sci. Total Environ.* **669**, 785–797 (2019).
99. Manaia, C. M. *et al.* Antibiotic resistance in wastewater treatment plants: Tackling the black box. *Environ. Int.* **115**, 312–324 (2018).
100. Ashbolt, N., Pruden, A., Miller, J., Riquelme, M. V. & Maile-Moskowitz, A. Antimicrobial Resistance: Fecal Sanitation Strategies for Combatting a Global Public Health Threat. in *Global Water Pathogen Project* (eds. Pruden, A., Ashbolt, N. & Miller, J.) (Michigan State University, 2019). doi:10.14321/waterpathogens.29.
101. Bürgmann, H. *et al.* Water and sanitation: an essential battlefront in the war on antimicrobial resistance. *FEMS Microbiol. Ecol.* **94**, (2018).
102. Clasen, T. & Edmondson, P. Sodium dichloroisocyanurate (NaDCC) tablets as an alternative to sodium hypochlorite for the routine treatment of drinking water at the household level. *Int. J. Hyg. Environ. Health* **209**, 173–181 (2006).
103. He, H. *et al.* Degradation and Deactivation of Bacterial Antibiotic Resistance Genes during Exposure to Free Chlorine, Monochloramine, Chlorine Dioxide, Ozone, Ultraviolet Light, and Hydroxyl Radical. *Environ. Sci. Technol.* **53**, 2013–2026 (2019).
104. Pickering, A. J. *et al.* Differences in Field Effectiveness and Adoption between a Novel Automated Chlorination System and Household Manual Chlorination of Drinking Water in Dhaka, Bangladesh: A Randomized Controlled Trial. *PLOS ONE* **10**, e0118397 (2015).
105. Graham, J. P. & Polizzotto, M. L. Pit Latrines and Their Impacts on Groundwater Quality: A Systematic Review. *Environ. Health Perspect.* **121**, 521 (2013).
106. *Evaluating the Potential of Container-Based Sanitation*. (2019).
107. Tilmans, S. *et al.* Container-based sanitation: assessing costs and effectiveness of excreta management in Cap Haitien, Haiti. *Environ. Urban.* **27**, 89–104 (2015).

108. Auerbach, D. Sustainable Sanitation Provision in Urban Slums -- The Sanergy Case Study. in *Broken Pumps and Promises: Incentivizing Impact in Environmental Health* (ed. Thomas, E. A.) 211–216 (Springer International Publishing, 2016). doi:10.1007/978-3-319-28643-3_14.
109. Hennigs, J. *et al.* Field testing of a prototype mechanical dry toilet flush. *Sci. Total Environ.* **668**, 419–431 (2019).
110. Kotloff, K. L. *et al.* Burden and aetiology of diarrhoeal disease in infants and young children in developing countries (the Global Enteric Multicenter Study, GEMS): a prospective, case-control study. *The Lancet* **382**, 209–222 (2013).
111. Barreto, M. L. *et al.* Effect of city-wide sanitation programme on reduction in rate of childhood diarrhoea in northeast Brazil: assessment by two cohort studies. *The Lancet* **370**, 1622–1628 (2007).
112. Pickering, A. J. *et al.* Integrating water, sanitation, handwashing, and nutrition interventions to reduce child soil-transmitted helminth and Giardia infections: a cluster-randomized controlled trial in rural Kenya. *PLOS Med.* **in press**, (2019).
113. Sanitation Hygiene Infant Nutrition Efficacy (SHINE) Trial Team *et al.* The Sanitation Hygiene Infant Nutrition Efficacy (SHINE) Trial: Rationale, Design, and Methods. *Clin. Infect. Dis.* **61**, S685–S702 (2015).
114. Luby, S. P. *et al.* Effects of water quality, sanitation, handwashing, and nutritional interventions on diarrhoea and child growth in rural Bangladesh: a cluster randomised controlled trial. *Lancet Glob. Health* **6**, e302–e315 (2018).
115. Matheu, J., Aidara-Kane, A. & Andremont, A. The ESBL tricycle AMR surveillance project: a simple, one health approach to global surveillance. in *AMR Control: Overcoming Global Antimicrobial Resistance* (2017). doi:10.1007/82_2012_224.
116. Huijbers, P. M. C., Flach, C. F. & Larsson, D. G. J. A conceptual framework for the environmental surveillance of antibiotics and antibiotic resistance. *Environ. Int.* **130**, (2019).

- 745 117. WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR).
746 *Integrated Surveillance of Antimicrobial Resistance in Foodborne Bacteria: Application of a*
747 *One Health Approach*. (2017).
- 748 118. Omulo, S. *et al.* Evidence of superficial knowledge regarding antibiotics and their use:
749 Results of two cross-sectional surveys in an urban informal settlement in Kenya. *PLOS*
750 *ONE* **12**, e0185827 (2017).
- 751 119. Wang, H. *et al.* Predictors of urinary antibiotics in children of Shanghai and health risk
752 assessment. *Environ. Int.* **121**, 507–514 (2018).
- 753 120. Larsson, D. G. J. *et al.* Critical knowledge gaps and research needs related to the
754 environmental dimensions of antibiotic resistance. *Environ. Int.* **117**, 132–138 (2018).
755

Tables

Table 1. Reported antibiotic use in the past two weeks (or if indicated, courses per child-year) among children <5 years old living in urban informal settlements, as compared to urban and rural settings in four low- and middle-income countries.

Country	Urban informal settlement		Country-Level Estimates ^a		
	Location (n)	Year	Urban (n)	Rural (n)	Year
Bangladesh	35.1% ^b (Dhaka) (n=2086)	2015	22.9% (n=2,550)	24.8% (n=5,793)	2014
	10.3 courses per child-year ^c (Dhaka) (n=265)	2009-2014			
India	3.9 courses per child-year ^c (Vellore) (n=251)	2009-2014	5.2% (n=59,222)	4.6% (n=188,521)	2015-2016
Kenya	49% ^d (Nairobi) (n=120)	2019	17.4% (n=6,532)	16.9% (n=13,561)	2015
Peru	3.8 courses per child-year ^e (Lima) (n=345)	2016-2018	19.7% (n=5,484)	14.3% (n=3,961)	2012

Note: Reports were identified through a review of relevant literature and supplemented by unpublished data from our team.

^aCountry-level urban and rural antibiotic use estimates were calculated from Demographic Health Survey data. Only living children who were ill in the two weeks due to fever (all four countries) and diarrhea (all but Bangladesh) were asked about antibiotic usage. We corrected for the percent of children who reported being ill out of the total number of living children surveyed in order to generate population-level antibiotic use estimates. Source: ICF. 2004-2017. Demographic and Health Surveys (various) [Datasets]. Funded by USAID. Rockville, Maryland: ICF [Distributor].

^bSource: Pickering, A. J. et al. Effect of in-line drinking water chlorination at the point of collection on child diarrhoea in urban Bangladesh: a double-blind, cluster-randomised controlled trial. *Lancet. Glob. Heal.* 7, e1247–e1256 (2019).

^cAmong children <2 years old. Source: Rogawski, E. T. et al. Use of antibiotics in children younger than two years in eight countries: a prospective cohort study. *Bull. World Health Organ.* 95, 49–61 (2017).

^dUnpublished data.

^eAmong children ≤2 years old. Unpublished data on behalf of the Norovirus Working Group in Peru.

Figures

Figure 1. Environmental transmission of antimicrobial resistance in urban informal settlements. Urban informal settlements are contaminated with human, animal, and industrial waste that can contain antimicrobial-resistant bacteria, antimicrobial resistance genes, and antibiotic residues. Deficiencies in the built environment coupled with overcrowding, poor hygiene, and high antibiotic use exacerbate the spread and selection of AMR. Residents are frequently exposed to AMR through contact with domestic animals and their feces, via vermin such as rats and flies, and through contact with contaminated food, water, soil, and surfaces.

Note: AMR=Antimicrobial resistance, here comprising: antimicrobial-resistant bacteria, antimicrobial resistance genes, and antibiotic residues. HGT=Horizontal gene transfer.

Figure 2. Ways improved water and sanitation services could reduce the burden of antimicrobial resistance in low- and middle-income country settings. Improved water treatment and sanitation can reduce antimicrobial resistance selection and carriage in humans by (1) reducing exposure to diarrhea-causing pathogens, which reduces the risk of diarrhea and subsequent antibiotic usage, and (2) disrupting exposure to AMR bacteria, resistance genes, and antibiotic residues present in the environment. Further, improved sanitation reduces the dissemination of antimicrobial resistance into the environment.

Note: AMR=Antimicrobial-resistant.