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A bottom-up view of antimicrobial resistance transmission in developing countries

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Antimicrobial resistance (AMR) is tracked most closely in clinical settings and high-income countries. However, resistant organisms thrive globally and are transmitted to and from healthy humans, animals and the environment, particularly in many low- and middle-income settings. The overall public health and clinical significance of these transmission opportunities remain to be completely clarified. There is thus considerable global interest in promoting a One Health view of AMR to enable a more realistic understanding of its ecology. In reality, AMR surveillance outside hospitals remains insufficient and it has been very challenging to convincingly document transmission at the interfaces between clinical specimens and other niches. In this Review, we describe AMR and its transmission in low- and middle-income-country settings, emphasizing high-risk transmission points such as urban settings and food-animal handling. In urban and food production settings, top-down and infrastructure-dependent interventions against AMR that require strong regulatory oversight are less likely to curtail transmission when used alone and should be combined with bottom-up AMR-containment approaches. We observe that the power of genomics to expose transmission channels and hotspots is largely unharnessed, and that existing and upcoming technological innovations need to be exploited towards containing AMR in low- and middle-income settings.

The ability of microbes to resist the effect of antimicrobials meant to inhibit their growth or kill them currently threatens humans with a dark age where common minor infections could be potentially deadly. The fallout of bacterial antimicrobial resistance (AMR) impacts heavily on global mortality, morbidity and economy, particularly in low- and middle-income countries (LMICs) where uncontrolled access to potentially life-saving drugs is expanding[1]. In 2019, bacterial antimicrobial resistance was associated with an estimated 4.95 million deaths globally[1]. Annual treatment costs arising from antimicrobial resistance are estimated at US$4.6 billion in the United States alone[2]. As a recent study[1] on the global burden of bacterial antimicrobial resistance in 2019 showed, the AMR burden in that year was highest in sub-Saharan Africa and higher in low- and middle-income countries (LMICs) than in East Asia, Australasia and Western Europe, with species of One Health importance in their transmission accounting for the highest attributable mortality. Rising selective pressure from judicious and injudicious use, as well as from disposal of antimicrobial waste, underpins much of the AMR crisis but is only one evolutionary driver. Bacteria carrying resistance genes on mobile genetic elements, which are capable of transposition within and between bacterial species, can be selected by other forces and are difficult to contain when their transmission is assured. The contribution of transmission to the evolution of resistance has received scant attention as the focus is often on the very visible impact of AMR in human clinical settings. However, outside health facilities, resistant organisms rarely move directly from one sick person to another. Instead, they circulate undetected among healthy and sick humans, domesticated and wild animal populations, and the environment[3–6]. In all these niches, some of which are hotspots of varied selective pressures due to the accumulation of antimicrobial waste, new resistant clones evolve and resistance genes and elements are disseminated among co-habiting species[7]. In this review, we examine AMR across the human-animal-environment continuum in LMIC settings. We overview the scope of the problem, highlight instances where resistance transmission has and has not been evidenced, and make a case for interrogating transmission in LMICs using genomic approaches. We also outline interventions that might be especially valuable for containing AMR spread.

Transmission of resistant bacteria among humans is rife and worsening

Low-income settings with poor access to antimicrobials and dense transmission networks have recorded AMR prevalence rates greater than 50%[8]. Rapid population growth and urbanization in LMICs can promote resistance by increasing bacterial transmission and access to antimicrobials[9]. In these informal and unplanned urban settings, subsistence strategies that maximize resource extraction, as well as shortfalls in regulatory oversight for water and sanitation[10] converge to amplify the transmission risk among humans, animals and their environment (Fig. 1). Eliminating resistance reservoirs and breaking transmission chains will stem the spread of pathogens, thereby reducing the need for antimicrobials[11]. Resistant bacteria and mobile elements selected in people, livestock, pets or pests are transferred among individuals or voided into sewage systems, underground soak-aways, pit latrines, drains or open spaces from where they can be acquired by wildlife or seep into irrigation, household and even drinking water, thereby creating hotspots for the emergence of antimicrobial resistance. Few studies examine these One Health niches or their connections, but worryingly high resistance levels have been recorded in all of them[12–14]. For example, only three Medline-indexed studies – all sampling ≤100 latrines – published before December 2021 reported antimicrobial resistance in pit latrines, a sanitation system predominant in many LMIC

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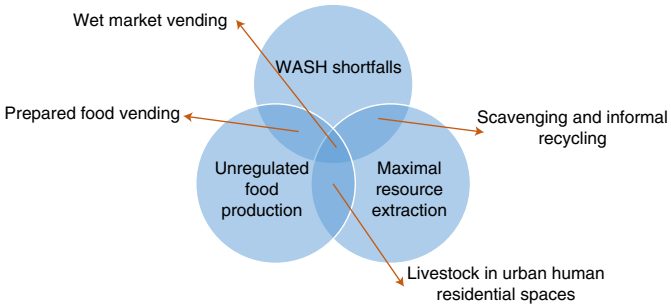

Fig. 1 | Common practices in low-resource settings that can exacerbate the transmission of antimicrobial resistance. Shortfalls in water, sanitation and hygiene, unregulated food production and economic pressures to maximize extraction from limited resources promote practices that exacerbate faeco-oral transmission of resistant organisms and resistance genes in many LMIC settings.

settings. In all three studies, >75% of the *Escherichia coli* isolates were resistant to at least one antimicrobial, while >45% were resistant to three or more of the tested antimicrobials; the two studies that searched for isolates carrying extended-spectrum beta-lactamase genes found them[15–17].

AMR in LMIC food-animal-related bacteria

While there are several published LMIC meta-analyses on resistant bacteria from humans[18–20], there is less synthesized information from non-human niches. Perhaps the most comprehensive systematic review is the study of Van Boeckel et al.[21] and its accompanying database (https://resistancebank.org/), which focuses on food animals. Food animals are hosts to resistant bacteria from other animals, their human handlers and the environment, and can potentially disseminate these bacteria to human consumers[22,23].

Van Boeckel and colleagues[21] used point surveillance data from 901 LMIC-based studies from 2000 to 2018 to report global trends of AMR in animals in LMICs for common indicator pathogens such as *E. coli*, *Campylobacter* spp., *Salmonella* spp. and *S. aureus*. These species are important not only in AMR in animal production but also in human infections[24]. The study revealed a 173% increase in the proportion of antimicrobials with resistance rates greater than 50% (P50) in chickens (0.15 to 0.41), including a 161.5% and 91.7% increase in P50 in pigs (0.13 to 0.34) and cattle (0.12 and 0.23). Hotspots of AMR (P50 > 0.4) were reported in parts of Asia (India, China, Pakistan, Iran, Turkey, Vietnam), South America (Brazil, Mexico) and Africa (Egypt, South Africa), whereas AMR emergence was reported in Kenya, Morocco, Uruguay, southern Brazil, central India and southern China. Commonly used antimicrobials in animal rearing, such as penicillins, sulfonamides and tetracyclines, recorded the highest resistance rates. For instance, the study reported quinolone and gentamicin resistance to be between 20–60% among *E. coli*, and 5–38% among *Salmonella* spp. The highest resistance rates to antimicrobials in *Campylobacter* were reported for tetracyclines and quinolones (both 60%). In *S. aureus*, the highest resistance rates were associated with penicillins (40–80%), whereas it was between 20–60% for tetracyclines, oxacillins and erythromycin antimicrobials. These findings emphasize the rapid increase in antimicrobial resistance in the food-animal sector in LMICs and highlight it as a sector deserving closer attention due to its high importance and sensitive position as a critical crossover point for resistance transmission.

Animal–human routes of AMR spread

An estimated 60% of all human pathogens and 75% of emerging diseases affecting humans are zoonotic (https://iris.wpro.who.int/bitstream/handle/10665.1/13654/9789290618171-eng.pdf). Human–animal interactions are increasing, raising the risk for zoonotic infections[25,26] and the subsequent emergence of resistant pathogens. In many LMICs, antimicrobials, which are poorly stewarded and easily obtained over the counter, are introduced as food additives for disease prophylaxis, metaphylaxis and growth promotion in aquaculture, poultry and livestock[27–29]. The quantity of antimicrobials used in animal production is predicted to increase by 11.5% between 2017 and 2030[30]. However, there are few or no reports on the sale of veterinary antimicrobials in African countries[30] despite indiscriminate and high usage of antimicrobials in animals in LMICs[31].

Since initial discovery in animal and human isolates in southern China in 2015, and coincident with intense colistin use in agriculture, ten mobile colistin resistance (*mcr*) gene variants have been described in over 40 countries across five continents[32–34]. Also, the recently reported existence of the mobile *tet*(X3) and *tet*(X4) genes among isolates from food animals and humans in China and elsewhere further limits the efficacy of last-resort antibiotics and underscores the imminent global health threat[35,36]. Existing reports predominantly highlight the dissemination of resistance from animals to humans, but humans also represent reservoirs for the transmission of AMR to animals[26]. For instance, Lowder et al.[37] described a single human-to-avian jump of *S. aureus* CC5, which acquired mutations adaptive to the avian niche and was subsequently disseminated around the world in poultry. Following the first report of the human *mcr-1* gene in Algeria, the gene was soon detected in Barbary macaques[38]. Similarly, the human epidemic ST22 methicillin-resistant *S. aureus* SCCmec IV clone is concurrently occurring in swine and primates[39]. The exposure of animals to human waste and the poor sanitation and hygiene associated with food-animal handlers in farms, retail shops and slaughterhouses are important contributors to the spread of antibiotic-resistant pathogens among animals[40].

In animal production operations in LMICs, sanitation, antimicrobial usage, animal overcrowding, lack of human protective gear and other farm management practices are important risk factors[29,41,42]. Moser et al.[43] reported that 429 (69.3%) birds from small-scale farms in Ecuador yielded multidrug-resistant isolates, compared with 58 (15.3%) birds in non-production villages. In that study, the increased prevalence of phenotypic antibiotic resistance and mobile genetic element markers in small-scale and household poultry in Ecuador were associated with confined spacing of birds and lacing of animal feed with antibiotics. Cleaning and wiping down farm equipment and sanitary disposal of dead birds were protective against *Salmonella* in farms, whereas a high bird density increased the risk of *Salmonella* detection in two Colombian state departments for poultry farming[42].

Disposal of human and animal waste close to human residences and farms is common and, indeed, inevitable in resource-limited settings with inadequate or unsafe sanitation[41]. This practice allows bacteria, including resistant ones, to filter into groundwater or onto produce. It also attracts insects such as houseflies and cockroaches, which are efficient carriers of multidrug-resistant bacteria[44,45]. In addition, without intervention, antimicrobials used in agricultural practices invariably run off into other soil and water ecosystems, eventually reaching human populations and scavenging wildlife[46–48]. Thus, even among wildlife, AMR is usually reflective of human anthropogenic activities[49,50]. Close interaction among the animal-human-environment tripod facilitates varied heterogeneous routes of AMR spread and can foster the amplification of novel AMR hotspots.

Genomic approaches for mapping transmission across the One Health continuum

There are multiple retrospective records of cross-species or cross-niche bacterial lineages[37,51,52]. However, recent studies that have set out to prospectively compare lineages from animals with

those from humans have found surprisingly few common clones, engendering the suspicion that concerns about transmission of resistance among humans, animals and the environment may be overblown[3,51,53–55]. Why is this? Successful bacterial transfer across species could be uncommon overall but become significant and visible in the face of selective advantage or when there are numerous crossover opportunities[52]. Alternatively, carriage by some species disseminating resistant organisms may be common but transient, but not without consequence, and therefore difficult to detect in the mainly cross-sectional surveys unless further adaptive evolution follows[56]. Many studies focus on hypotheses defining the movement of resistant bacteria towards humans and assume short paths of transfer, and therefore bias study design accordingly. However, more open multidirectional or circular models of transmission involving one or more intermediate hosts may be in play. Moreover, the transfer of bacterial lineages may be less significant than the movement of mobile elements and genes, which is harder to detect and confirm[57].

The probability of any of these scenarios occurring in LMIC settings is probably higher than elsewhere, but fewer investigations have been conducted outside Europe and North America, and LMIC studies need to use methods more likely to detect transmission when it is uncommon. Methods based on whole-genome sequencing provide the necessary granularity to rule in or out the inter-host transmission or other niche-entry events[52,53]. With falling sequencing costs and improved methods for designing and interpreting metagenomic studies, approaches that could identify crossover points and determine their frequency may now be within reach. However, One Health genomic studies are few and far between in LMICs; the often large and diverse specimen collections needed for this type of study preclude the helicopter and postal research approaches that accounted for most of the LMIC-derived bacterial genomes at the turn of the century[58]. Today, the higher cost of sequencing overall in these resource-limited settings continues to present challenges to implementing a study sensitive enough to determine whether, when and how resistant organisms, elements or genes cross from one niche to another. However, as summarized in Box 1, when transmission is intensively occurring, the potential for capturing informative snapshots is high.

Box 1 | One Health circulation of resistant Enterobacteriales in Zanzibar island

The near absence of information on resistance reservoirs and transmission pathways in LMIC settings before the 2000s is most probably tied to the infrequent application of suitably sensitive techniques. When molecular methods have been applied to study resistance in these countries, or more commonly to study strains that had been shipped from them, these methods have shown that pandemic, as well as locally predominant clones, circulate.

In 2020, Büdel et al.[103] reported recovering two independent *E. coli* and three *Klebsiella pneumoniae* over-represented clones from humans, poultry and chicken meat in Zanzibar. The clones were not predominant pandemic lineages but have been recovered from bloodstream infections elsewhere on the African continent. The investigators were tracking uncommon cephalosporin-resistant and colistin-resistant Enterobacterales in an island population, which allowed them to select bacteria of interest by cefuroxime enrichment and to infer clonality from a very small number of bacterial genomes. Thus, low sequencing capacity was not a barrier to finding disseminated clones. In all, they were able to verify these five clones by sequencing only 46 genomes from a pool of 144 isolates. A subsequent study revealed that travellers visiting Zanzibar from Europe became colonized by predominant resistant clones during their visit and exported them on their return home[43], illustrating the potential of spread that One Health crossovers at one location hold.

Data from this study demonstrate that it is possible to identify suspect clones using phenotypic and PCR-based typing; however, confirming them and understanding transmission dynamics required whole-genome sequencing. Larger and more complex communities with many more circulating clones would require the high resolution that whole-genome sequencing could offer and would necessitate sequencing many more isolates. As with similar studies, Büdel et al. could not identify the origin of the clones or their direction of transmission on the basis of the point prevalence data alone. However, given the relative simplicity of the setting, this could be uncovered through longitudinal studies and/or sampling environmental niches suspected to be part of the chain.

LMIC-specific features of the livestock industry exacerbating resistance transmission

In LMICs, the variety of livestock production systems generate much greater contact between humans, animals and the natural environment than in high-income countries (HICs). Agricultural employment represents less than 5% of total employment in HICs but reached 23% in the Philippines, 30% in Ecuador, 54% in Kenya, and up to 86% in Burundi in 2019 (https://www.theglobaleconomy.com/rankings/employment_in_agriculture/). Urban subsistence farming is rare in HICs but common in LMIC settings, including informal settlements. Biosecurity measures that mitigate sanitary risks in high-income settings require capital expenditure and higher technical skills, and are often not implemented in LMICs, particularly in smallholder/subsistence farming systems, which represent up to 80% of the production in Asia and sub-Saharan Africa (http://www.fao.org/fileadmin/templates/nr/sustainability_pathways/docs/Factsheet_SMALLHOLDERS.pdf). Larger contacts between livestock and humans in LMICs than in HICs can be evidenced along the entire food system value chain, as illustrated by the central place that live and wet markets play in the commercialization of livestock and the access to food in Asia and Africa[59] (Fig. 1).

Informal livestock trade in LMICs exacerbates the risk of resistance transmission. Informal trade cannot, by definition, be easily and precisely assessed; however, some evidence-based evaluations suggested that the proportion of informal livestock trade in LMICs is significant. For example, informal trade in live cattle from India to Bangladesh was estimated at US$620 to 660 million per year in 2018, and the year before that, 70% of frozen chicken trade in Nigeria was assessed as informal[60]. Similarly, an evaluation by the Colombian Federation of Cattle producers (FEDEGAN) found that 62% of the national cattle production in 2018 was commercialized through informal channels (https://www.fedegan.org.co/noticias/ganaderia-colombiana-hoja-de-ruta-2018-2022). On one hand, informal livestock trade in LMICs offers small-to-medium benefits such as improved food security, reduced price instability, employment opportunities and avoidance of large, multiregional foodborne outbreaks. On the other hand, it undermines the possibility of sanitary inspections and the overall effective governance of value chains[11].

The third critical LMIC pattern that exacerbates the risks of resistance transmission from livestock is limited access to veterinary services. In a recent survey in five African countries (Ghana, Kenya, Tanzania, Zambia, Zimbabwe)[61], the veterinarian-to-livestock ratio was shown to be on average 20 times lower than in HICs such as Denmark, France, Spain and the United States. The World Organization for Animal Health, formerly the Office International des Epizooties (OIE), has launched a global initiative to assess and improve the level of performance of national veterinary services (https://www.oie.int/app/uploads/2021/03/2019-pvs-tool-final.

pdf). Poor animal health services stemming from inadequate access to veterinary resources are precursors to the misuse of antimicrobials for prophylaxis or as feed additives, including the poor institution of proper farm biosecurity and other animal health infrastructures in animal rearing[62] (https://www.oie.int/app/uploads/2021/03/en-oie-amrstrategy.pdf). On the other hand, even when veterinary services are available, the high reliance on cultural and historical perspectives in animal rearing practices by animal handlers, as with the Maasai pastoralists in Tanzania, may mean that veterinary professionals are not consulted or are consulted only as a last resort[63].

The importance of country-owned and developed national action plans to combat AMR using appropriately tailored interventions cannot be overstated. Indeed, the typical practice of modelling LMIC action plans on HIC templates may account for the understatement, or in many cases complete absence of key transmission-blocking interventions, such as water sanitation and hygiene (WASH)[64]. In our opinion, many other National Action Plan (NAP) pillars under-exploit opportunities for impact because they prioritize top-down interventions aimed at combatting resistance in high-income settings that may not always be suitable for or effective in other parts of the world (Table 1). In HICs, the top-down implementation of One Health AMR interventions has the benefits of speed, leverage and scale within specific socio-economic and regulatory environments[65]. In the complex systems of livestock sectors in LMICs, a top-down approach is less likely to succeed. The multitude of contacts between animals and humans, the large informal livestock trade and the deficiency of veterinary services require integrated top-down and bottom-up national action planning and implementation of interventions that may be less prone to failure where regulation is not strong[61].

AMR is a complex problem, and its development has the characteristics of nonlinearity, emergence, positive and negative feedback, and adaptation that are particularly prominent in LMICs. The stakes for resistance are higher and the value chain is uncertain in LMICs. These, combined with the high uncertainty from limited surveillance and the urgent need to avoid catastrophe from resistance, necessitate a post-normal science approach[66] for addressing resistance in a One Health context.

Technological tools with promise for addressing resistance transmission

There is considerable academic interest but a lack of general appreciation and clear translational paths for promising technologies for preventing resistance transmission. Given that the development of new antibiotics has stalled globally in the last few decades[67] and new drugs are typically only available in LMIC settings after a lag, anti-transmission tools and approaches deserve serious consideration. Technological tools with the potential to contain the spread of resistance, such as bottom-up approaches to directly prevent transmission, may have greater potential in LMIC settings.

Infection control and prevention measures present arguably the most feasible and cost-effective approaches to limiting the evolution and spread of antibiotic-resistant microbes in any setting[68]. With reduced prevalence of infections, antimicrobial use can be limited, consequently reducing the selection pressure and evolution of resistant organisms. Vaccines do exactly this; they are typically administered prophylactically to prevent microbial infections in humans and animals. Although vaccines also exert selective pressure on microorganisms, there is a reduced risk of evolution of resistance to vaccines compared with antibiotics[69]. Additionally, when vaccine resistance does occur, public health benefits such as herd immunity and reduced prevalence of infectious organisms are often sustained. In addition to lowering infectious burden and the need for antimicrobials, vaccines can also directly address resistance and, in particular, the contribution that transmission makes to resistance spread, by preferentially targeting resistant lineages of bacteria (as with polyvalent pneumococcal vaccines, which are the textbook example of how vaccines can temper resistance) or by specifically targeting antigens associated with AMR[70].

Vaccine development has seen a recent resurgence, with more and newer technologies applied[71]. A bioconjugate vaccine (ExPEC4V) against extraintestinal pathogenic *E. coli* (ExPEC), which are among the leading causes of life-threatening invasive drug-resistant infections in humans[72], is currently under development by Janssen Pharmaceuticals. This vaccine has been shown in clinical trials to be well-tolerated, safe and capable of eliciting robust immunological responses against all tested ExPEC serotypes, many of which are antimicrobial resistant[73,74]. ExPEC are disseminated faeco-orally and are also reservoirs for resistance genes that can be transmitted to other pathogens in the guts of humans and animals, as well as in the environment. Therefore, ExPEC vaccines in development may have beneficial effects on the prevalence of resistance, although yet to be demonstrated, and existing vaccines targeting organisms that colonize animate and inanimate niches could offer similar benefits (Box 2).

Antimicrobial misuse is driven by ineffective diagnostic stewardship[75]. Lack of access to essential diagnostics, shortage of skilled laboratory personnel, and high cost and long turn-around times exacerbate diagnostic insufficiency in LMICs[76,77]. The common practice for the management of infections in low-resource settings involves symptom-based and endemicity-guided diagnosis, and the subsequent prescription of broad-spectrum antimicrobials for unconfirmed infections[76,78]. A recent study in a tertiary health facility in Nigeria found that under 25% of the patients who received prescribed antibiotics had confirmed bacterial infections[79]. The proportion of patients for whom antimicrobial susceptibility testing (AST) is conducted is often lower. Culture-based AST, the cornerstone of bacterial infection and resistance detection, works well in many settings but its turn-around time is long and some LMIC institutions caring for infected patients lack the requisite personnel and infrastructure. However, culture-based AST is critical to identifying novel mechanisms of resistance, which are periodically reported from LMICs with better surveillance. Cases in point are the discovery of mobile elements conferring resistance against reserve antimicrobials, noteworthily including *mcr-1* and *tetX* alleles in China[32,33,35], and NDM-1 in India[80], all of which have subsequently been shown to be globally disseminated. The development of rapid point-of-care pathogen detection and AST platforms to increase access and affordability, lower the skill barrier for diagnostic stewardship and decrease turn-around times would greatly limit the empirical administration of broad-spectrum antibiotics and also reduce transmission of resistant bacteria from undiagnosed patients[81]. New clustered regularly interspaced short palindromic repeats (CRISPR)-Cas-based diagnostic technology appears to be promising for the development of rapid point-of-care pathogen detection[82].

Non-antibacterial approaches to eliminating pathogenic and non-pathogenic resistant bacteria are needed and could be used in humans, animals and even the environment. Therapeutic monoclonal antibodies have been explored, albeit with modest results[83]. Promising lower-cost therapeutic approaches include the use of bacteriophages, probiotics, synthetic peptides and nanostructured polymeric materials. Metal nanoparticles are being explored for use as self-sterilizing coatings for medical devices, as well as for controlled antibiotic and antibody release for treatment and prevention of biofilm- and medical device-associated infections[84]. Phage therapy has the advantages of being highly specific to the target bacteria, non-toxic to the host and can be administered in small doses. This may be desirable in LMICs where the use of unprescribed, non-targeted antimicrobials is common, thus reducing transmission and evolution of resistance. Although phage therapies are also

Table 1 | The principal NAP pillars remain to be exploited in ways that could address LMIC transmission, particularly in One Health contexts

Global Action Plan pillar (Quoted from WHO, https://apps.who.int/iris/handle/10665/193736)	Commonly under-exploited aspect within the pillar	Opportunities	Challenges	Surveillance and innovation needs
Improve awareness and understanding of antimicrobial resistance through effective communication, education and training	Insufficient use of data for improving awareness. AMR outreach versus changing behaviour[96].	Improving surveillance (Pillar 2) offers new opportunities to compile convincing evidence on local AMR patterns and risk. Communication and educational interventions are often viewed as inexpensive as they can be delivered without imported or highly technical infrastructure.	Very few stakeholders currently access and use surveillance data. AMR knowledge is being communicated more today than ever before but there are low levels of appreciation of the consequences of AMR and/or shifts from high-risk behaviours[97,98]. Communicating knowledge and changing behaviour are not the same and not enough is known about the latter.	Stakeholder-friendly ways to present and use resistance data. Social science research to identify behavioural root causes and the best approaches for intervention.
Strengthen the knowledge and evidence base through surveillance and research	Sequence-based surveillance approaches are rarely deployed beyond specialized research.	Surveillance makes resistance control goal-based and measurable and improving it has the potential to synergize with other pillars.	Surveillance systems in many LMICs lack good coverage and representation outside (and sometimes inside) clinical settings. Surveillance methods are typically too insensitive to identify transmission across niches when it occurs.	Lower-cost approaches to exploit sensitive techniques like whole-genome sequencing.
Reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures	WASH	Around the world, improvements in infection prevention and control in health facilities will lead to major declines in nosocomial resistance. WASH shortfalls may account for much of the excess resistance transmission problem in LMICs in and beyond health facilities. Providing safe water and sanitation offers the added gain of disrupting disease transmission[91]. Antimicrobials are used to address and conceal WASH lapses and therefore WASH could also help reduce selective pressure[96].	WASH, by current standards (based on HIC sanitation systems), requires high upfront costs and considerable technical expertise for maintenance. Absence of this, as in sub-standard WASH infrastructures, including waste disposal methods, encourage the spread of pathogens and diseases[99]. Shallow groundwater and underground sludge systems often implemented as safe sanitation mimics may create hidden transmission niches.	Data showing the impact of WASH interventions on AMR, particularly in LMIC settings. New WASH mechanisms that are less water-intensive and offer better recycling[100].
Optimize the use of antimicrobial medicines in human and animal health	Stewardship	Antimicrobial resistance stewardship programmes offer an excellent recursive problem-solving approach and have been recognized to play significant roles in reducing the impact of AMR in clinical settings[101]. Diagnostic stewardship in hospitals increases the chance that resistant pathogens are rapidly identified and eliminated before they can spread.	Antimicrobial stewardship programmes outside health facilities are non-existent and under-developed but could be critical in containing resistance in settings where both access to antimicrobials and knowledge about resistance are sub-optimal.	Defining best practices outside clinical settings and roles for non-healthcare worker actors that could implement stewardship in other human, animal and environmental settings are highly needed in LMICs[102].
Develop the economic case for sustainable investment that takes account of the needs of all countries, and increase investment in new medicines, diagnostic tools, vaccines and other interventions	AMR as an economic concern	In the human sector, AMR concerns are for reducing morbidity and saving lives, with some emphasis on the potential of AMR to raise the cost of care. However, in LMIC animal sectors, the considerations are largely economic; hence, the failure to frame AMR as an economic, as well as a health issue is a missed opportunity.	AMR planning and activities are typically led by the health and agricultural sector, sometimes with input from the environment. Finance sectors need to be directly engaged in AMR action planning.	There is a dearth of health and agricultural economists in many LMIC countries. Simple methods for translating human and veterinary health and other AMR costs and benefits to metrics used in financial planning may be helpful.

Box 2 | Vaccine-based containment in cholera epidemics has overcome the in-outbreak evolution of resistant *Vibrio cholerae*

Toxigenic *Vibrio cholerae* are among the deadliest epidemic-prone organisms, and present-day outbreaks are limited to Africa, South Asia, Latin America and the Caribbean. Cholera patients not properly rehydrated risk death within 24 h. When case fatality is high in an epidemic, the typical root cause is poor access to effective rehydration. The direct consequences of poor access to quality emergency care are exacerbated by uncontrolled transmission. The difficulty in breaking faeco-oral transmission chains for *V. cholerae* in many settings, such as in complex emergencies, and across much of Africa is illustrative of the transmission routes available to other bacteria, including those that are reservoirs for resistance genes. Antibiotics, the perennial quick fix stopgap for WASH lapses[96], have played a central role in outbreak mitigation over the past 60 years. They are given to shorten the duration of symptoms and reduce the shedding of infectious bacteria by the infected, and have in the past been administered to protect anyone at risk of being exposed.

The last two justifications are made to reduce the size of the outbreak, which antibiotics have been shown to do. However, the administration of tetracycline in the 1970s, sulfamethoxazole-trimethoprim in the 1980s, quinolones in the 2000s, and then azithromycin[104–106], invariably led to the evolution of resistant strains that often appear during the very outbreak that antibiotics are deployed to contain. In one outbreak in Ghana, sulfamethoxazole-trimethoprim was used to treat infected patients and *V. cholerae* isolates obtained late in the epidemic carried two different resistant dihydrofolate reductase genes on separate mobile elements[107].

Multidrug-resistant *V. cholerae* are to be expected in cholera-endemic areas and drug choice options are few[108]. Overall, and particularly at the turn of the century, when antibiotics were a critical component of outbreak management in Africa but case-fatality rates remained untenably high[109] due to resistance, there is little evidence that antibiotics met their theoretical potential for epidemic control. Currently, their recommended use is restricted to severe infections or for the immunocompromised, with the goal being to provide benefit to patients that may need these drugs without ramping up selective pressure for resistance in an epidemic. Cholera vaccines, and indeed other vaccines targeting faeco-orally transmitted bacteria[110], are a quintessential cost-effective transmission-blocking tool. Each vaccine is more expensive than earlier deployed antibiotic courses; however, unlike antibiotics, vaccines protect against future outbreaks, greatly reducing the need for antibiotics overall. This is an important consideration since antimicrobials that could be used empirically today for cholera, such as azithromycin or fluoroquinolones, are much more expensive.

amenable to bacterial phage resistance[71,85] and require diagnostic proficiency to sub-type level, the approach still offers the potential for propagative effects outside the sick host that could help stem transmission, something that probiotics might also offer.

Alternative growth promoters and feed additives such as probiotics, prebiotics and synbiotics[86], lactic acid bacteria and bacteriocins[87], organic acids[88], vitamins and minerals[89] have been recommended to greatly improve food-animal health and production. For example, probiotics and prebiotics stimulate commensal flora growth and improve animal health and immune status[86,90]. Probiotics aid the neutralization of enterotoxins and necrotizing enterocolitis[86]. Varying levels of success have been reported for these feed additives and more research is required to support their use as alternatives to antibiotics. These could augment sanitary interventions in animal production facilities in LMICs to reduce the underappreciated impact of animal faeces as an AMR vehicle and reduce threats to human health not covered by conventional WASH programmes[91]. The potential that probiotics could offer for human health is under investigation, but their impact on resistance does not appear to have been intensively studied. It is also worth hypothesizing, albeit as yet untested, that probiotic or other non-antimicrobial tools could offer an alternative to mass drug administration for child survival[92], indirectly ameliorating the potential abuse of antimicrobials.

Antimicrobials proffer strong selective pressure by killing the bacteria they attack or at least inhibiting their growth. Compounds that inhibit virulence or colonization factors would presumably have a lower selection for resistance and a few are in development[93]. As with many anti-transmission technologies, questions remain about how they could be used therapeutically. Potentially useful tools against resistant bacteria might not be able to scale a non-inferiority clinical trial against an antimicrobial, posing a regulator barrier to their use[67]. It has been proposed that anti-virulence agents be trialled in combination with existing antibiotics. However, anti-colonization factors, in particular, could have the added benefit of dislodging resistance reservoirs, and the design of studies that include resistance reduction endpoints is worthy of consideration. Also, the use of anti-transmission approaches outside clinical medicine will not require clinical trials. Other technological tools that could impact the transmission of resistance and therefore have potential applications in the settings we have described include agents that inhibit horizontal gene transfer. These include but are not limited to anti-conjugation factors. CRISPR technology has been used to target resistance genes in enterococci[94]. Similarly, there is experimental work in progress aimed at blocking the transmission of conjugative elements[95]. The translational pathway for such agents is even more unclear. As the specific application of tools with the potential to stem the transmission of resistance in HIC clinical medicine is somewhat elusive, development and deployment for proof of concept might be applicable in a One Health transmission context, particularly in a setting where inter-individual contact is high and drug use and transmission controls are low.

Conclusion

Resistant bacterial variants evolve continuously but are selected when antimicrobials are applied and can be transmitted among humans, animals and their environments. Surveillance of resistance is improving and increasingly incorporating genomic approaches, but many intervention points for stemming the flow of resistant organisms and genes remain under-exploited or unknown. In LMIC settings where humans and animals converge at high density with insufficient sanitation and biosecurity infrastructure, the risks of selection of resistant bacterial variants and their transmission among humans, animals and the environment are high, and patterns of transmission are likely to be different. The relative importance of the numerous risk factors needs to be further investigated in specific LMIC settings to develop the most appropriate responses to the development of antibiotic resistance.

Significant modifications of One Health approaches optimized for HICs should combine top-down approaches with appropriate bottom-up actions for LMIC settings to compensate for institutional weaknesses. There may also be a role for technical disruption of transmission. The promise of recent innovations and technologies that could accomplish this may vary with landscape and thus require independent evaluations by LMIC scientists and actors who may be better served by engaging directly in early-stage innovation rather than merely adapting their uses in HIC to LMIC conditions.

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Competing interests

The authors declare no competing interests.

Additional information

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