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

Maya L. Nadimpalli[1,2], Sara J. Marks[3], Maria Camila Montealegre[3], Robert H. Gilman[4,5], Monica J. Pajuelo[4,6], Mayuko Saito[6], Pablo Tsukayama[5,7], Sammy M. Njenga[8], John Kiiru[8], Jenna Swarthout[1], Mohammad Aminul Islam[9,10], Timothy R. Julian[3,11,12], Amy J. Pickering[1,2#]

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

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

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

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

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

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

[7]Instituto de Medicina Tropical 'Alexander von Humboldt', Universidad Peruana Cayetano Heredia, Lima, Peru

[8]Kenya Medical Research Institute, Nairobi, Kenya

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

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

[11]Swiss Tropical and Public Health Institute, Basel, Switzerland

[12]University 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

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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 2010[8]. 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 2050[10]. 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 travelers[12]. This concern has been exemplified by the rapid global dissemination of the carbapenemase gene $bla_{\mathrm{NDM\text{-}1}}$ through personal travel and medical tourism to South Asia[13], as well as growing risks of ESBL-*Enterobacteriaceae* infection among travelers to endemic LMICs[14].

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 communities[15]. 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 2015[18].

Self-medication practices may accelerate the selection and dissemination of antimicrobial-resistant bacteria among residents of urban informal settlements[19]. In most LMICs, antibiotics can be purchased at drug stores without a prescription[20] 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 neighborhoods[15]. These individuals are less likely to refer patients who require medical care to seek treatment[23]. 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 prices[24]. 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 cost[3]. 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 resistance[26]. 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 organisms[19]. 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 neighborhoods[32]. Compared to formal neighborhoods located a similar distance from the center of Nairobi, urban informal settlements were also approximately 10 times as dense by 2009[32]. 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 residual[36]. Under intermittent supply conditions households' daily water supply may also be insufficient and they can be forced to reduce the frequency of daily handwashing[37] 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 tuberculosis[38], 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 income[41]. 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 needs[41]. 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 slaughter[43]; failure to respect antibiotic withdrawal times can lead to deposition of antibiotic residues in meat, eggs, and milk intended for human consumption[44]. 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 2018[45].

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 play[46]. In addition, drinking water, food, soil, and household environments can be contaminated by excreta and grey water from nearby city-dwellers[47]; 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 survive[51]. 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 environment[52]. 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 home[57]; 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 likely[51]. 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 residents[60]. Currently, children living in urban informal settlements in several LMICs have significantly higher diarrhea prevalence than their wealthier urban counterparts[29]; 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 children[61]. 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 risks[63]. 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 whole[65], not considering the impacts of flood protections such as drainage systems that are unlikely to be equitably distributed between urban informal settlements and wealthier neighborhoods[63]. 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 events[70]. 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 typhoid[75] 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 gradient[77]. 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 surveillance[78]. 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 years[79]. 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 landlords[34]. 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 worldwide[9]. 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 antibiotics[82] (**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 LMICs[83]. 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 ineffective[11]. 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 residents[19]. 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 scenario [82]. Similar trends were predicted for improved water and sanitation scenarios in LMICs in Asia and South America[82]. 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 environment[88], 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 infrastructure[96]. 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 settings[97].

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 explore[104]. 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 conditions[105]. 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 improvements[96].

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 surveillance[115].` Alternatively, environmental surveillance of feces-impacted sites has recently been proposed as a method for assessing community-level prevalence of AMR[116]. 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 association[84]. 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 Resistance[117]. 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-reporting[118]. 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 use[119]. 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 population[116]. 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 methods[119]. 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 estimate[116].

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 well[96]. 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 AMR[34]. 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 heath and economic consequences, and how stakeholder activities could make a difference[120]. 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 settlements[120].

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 AMR[96]. 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.

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Correspondence

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

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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.

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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.

	Urban informal settlement		Country-Level Estimates[a]		
Country	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.

[a] Country-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].

[b] Source: 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).

[c] Among 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).

[d] Unpublished data.

[e] Among 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.