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Defining and combating antibiotic resistance from One Health and Global Health perspectives

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Several interconnected human, animal and environmental habitats can contribute to the emergence, evolution and spread of antibiotic resistance, and the health of these contiguous habitats (the focus of the One Health approach) may represent a risk to human health. Additionally, the expansion of resistant clones and antibiotic resistance determinants among human-associated, animal-associated and environmental microbiomes have the potential to alter bacterial population genetics at local and global levels, thereby modifying the structure, and eventually the productivity, of microbiomes where antibiotic-resistant bacteria can expand. Conversely, any change in these habitats (including pollution by antibiotics or by antibiotic-resistant organisms) may influence the structures of their associated bacterial populations, which might affect the spread of antibiotic resistance to, and among, the above-mentioned microbiomes. Besides local transmission among connected habitats—the focus of studies under the One Health concept—the transmission of resistant microorganisms might occur on a broader (even worldwide) scale, requiring coordinated Global Health actions. This Review provides updated information on the elements involved in the evolution and spread of antibiotic resistance at local and global levels, and proposes studies to be performed and strategies to be followed that may help reduce the burden of antibiotic resistance as well as its impact on human and planetary health.

Antimicrobial resistance (AMR) is recognized as one of the major Global Health challenges of the 21st century by all major regulatory, economic and political bodies, including the International Monetary Fund, the WHO, the World Bank and the G8. All subscribe to the scientific view that AMR can no longer be addressed by simply studying the problem in healthcare facilities since most ecosystems contribute to the emergence, acquisition and spread of AMR[1]. The problem of AMR is therefore currently viewed from two complimentary concepts, One Health and Global Health, which have been used to address problems associated with infectious disease in general, and AMR in particular. Both concepts are holistic and interdisciplinary and are based on the idea that human health and animal health are interdependent as well as being linked to the health of the ecosystems of which they are part.

The concepts of One Health and Global Health both integrate knowledge of the biological elements necessary for understanding the evolution of AMR, including the microorganisms or vectors involved in its emergence and dissemination, the host organisms (humans or animals) and the environments involved, and the cultural and socioeconomic features that may facilitate its spread. The differences between One Health and Global Health are, therefore, not always clear[2].

One Health focuses on the role of interconnected (and hence geographically close) ecosystems in the emergence and dissemination of AMR (Fig. 1), and therefore addresses AMR at the local level as well as focussing on the implementation of integrated interventions for fighting AMR at, say, the city or regional level. Global Health, in contrast, addresses the global conditions that facilitate the worldwide spread of AMR (Fig. 1) and is rooted in the idea that the control of AMR requires integrated political and socioeconomic actions to be taken by countries, international organizations and other actors on the global stage[3].

Global Health and One Health are interconnected (Fig. 1) and may use similar tools, but One Health local interventions are certainly more feasible than Global Health interventions, as the latter require a worldwide policy and need to be planned with deep international and intercultural understanding. In this regard, it is worth mentioning that actions that can be easily implemented as interventions at the local, One Health level would be just recommendations at the Global Health level due to the different regulations in each country. Global plans to fight AMR[4] require the support of balanced and comprehensive epidemiological and ecological surveillance networks[5]; multivariate analysis of AMR drivers, including the sociodemographic and economic factors that may influence AMR[6], as well as estimates of the economic impact of interventions to reduce it, are also required (https://amr-review.org).

Defining the entities involved in antibiotic resistance

Technically, the term 'AMR' should be applied only to bacteria resistant to antibiotics; as stated by the WHO, "bacteria, not humans or animals, become antibiotic-resistant"[7]. However, it might be useful to expand this term to other entities in order to rank them according to their AMR transmission risk. For instance, the term 'antibiotic-resistant infections' is commonly used in clinical medicine, as is 'antibiotic-resistant patients', which refers to patients known, or suspected to harbour, antibiotic-resistant bacteria (ARB). In this context, the term 'antibiotic-resistant patients' is useful as a means of identifying those who should be the object of cross-infection precautions to prevent the spread of AMR. Similarly, since the dispersal of hospital-acquired resistant pathogens depends on hospital-to-hospital interactions[8], designating 'antibiotic-resistant hospitals' with high rates of AMR would help identify sites requiring corrective interventions to reduce AMR and prevent AMR transmission.

Scaling up to the idea of 'antibiotic-resistant environments' (for example, polluted rivers, beaches or soils) would enable the ranking of hospitals, farms and environments according to their level of AMR transmission risk and, consequently, the design of evidence-based interventions to reduce these risks, such as isolating these

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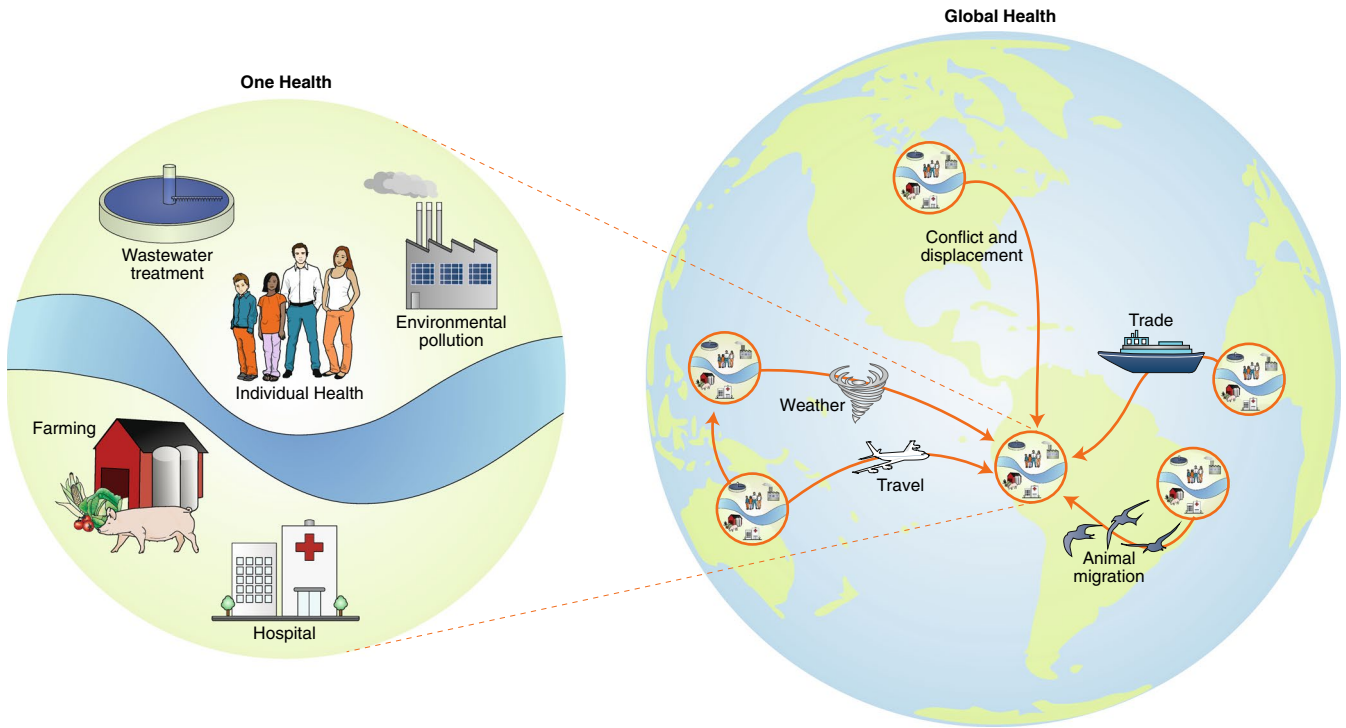

Fig. 1 | The One Health and global Health axes of antibiotic resistance. The transmission of AMR occurs at the local level across the borders between different ecosystems, such as farms, hospitals, wastewater treatment plants and natural environments. This is a One Health problem, where the health of any of these ecosystems may affect the health of the others, including human health. One Health can therefore be understood as a 'local version' of Global Health, which addresses communication among local ecosystems and the global conditions that facilitate the worldwide spread of AMR. This may occur through the global interchange of goods by human travellers, migrating animals and even through the help of natural phenomena such as El Niño, which can expand the area for interchange among geographical areas. Corridors and bridges therefore exist that promote the globalization of gene spread, encouraging the appearance of similar microbial communities wherever the same processes occur.

'antibiotic-resistant entities' from neighbouring non-contaminated ones and reducing the flow of AMR-containing materials, that is, hosts, food or sewage.

Criteria for identifying 'resistant' patients, hospitals, farms and environments should be based on the risk that these entities impose to human and animal health. For this purpose, detection of ARBs is considered a priority by the WHO[9], as is the potential implementation of quantification of antibiotic resistance genes (ARGs) using novel tools (for example, gene capture strategies[10] or highly parallel real-time PCR procedures[11]). Particularly relevant will be the analysis of ARBs and ARGs involved in AMR dissemination from high-incidence to low-incidence environments.

Local and global dissemination of AMR

The microbiomes of humans, animals, plants, water and soils are interconnected sinks through which the bacterial pangenome, including ARGs, may flow with some restrictions[12]. Although simulations based on membrane computing models have recently been proposed for studying the multilevel dynamics of AMR[13], quantitative analyses describing the contribution of each of these microbiomes and their corresponding ecosystems to the origin and spread of AMR are still required[14,15].

The One Health component of antibiotic resistance. AMR emerges as the result of local confluences between bacteria colonizing different hosts (including humans and animals) and their shared environments where ARGs can be transferred from their original hosts to bacterial pathogens. While resistomes across habitats are linked to the phylogeny of microbial populations along ecological gradients, clinically important resistance genes associated with mobile genetic elements (MGEs) can cross habitat boundaries[16]. Besides, microorganisms that form part of non-clinical ecosystems are, on many occasions, the original hosts of clinically important ARGs that have been transferred from environmental microorganisms to human pathogens[17,18].

The recent collapse in animal and plant genetic diversity due to urban spread, habitat destruction and the anthropogenic selection of a limited range of varieties of economic interest implies the homogenization of hosts that favours the dissemination of ARGs among common microbial communities (Fig. 2a). Economic and cultural factors, such as those influencing access to water or food habits, may also favour specific transmission pathways among ecosystems[19].

The spread and maintenance of ARGs also depends on their integration into hierarchically organized systems, such as integrons, and on interaction networks between ecologically connected bacterial populations (also known as gene exchange communities (GECs))[20] or between colonized human and animal hosts (Fig. 2b).

Generalist clones and plasmids at the human–animal microbiota interface. AMR in animals can only impact on human health if animals and human microbiomes share the same ARB species or ARGs. In this regard, host niche adaptation—seen both in 'commensal opportunistic pathogens' (for example, extraintestinal pathogenic *Escherichia coli* (ExPEC) and *Staphylococcus aureus*) and 'frank pathogens' that cause foodborne zoonotic infections (for example, *Salmonella* sp. and *Campylobacter jejuni*)[21,22]—limits transmission between humans and food animals. Cross-species AMR transmission has been unequivocally demonstrated only a few times[23]. Further, it is not easy to distinguish between pathogens originating

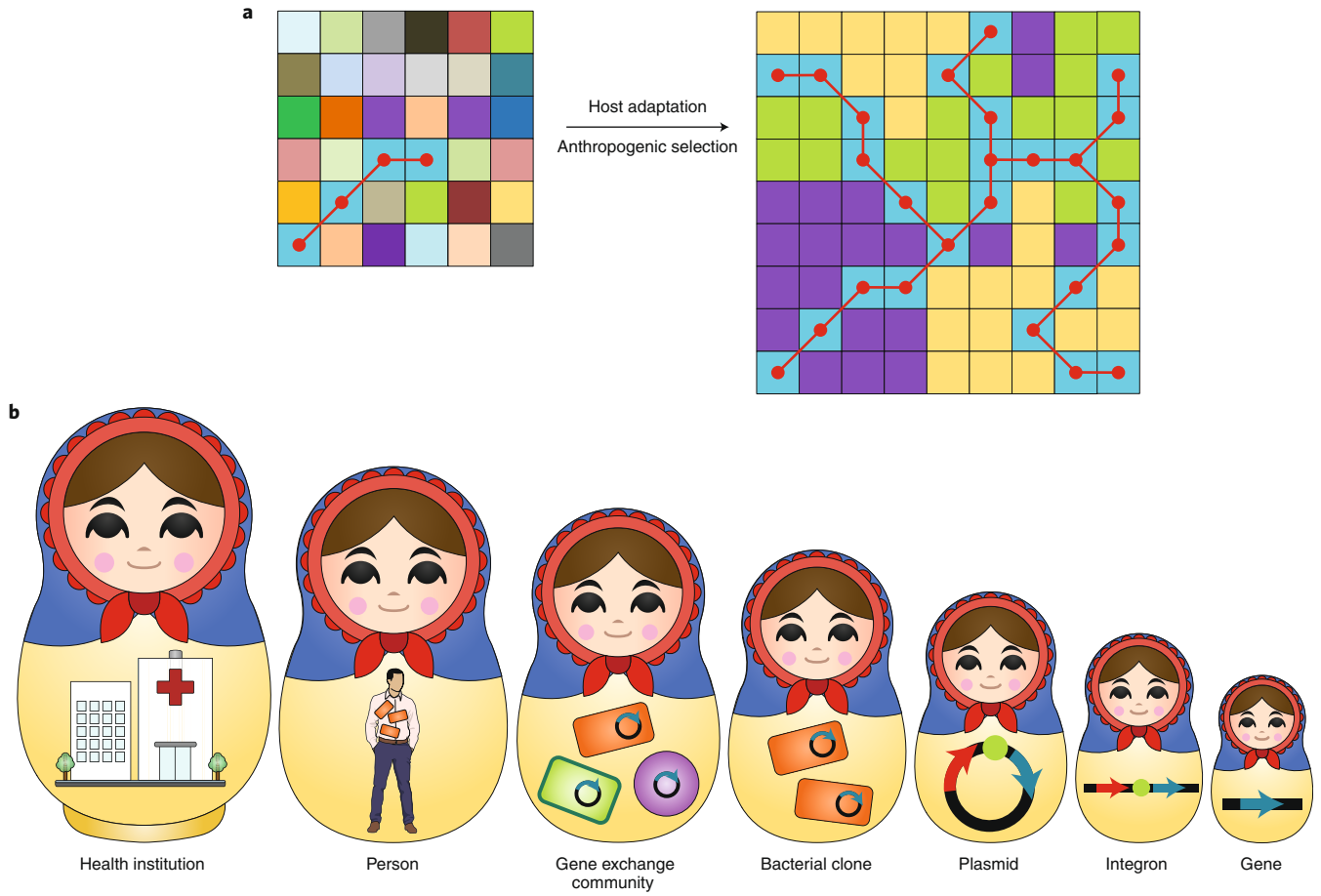

Fig. 2 | The hierarchy and spread of antibiotic resistance. a, Bacterial pathogen adaptation to their hosts is frequently concurrent with de-adaptation to an alternative one[21], suggesting host variability is a barrier to inter-host spread. Recently, the anthropogenic selection of a small number of animal and plant varieties of economic interest (blue square) has led to the homogenisation of hosts. In addition, increases in the absolute numbers of hosts able to interact with human pathogens favours the dissemination of the latter. These changes imply the blending of host-associated microbiomes, favouring the dissemination of ARGs (red circle) among common bacterial communities. The loss of microbial diversity correlates with AMR increase in man-made built environments[143]. **b**, Transmission of resistance is a multi-layered, hierarchical, Russian nesting doll-like process in which the different elements involved influence one another[19]. ARGs are recruited by integrons and other mobile elements, which may in turn be acquired by specific bacterial clones through HGT. These clones circulate ARGs in bacterial gene-exchange communities and may infect humans and animals that then transmit them to other populations in, say, hospitals, or to faraway locations when they travel. These layers of selection influence one another, as the acquisition of an ARG may select for the expansion of the bacterial clone carrying it in antibiotic-rich environments, for example, hospitals. Conversely (and depending on the associated fitness costs), the introduction of an ARG into an already successful clone may increase its chances of dissemination in environments where there are no antibiotics. Thus, the process of transmission is a mechanism that facilitates the evolution of resistance traits[19].

in animals from those originating via the manipulation of food (the latter with a human origin)[24].

In light of potentially 'mutually exclusive' bacterial colonization of humans or animals by adapted clones, the risk of animal-based AMR transmission to humans appears linked to particular generalist clones[23] that can act as shuttles of AMR by colonizing and infecting both types of host. The transmission of high-risk AMR shuttle clones is facilitated by food animal–human contacts and by the collapse in farm animal diversity (Fig. 2a). An example of these generalist clones is provided by subpopulation B (*fim*H22) of the pandemic ExPEC clone sequence type 131 (ST131), which may have been selected in poultry after acquisition of the ColV FIB plasmid during the 1940s and eventually entered the human food chain on several occasions, carrying with it, or acquiring, different plasmids (often encoding ARGs) over time[25]. Similarly, methicillin-resistant *Staphylococcus aureus* (MRSA) CC97 jumped from livestock to humans 40 years ago and became MRSA, as it is now known[26].

Transmission from humans to animals has been also reported, such as in the case of the MRSA CC398 lineage. The CC398 progenitor jumped to livestock and acquired resistance due to antibiotic selection pressure on pig farms[27,28]. The acquisition of AMR by frank pathogens such as *Salmonella* or *Campylobacter* has contributed towards their increased prevalence, compromising livestock production and causing major food security problems. For example, a global epidemic of multidrug-resistant (MDR) *Salmonella* Typhimurium definitive type 104 (DT104) in animals and humans was recorded in the 1990s, which was preceded by MDR emergence in the 1970s[29] following the acquisition of a 43-kb genomic island encoding resistance against five first-line antibiotics[30]. Nevertheless, it is worth remarking that most DT104 transmission events seem to have occurred within each host population, with only a small proportion of livestock-to-human transmissions.

MGEs that can be transferred among different bacteria are also major drivers of the dissemination of ARGs between different hosts and different bacterial species or clones[31]. Examples include several plasmids coding for extended spectrum β-lactamases[32]; Inc HI2 pST4 plasmids carrying the *mcr-1* gene that encodes resistance to colistin and blaCTX-M-1 (ref. [33]); the MDR plasmid p60006, which

can spread among pandemic clones of *Enterobacteriaceae*[34]; and Inc18 plasmids harbouring *vanA* in enterococcal species inhabiting humans and animals[35].

AMR in a Global Health context. A dominant hypothesis in the AMR field is that novel mechanisms of resistance start in a given place and then spread worldwide[36]. Indeed, bacteria carrying clinically important resistance genes can be found in nearly every habitat, including wild animals, natural ecosystems and even in people belonging to isolated populations that have no contact with antibiotics[37–41]. Further, the analysis of archived soils has shown an increase in the abundance of ARGs since 1940 (ref. [42]). Besides this monophyletic origin, some ARGs are acquired independently in the same or different geographic locations[43,44]. In line with the Baas–Becking hypothesis, "everything is everywhere, but the environment selects"[45]; 'global' in this sense means the emergence of similar resistance traits in different locations[42].

Genes present in MGEs are even more 'global' than organisms, as illustrated by the capacity of mobile ARGs to cross habitat boundaries[16,46]. While the genes causing resistance in clinical and/or veterinary settings are of the utmost public health concern[47], it remains unclear whether ARGs not present in pathogens but in commensal or environmental bacteria represent a significant reservoir of resistance that can be transmitted to pathogens[48,49]. However, studies on commensal or environmental ARGs may be of some interest from a Global Health viewpoint, as it is possible to estimate the resilience of bacteria when exposed to antimicrobials[50] and to detect changes in the ARG composition of the corresponding microbiomes at an early stage. This enables prediction of the importance of such genes in the resistance of human pathogens before classical epidemiological studies are performed.

The political, socioeconomic and cultural factors that influence the dissemination of AMR are still far from being fully understood. The increased exchange of goods[51] as well as globalization of food production and land usage methods have had major impacts on environmental health and food security[52]; for example, worldwide expansion of a limited set of animals, plants and their derived products as foods also enriches for particular host-adapted bacteria, which include ARBs[53].

In addition, the increased connectivity among environments and hosts at different geographical scales have contributed to AMR spread[54]. Once an ARG has been acquired by a bacterial pathogen, the spread of AMR may involve mechanisms of transmission that do not require selection. For instance, migrating animals can carry ARBs[36], as can international travellers. Even healthy people not receiving antibiotics may contribute to the transfer of AMR among geographic regions[55,56]. If refugees are carrying ARBs[57,58], dissemination might be favoured by poor sanitary conditions and overcrowding in refugee camps. Migrants might also spread relevant ARBs (such as MDR *Mycobacterium tuberculosis*) from endemic to low-incidence countries[59]. These categories of travellers—especially migrants in an irregular legal situation—may not have access to health services, which could impede the early detection of AMR, and incorporation of these citizens into health programs—something that some countries have already implemented[60]—is an urgent matter for the early detection and surveillance of AMR spread.

While the elements involved in the dissemination of resistance are well studied at the qualitative level, quantitative models that can help in risk assessment studies are urgently needed[14]. Such models should include information from surveillance programs of citizens and goods able to detect the emergence and worldwide dissemination of AMR at an early stage. The improved knowledge of transmission dynamics that such programs could bring may help to counteract transmission.

Anthropic drivers of antibiotic resistance

While ARGs were present in nature long before antibiotics were used in therapy (ref. [12]), the spread of antibiotic resistance in human pathogens is a recent event in evolutionary terms, which has occurred after the human development of such drugs. In this respect, the current problem of antibiotic resistance should be considered as an example of anthropic-driven evolution due to different factors that are reviewed below.

Antibiotic use in the clinic and farms. Despite regulations and controls for reducing the use of antibiotics, a recent study reported a substantial increase in global antibiotic consumption between 2000 and 2015, and predicted a further 200% increase by 2030 (ref. [61]). This increase is predicted to be faster in low- and middle-income countries (LMICs) as their economies develop and access to health services improves. The amount of antibiotics sold in LMICs is largely unknown and antibiotics are often consumed in the absence of medical supervision[62], possibly favouring the emergence of ARBs[63]. However, it is also important to note that increased access to antibiotics has contributed (alongside vaccination and improved sanitation) to a reduction in endemic illnesses and child mortality in places such as Sub-Saharan Africa[64]. Thus, while a global decline in the use of antibiotics may be desirable to reduce the problem of AMR, there are still areas where antibiotic use should be increased to fight infection.

Antibiotic use in humans is overshadowed by their use in farming, with two-thirds of overall antibiotic usage destined for animal production[65]. The use of antibiotics as growth promoters has been banned in many countries[66] but is still allowed in many others; 131,000 tons of antimicrobials were used globally in food animal production in 2013, a figure that may rise to approximately 200,000 tons by 2030 (ref. [67]). The rapid growth of antibiotic use in livestock production in LMIC countries[68] reflects the increase in the demand for meat products following the increase in income per capita. International competition exhibited by these countries regarding meat production, exemplified by their appearance in markets in which they have traditionally been absent[51], has also favoured increased antibiotic usage among livestock. However, antibiotic consumption has also been on the rise in the USA[68], where around 80% of all antimicrobials purchased in 2011 were used for non-therapeutic purposes in livestock production and fish farming[65].

Heavy metals are present as the most abundant pollutants in both industrialized and developing countries[69], and are also used as animal food supplements. Heavy metals and other biocides can co-select for AMR[70], may stimulate horizontal gene transfer (HGT)[71] and may modify the dynamics of antibiotics in natural ecosystems[72]. Consequently, their role in AMR selection, spread and maintenance worldwide should be taken into consideration.

The sanitation landscape of antibiotic resistance. Although economic activity in LMICs may increase antibiotic consumption and hence the risk of AMR development, it also allows for the implementation of infrastructures that might reduce the risks of infection and the spread of AMR. For example, antibiotic-resistant pathogens that contaminate natural ecosystems are mainly introduced by the release of human or animal stools[73], and drinking water has been an important vehicle for the spread of the *New Delhi metallo-ß-lactamase-1* ARG in different countries[74]. Thus, public health interventions in the areas of food and water quality as well as sewage disposal, for example, could have a positive impact (Table 1). However, even when wastewater treatment plants (WWTP) are available, ARBs can appear in drinking and coastal waters[75,76], and reducing ARGs to non-detectable levels would be extremely difficult. Recent work has shown that the antibiotic resistome of urban WWTP mirrors the pattern of clinical antibiotic resistance prevalence[11], and "metagenomic analysis of sewage as an ethically acceptable and economically feasible approach for continuous global surveillance and prediction of AMR" has been proposed[77]. Having a standard definition of polluting sentinel AMR bacteria/gene

Table 1 | Examples of actions for reducing AMR burden

	Individual Health	One Health	Global Health
Therapeutic approaches	• Development of new ABs, including multitarget drugs. • New policies on anti-infective combinations, including cycling strategies based in collateral susceptibility. • Use of adjuvants and enhancers of AB action, including resistance inhibitors and hybrid ABs. • Anti-resistance drugs, such as inhibitors of membrane microdomains for treatment against MRSA. • Use of immunomodulators, antibodies and stem cells. • Vaccines, particularly against ARBs. • Fast diagnostic tools and species-specific antibiotics to allow for personalized medicine.	• Policies for antibiotic use, considering the local burden of antibiotic resistance. • Development of new ABs for animal use only, as well as PK/PD modelling in animals. • Development of predators as bacteriophages and *Bdellovibrio* use against bacterial pathogens. • Vaccines against animal pathogens.	• Global prioritization of needs in anti-infection research. • International academic, public and private partnership in anti-infection research and development. • Incentives and regulatory changes to specifically favour the development of anti-infectives. • Stable international platforms for clinical trials. • Global quality control of ABs in the legal market and general reduction of uncontrolled sales. • Global improvement of public health services. • International vaccination programs.
Reduction of antimicrobial selective pressure	• Evidence-based prescription of ABs. • Personalized prescription based on rapid identification of ARBs and ARGs. • Awareness of local resistance burden to orientate prescription. • Reduction of the time of AB selective exposure. • Moving from general to personalized PK/PD. • Use of species-specific antibiotics versus wide-spectrum. • Use of delivery systems to target an antibiotic to the point of infection. • Use of AB adsorbents or compounds able to degrade ABs for decreasing ABs concentration at the gut. • Vaccines against bacterial pathogens, including preventive and therapeutic vaccines.	• Surveillance of AB consumption in hospitals, the community and agriculture. • Control and supervision of the sale of ABs for human health and animal production. • Local guidelines for prescription considering AMR burden. • Local control and regulation of AB release in the environment. • Removal of antibiotics and ARBs from the environment. • Improvement of decontamination of metals and biocides. • Continued local surveillance of known and emergent AMR traits in humans and animals. • Surveillance of AB pollution in water and food. • Development of rapidly degradable antibiotics. • Novel systems in animal production focusing on the reduction of antibiotic use. • Use of non-antibiotic compounds for prophylaxis and metaphylaxis. • Vaccines against animal pathogens.	• Worldwide surveillance of AB production and consumption. • Worldwide guidelines for ABs utilization based on evidence-based studies. • Global regulation of pharma-chemical industry concerning release of ABs in the environment. • Global regulation of hazardous industrial wastes, particularly in countries that receive waste from other countries. • Global regulation of AB contamination in food, animals and generally in goods.
Reduction of transmission of ARBs and ARGs	• Surveillance of commensals that can be carriers of ARGs. • Antibacterial vaccination to prevent colonization and transmission of AMR clones. • Isolation of patients infected with high risk ARBs or ARGs. • Intestinal decontamination of resistant bacteria.	• Development of anti-conjugation drugs. • Prevention of cross-colonization and infection among different ecosystems. • Increase local hygiene and sanitation within the local agro-food chain management systems. • Increase local hygiene, sanitation in LMICs, including safe collection, treatment and disposal of waste, and safe food storage. • Implementation of surveillance networks to analyse the risks in hubs of the food chain. • Implement risk assessment of food management systems at the local level. • Control of AMR in local animal and food trade. • Prevention of environmental commingling of wastes from hospitals, farms and AB-contaminating industries, including pharma. • One Health surveillance systems, such as integrated analysis of surveillance data.	• Surveillance of global ecological disturbances attributable to exposure to AB (for example, in primary producers). • Global surveillance of AMR pollution in the Earth (such as in air currents, oceans and migratory animals). • Monitoring of climate changes to predict infectious diseases and spread of ARBs. • Early identification and medical control of travellers from countries with high AMR incidence. • International surveillance of the emergence and spread of high-risk ARGs and ARBs. • Surveillance and control of transnational movement of humans, goods, animals and food polluted with ARBs. • Global centralized electronic reporting of national One Health surveillance systems; for example, global analysis of surveillance data. • Educational policy, integrating human, animal and ecosystems health.

Continued

Table 1 | Examples of actions for reducing AMR burden (continued)

	Individual Health	One Health	Global Health
Restoration of populations of antibiotic susceptible bacteria	• Preservation of autologous microbiota before clinical interventions for potential microbiome transplantation. • 'Selection for susceptibility': antibody–drug conjugates, enhancers of fitness costs, pairs of ABs with reciprocal collateral susceptible profile and drugs activated by mechanisms of resistance. • Genetic engineering to disrupt AMR; for example, CRISPR-based editing and metagenomic engineering. • Heterologous microbiota/probiotic transplantation for displacing ARBs. • Vaccines against ARBs. • Drugs targeting the metabolism of resistant organisms.	• Microbiota transplantation procedures for ecological displacement of ARBs. • Genetic engineering to disrupt AMR; for example, CRISPR-based editing and metagenomic engineering. • Phage cocktails against ARBs. • Vaccines against animal AMR pathogens.	• Regulation of biobanks of susceptible human, animal and environmental microbiotas. • Regulation of genetic engineering to disrupt AMR; for example, CRISPR-based editing and metagenomic engineering.

It is notable that some of the proposed actions have an impact on different categories and at different levels, from Individual Health (which focuses on patient outcomes) to Global Health. AB, antibiotics; PK, pharmacokinetic; PD, pharmacodynamic.

markers, and their acceptable levels, is needed to ensure drinking water quality, the safe re-use of water, and the safe land-application and release of sewage effluents[78,79].

Most antibiotics used for therapeutic purposes are released in water and can act as chronic pollutants, constituting an important problem in water reuse. In addition to the development of rapidly degradable antibiotics[80], advanced water treatments[81,82] that reduce the concentration of antibiotics in natural ecosystems would help reduce selection pressure towards AMR. Particularly relevant should be on-site hospital wastewater treatment (WWT), since this can reduce the amount of antibiotics, ARBs and ARGs in downstream communal water systems[83].

The effectiveness of different types of WWT in reducing AMR is still under study. Recent work indicates that, while secondary water treatment in sewage treatment plants strongly reduces the number of bacterial pathogens (including ARBs), tertiary treatment has little impact in comparison[84]. Further, some studies indicate that tertiary processes such as chlorination or ultraviolet treatment can actually induce horizontal gene transfer, triggering the spread of ARGs[85]. Other studies, however, indicate that WWT reduces the variability of hosts carrying ARGs, and hence reduces the chances of their dissemination[86].

Climate effects on antibiotic resistance. Modifications of natural ecosystems due to human activities can also affect the spread of AMR. Global warming is likely increasing the global biological space in which microorganisms, humans, animals and vector species (such as flies, fleas or birds) interact[87,88], while weather patterns such as El Niño can modify oceanic currents and therefore the intercontinental distribution of bacterial pathogens[89], which may include ARBs. An increased number of pathogenic bacteria was also reported in Houston after the flooding associated with Hurricane Harvey[90]. However, the contribution of these phenomena to the dissemination of AMR, as well as the effects of such dissemination on ecosystem health (Box 1), remains to be quantified.

Approaches for controlling AMR

An important, though not always addressed, aspect in the AMR debate is that controlling AMR is a part of a larger global strategy to reduce the impact of infectious disease on human health. Thus, AMR may not necessarily be pushing us towards the high mortality rates of the pre-antibiotic era, and modern medicine (at least in countries with a high level of medical care) is increasingly able to compensate for the harmful effects of infections, even without antibiotics. Therefore, the AMR-driven consequences for human health are more relevant in countries where health services are poor.

An important condition for any intervention is the precise identification of the significant factors that trigger AMR, with the aim of counteracting them using multipronged strategies[91]. As might be expected, One Health and Global Health interventions are frequently intertwined (Table 1). For instance, the main impact of a new antibiotic will be treating specific infections at the individual patient level, but regulations regarding its use at the country level are a One Health issue; additionally, the implementation of international surveillance networks for tracking the prevalence and dissemination of resistance to any new antibiotic, or international regulations regarding its use, fall under the Global Health umbrella. Regardless of level, all strategies—which may include approaches to combat resistant microorganisms with new antimicrobials, reduce AMR selection pressure, contain AMR transmission or restore antibiotic susceptibility to resistant organisms or sites—will influence the interactive landscape between hosts and microorganisms, and thus all proposed actions must be evaluated before being launched for possible unwanted secondary effects.

Therapeutic approaches to combat AMR. The design of novel antimicrobials should focus on not just identifying new cellular targets, but also defining the organism's inhibition activity profile (species-specific antibiotics or combinations[92] versus wide-spectrum) of these drugs. Further, antibiotics likely to be useful in reducing the AMR burden (with a particular focus on anti-resistance[93], hybrid[94] or multitarget[95] drugs) should be developed. Economic incentives for pharmaceutical companies[96], private-public collaborations such as ENABLE (http://nd4bb-enable.eu/) and initiatives such as The Global Antibiotic Research & Development Partnership (https://www.gardp.org) may recover forgotten or undeveloped antibiotics, which would help fill the gap in antimicrobial development.

For critically ill patients with untreatable resistant infections, aggressive therapeutic strategies might be used. As in patients with cancer, the use of expensive drugs, in this case, antimicrobials, might be considered (even those with important adverse effects) given the likely negative outcome of following a more classical line of treatment[97]. Such antibiotics would only be used in a small number of patients, meaning that such patients could be closely monitored for

Box 1 | Ecological consequences of antibiotic resistance

AMR is not only a problem for the treatment of infections—massive pollution with antibiotics, biocides, heavy metals and other anthropogenic substances able to select for AMR bacterial populations may lead to imbalances in the homeostasis of microbial communities across the biosphere. These ARBs might replace those that are susceptible, and imbalances produced by antibiotics among primary producers and decomposers could disrupt natural ecosystems, with severe consequences for the environment as a whole[144].

Consider, for example, cyanobacteria, which make up to 70% of the total phytoplankton mass and are responsible for more than 25% of total free oxygen production and about an equivalent proportion of carbon dioxide fixation. Cyanobacteria are often susceptible to widely used antibiotics[145], and the question of whether they might be replaced by more resistant bacterial species has caught the attention of the European Medicine Agency and spurred the development of tests to evaluate the effect of antimicrobial agents in the aquatic environment[145]. Surprisingly, class 1 integrons containing *sul1* genes have been found in cyanobacteria, indicating they share this ARG acquisition platform with ARBs[146]. The convergence of public health and environmental protection strategies becomes clear when analysing the ecological consequences of the use of antibiotics, as the preservation of ecological conditions that maintain the diversity and abundance of green algae and cyanobacteria, which help protect the food web and biogeochemical cycles, also influence the biodegradation of antibiotics[147].

The potential ecological problem of antibiotic pollution is not, however, restricted to environmental microbiomes. Antibiotic-induced disruption of gut microbiomes may favour the acquisition of different diseases in humans (where most studies in this field focus[148]) and other hosts (for example, exposure to antibiotics modifies the gut microbiome and increases the mortality of honeybees[149]). It remains unclear, however, whether the results of these laboratory-based studies translate directly to the field setting.

The replacement of key environmental players by ARBs might, however, not be the only factor to consider, as the extensive use of other environmentally-released biocides, such as herbicides and insecticides (that kill the hosts of microorganisms), must also influence overall microbial ecology and consequently, AMR. In fact, AMR depends on the One Health triad (humans, animals and environment)[150,151], and humans benefit from a diverse, balanced, healthy environment in which the potential dangers are reduced and ecosystem services and their potential evolution (evosystem services) are preserved[152,153].

emergence of AMR and any arising ARBs could be eliminated prior to patient discharge from hospital. The efficient use of antibiotics also requires new surveillance and diagnostic methods, including the rapid identification of ARBs and ARGs[98,99], which will help move us from empirical to personalized therapies[100,101].

Non-antibiotic therapeutic interventions include the use of antibodies, some of which target resistant bacteria[102], immunomodulators, which can sometimes have antimicrobial activity[103], or even stem cells[104]. Reverse vaccinology[105] or approaches using attenuated auxotrophs[106] may help in the development of vaccines against ARBs[107]. These types of strategies could also reduce selective pressure and, in the case of vaccines, AMR transmission. Indeed, massive immunization programmes against *Streptococcus pneumoniae* and *Haemophilus influenzae* have shown vaccination be an effective means of reducing AMR[107]. Some studies have shown that even anti-viral vaccination may have an indirect effect on reducing AMR, as vaccination may result in a reduction of antibiotics prescribed[108]. This is critical in light of global instances of vaccine hesitancy driving preventable infections that might increase antibiotic use, although the impact of this issue on AMR is still unknown. It should be noted that while vaccination is important in the prevention of both human and animal infections, the cost of vaccines against animal infections needs to be low enough to not unduly affect the price of farm products[109]. The development of such vaccines may at least reduce the therapeutic use of antibiotics in farming[110]. Finally, the use of bacterivores, such as *Bdellovibrio*, to eliminate pathogens without the need for antibiotics has been explored to some extent[111]. Although these predators seem to be present in human lungs[112], their use in human health interventions remains controversial. Certainly, however, their use for controlling infections in animals[113,114] and plants[115] should be investigated in more detail.

Reducing antibiotic selection pressure. Most strategies for reducing AMR selection pressure have been based on reducing antibiotic consumption. Integrated multi-level actions in this space should encompass cultural and regulatory interventions to promote the evidence-based use of antibiotics, the control and supervision of the sale of antibiotics and their prescription-based access. However, evidence-guided use of antibiotics alone is not sufficient to reduce the current AMR burden[7], and some models even predict that restricting the use of antibiotics may sometimes facilitate multidrug resistance[116]. The use of delivery systems to target an antibiotic to the point of infection[117], adsorbents (some already in Phase II of development) that remove antibiotics from the gut or in water bodies to avoid selective pressure on commensal[118] or environmental microbiomes[119], compounds that trigger the degradation of antibiotics[120,121] as well as the development of easily degradable antibiotics[80] would all help reduce selective pressure in patients, animals and, eventually, in WWTP. For example, a recent study showed that use of an oral ß-lactamase protects the gut microbiome and reduces emergence of AMR in pigs treated with carbapenems[122].

In addition to controls regarding the use of antibiotics, biocides and antiseptics, novel animal feeding methods, control of housing or stocking densities, animal transport systems that avoid cross-infection (and hence reduce metaphylaxis)[123] as well as the use of non-antibiotic compounds in prophylactic or metaphylactic procedures[124] may also help reduce antibiotic use. Environmental interventions to specifically counteract AMR spread include the removal of antibiotics and ARBs, and the biorestoration of antibiotic-susceptible populations.

Reducing the transmission of antibiotic-resistant bacteria. Reduction of transmission can be achieved by acting on microorganisms or their hosts. At the microbial level, drugs used as additives in animal feed capable of inhibiting plasmid conjugation have been proposed[125]. Additionally, certain water treatments may reduce plasmid conjugation[126], which might be involved in AMR transmission in water bodies[127], particularly in the presence of low concentrations of antibiotics[128].

At the host level, hygiene measures that reduce the contacts of AMR carriers with the rest of the population could certainly help reduce the transmission of ARBs and ARGs. Controlling the presence of human, animal and plant pathogens and restricting goods coming from 'infected points' are strategies regularly followed to avoid pathogen dissemination[129]; the same principles could be applied to restrict the dissemination of AMR. Proposals such as 'Reinvent the Toilet Challenge' promoted by the Bill and Melinda Gates Foundation[130], which aimed to "bring sustainable sanitation solutions to the 2.5 billion people worldwide who don't have access to safe, affordable sanitation", could help reduce the water body-disposal of non-treated stools containing ARBs in LMICs.

Barriers should also be in place to prevent transmission among 'resistant entities', such as 'resistant hospitals' or even 'resistant ecosystems'. In the establishment of these actions, the implementation of surveillance and specific control measures that allow interventions to be taken with reference to the abundance, diversity and transmission of ARGs and ARBs are required.

Restoring populations of antibiotic-susceptible bacteria. Since antibiotics are societal drugs, the use of antibiotics increases the total population size of ARBs, which has facilitated the overflow of AMR from health institutions, the invasion of patients by ARGs and the potential modification of the health and dynamics of the global microbiosphere (Box 1). The removal of resistant organisms will likely require the use of so-called 'eco–evo' (ecological–evolutionary) interventions[131], the aim of which is to control AMR through the bio-restoration of susceptible populations by 'selecting for susceptibility'.

In these approaches, it must be ensured that key drug-susceptible bacteria that have coevolved with humans and animals are preserved. Microbiome samples are beginning to be stored in biobanks[108], and it would seem advisable to include antibiotic-susceptible communities. Also, ARBs should be specifically removed (for example, using drugs activated by mechanisms of resistance[132], vaccines targeting ARBs[105,133], phage cocktails[134] and drugs targeting the metabolism of resistant organisms[135]). And, given that the first line of defence against colonization by bacterial pathogens is in the normal microbiota[136], faecal transplantation, either using whole susceptible microbiota[137,138] or specific probiotics[139], might reduce colonization by ARBs[137]. Indeed, a recent work has shown that naive microbiota suppresses growth of antibiotic-resistant clinical isolates of *Enterobacteriaceae*[140].

More recently, in situ modification of the microbiome using metagenomic engineering tools has been proposed for eliminating ARGs in infecting commensal bacterial populations[141]. Genetic methods to remove ARGs, such as those involving CRISPR editing[142], are still in their infancy, and it is difficult to foresee what their contribution might be in restoring antibiotic susceptibility.

Outlook

Being conscious of AMR is of huge heuristic value for illustrating principles and generating hypotheses that guide human activity. The global spread of resistant organisms caused by our actions (for example, the use of antibiotics and general pollution) and inactions (for example, lack of proper sanitation) shows how a defined and measurable biological risk, influencing both our health and the health of the planet, can alter our biosphere. As such, AMR should be treated as a Global Health problem that requires, as do many other problems, a sense of 'selfish equity' on the part of developed nations. Anything that improves global equality—increasing the wealth and dignity of people around the world—where AMR is emerging due to shortage of resources will benefit everyone with respect to AMR.

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Competing interests

The authors declare no competing interests.

Additional information

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