Assessing antimicrobial resistance connectivity across One Health sectors

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The first therapeutic use of antimicrobial agents initiated their endless arms race with antimicrobial resistance (AMR). Although the genes encoding antimicrobial resistance are ancient and ubiquitous in various environmental compartments, including aquatic environments, over eight decades of exposure to selective pressure has changed the way antimicrobial resistance genes (ARGs) emerge and transmit among the three One Health sectors (that is, the intersected sectors of humans, animals and the environment). The dissemination of ARGs has been facilitated by the widespread use of antimicrobials, along with direct and secondary pollution pathways. Current global consensus dictates that AMR should be addressed under a One Health framework. AMR National Action Plans have frequently been formulated. However, the capacity for implementation is not ready in most countries, especially in low- and middle-income regions. This is in part due to the substantial challenges in documenting and controlling cross-sector AMR connectivity. Here we describe the past and current status of AMR, emphasizing the contribution of connectivity to global AMR burden. We discuss connectivity at ecological, microbial and genetic levels; propose an approach based on genomics and metagenomics to assess connectivity; and finally advocate for cross-sector studies to better understand AMR connectivity and mitigate dissemination. We believe that such harmonized connectivity studies will facilitate coordinated actions and investments across sectors and regions to scale up AMR management globally.

Antibiotics and other antimicrobials have saved many millions of lives, but the rise of antimicrobial resistance (AMR) is renewing the spectre of untreatable bacterial infections. The estimated 4.95 million annual deaths associated with AMR have made what has been called the 'silent pandemic' no longer silent[1]. If left unaddressed, AMR is going to reduce global life expectancy and impose unprecedented healthcare costs and socioeconomic burdens[2].

The fundamental determinants of AMR are antimicrobial resistance genes (ARGs), which are typically harboured by antimicrobial-resistant bacteria (ARB). ARGs are ubiquitous and ancient, serving as the key defence mechanisms of bacteria in competition for limited resources in the environment[3]. Initial anthropogenic use of antimicrobial agents imposed selective pressure and facilitated ARG spread in clinical settings, and later in animal farms and the environment. Over eight decades of exposure to anthropogenic selective pressure has changed the behaviour of ARGs of different origins, driving their movement across ecological and phylogenetic barriers. The impacts of AMR are most apparent in anti-infective treatment failures, but its evolution, transmission and spread have occurred in various settings, including clinical, environmental and agricultural[3,4]. This underlies the principle of the One Health approach proposed by the Quadripartite bodies—the World Health Organization (WHO), the Food and Agriculture Organization (FAO), the World Organization for Animal Health (WOAH) and the United Nations Environment Programme (UNEP)[5]. The concept of One Health is holistic and interdisciplinary, grounded in the systematic idea that the three sectors of humans, animals and the environment

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are intricately interconnected and interdependent in addressing the global public health threat of AMR[6–9]. Direct or potential pathways that disseminate ARB and ARGs have been widely reported[10–12]. However, integrated cross-habitat, especially cross-sector studies along the One Health continuum, are rare[13–15]. Substantial knowledge gaps remain in assessing AMR connectivity, which is hindering the development of science-informed solutions to tackle AMR.

Nevertheless, fundamental questions, including how to effectively identify and quantify the connectivity of AMR, remain unresolved. In this Perspective, to address these questions, we review the connectivity from ecological, microbial and genetic perspectives, then discuss methods to assess the connectivity, and propose a standardized approach coupling culture-dependent genomics and culture-independent metagenomics for a systematic analysis of connectivity. Finally, we advocate cross-sector AMR connectivity investigation to inform future control strategies to curb AMR. This calls for coordinated action and investment to scale up AMR management across the globe, especially for low- and middle-income countries (LMICs).

The burden of AMR, past and present

The myriad benefits of antimicrobial agents have led to widespread overuse and misuse in humans, animals and plants, despite numerous warnings regarding the long-term consequences of this behaviour[16–19]. Simply restricting antimicrobial use could largely address the propagation of AMR, as resistance often confers fitness costs under non-selective conditions[20], especially for bacteria in a nutrient-rich, high-density environment like the gut of animals. Nonetheless, the impact of AMR on bacteria relies on resistance mechanisms, the genetic background, the host species and the specific environmental context[21]. This multifactorial dependence greatly challenges the formulation of effective mitigation strategies.

The lack of judicious antimicrobial use and appropriate pollution control has accelerated the development and spread of AMR. The frequent occurrence of critical human pathogens carrying ARGs has become the norm rather than the exception[22]. The global dissemination of AMR has been fuelled by the increasing connectivity between humans, animals and the environment[13,23]. Unlike classical ecological connectivity (that is, the ability of animal species to move freely between places), we here define connectivity as the homogenization of bacteria or genes within and between habitats of the three One Health sectors (details are provided in the section Definition of AMR connectivity). Globally, such connectivity reflects the combined effects of various mechanisms and drivers, including anthropogenic pollution, globalization and other human activities[24]. Such connectivity has driven the AMR pandemic, with successive waves of ARGs circulating the world, such as the plasmid-borne colistin resistance gene *mcr-1*, first reported in farmed pigs in China[25,26].

Before widespread urbanization, interactions among humans, animals and the environment occurred primarily within localized contexts. The combination of low population densities and minimal anthropogenic impact allowed for effective environmental self-purification (that is, the ability of an environment to rid itself of pollutants)[27,28]. However, rapid urbanization and industrialization following the industrial revolution led to widespread environmental deterioration. Concomitant with such declines, material exchanges have been intensified across human–animal–environment interfaces, as exemplified by contaminated surface runoffs and discharges of untreated and partially treated wastewater in urban areas, contamination by human and animal waste, and intensive livestock farming systems. This trend is quantitatively demonstrated by an analysis of Dutch soil archives (1940–2008), revealing a 15-fold increase in the abundance of selected ARGs over eight decades[29].

This increase in AMR is also driven by the extensive use of antimicrobial agents in infectious disease treatments and prophylaxis for humans, animals, and plants. Large quantities of ARB and ARGs are then released into the environment from human and animal sources, where their persistence is enhanced by co-pollution with selective agents[30,31]. The discharge of such biological and chemical pollutants into the environment is expected to continue and intensify, particularly in LMICs[32], which often lack efficient wastewater treatment infrastructure. Although modern wastewater treatment systems and hygiene infrastructure have protected human health for decades by removing and attenuating a wide array of pollutants, including ARB and ARGs, it is unclear whether they have the capacity to remove these emerging pollutants (which are not yet regulated) sufficiently to slow down the global increase in AMR[12]. Furthermore, multiple sources, including pharmaceutical industries, hospitals and animal farms, continue to generate untreated or under-treated wastewater, drainage or solid waste, which are important sources of ARB and ARGs, as well as selective and co-selective agents. These pose substantial challenges to deciphering connectivity, identifying sources and designing efficient pollution management strategies[33,34].

Importance of connectivity under One Health

Advancing ARG identification and tracking systems is crucial for uncovering their origins and understanding their transmission across ecological and phylogenetic boundaries. ARGs can have both human/animal and environmental origins. In addition to the intrinsic ARGs in the environment, spontaneous gene mutations under antimicrobial selective pressure may lead to the emergence of novel ARGs[35]. Before the mass production of antimicrobials in the 1940s and their global use in medicine, agriculture and animal production, naturally occurring ARGs were confined mainly to their original hosts and local environments. Furthermore, novel mutations are rare, often immobile (that is, not associated with mobile genetic elements), and they often reduce bacterial fitness. Thus, there was pressure for their elimination from a community microbiome in the absence of sustained selection[20].

Human-driven increases in the concentrations of antimicrobial agents in various environments have resulted in increased selective pressure across the One Health continuum and decades of bacterial evolution. This reality has substantially altered the nature and prevalence of some ARGs, decreasing their fitness burden via compensatory mutations[36] and epistasis[21], and increasing their mobility via association with mobile genetic elements[37,38] (Fig. 1a). These genetic mechanisms may function differently across environmental contexts, depending on community composition, ecological dynamics, physicochemical conditions and other factors[24]. In particular, the problem is compounded by the multitude of transmission mechanisms by which genes encoding resistance to antimicrobial agents and metals have been found to co-assemble on mobile genetic elements[39], such as plasmids[37], integrons[40] and integrative conjugative elements[41]. These have promoted the occurrence and transmission of ARGs across diverse habitats. Indeed, some of the ARGs that have arisen in the natural environment have been co-opted to provide resistance in clinical contexts[42]. For instance, aminoglycoside inactivation by soil-dwelling *Actinomycetes* spp. was among the first documented cases of environmental sources of clinical resistance[43], preceding the later identification of β-lactam[44] and glycopeptide[45] resistance origins in the environmental reservoir.

Specific locations are critical hubs for intensive microbial interaction and gene transfer between environmental bacteria and human/animal microbiota. These include wastewater treatment plants[46], agricultural systems[15], anthropogenically polluted downstream rivers[47] and locales under poor sanitation and hygiene conditions[14,48]. In addition, environmental pollution, often including complex mixtures of micropollutants, creates conditions that may result in the (co-)selection for ARGs[49–51] or enhanced gene exchange[52,53]. These transmission dynamics may be further amplified by international travel and trade networks in an increasingly globalized world[54,55]. Expanding human footprints, such as land transformation, food production and environmental pollution, and the consequent microbial homogenization and diversity

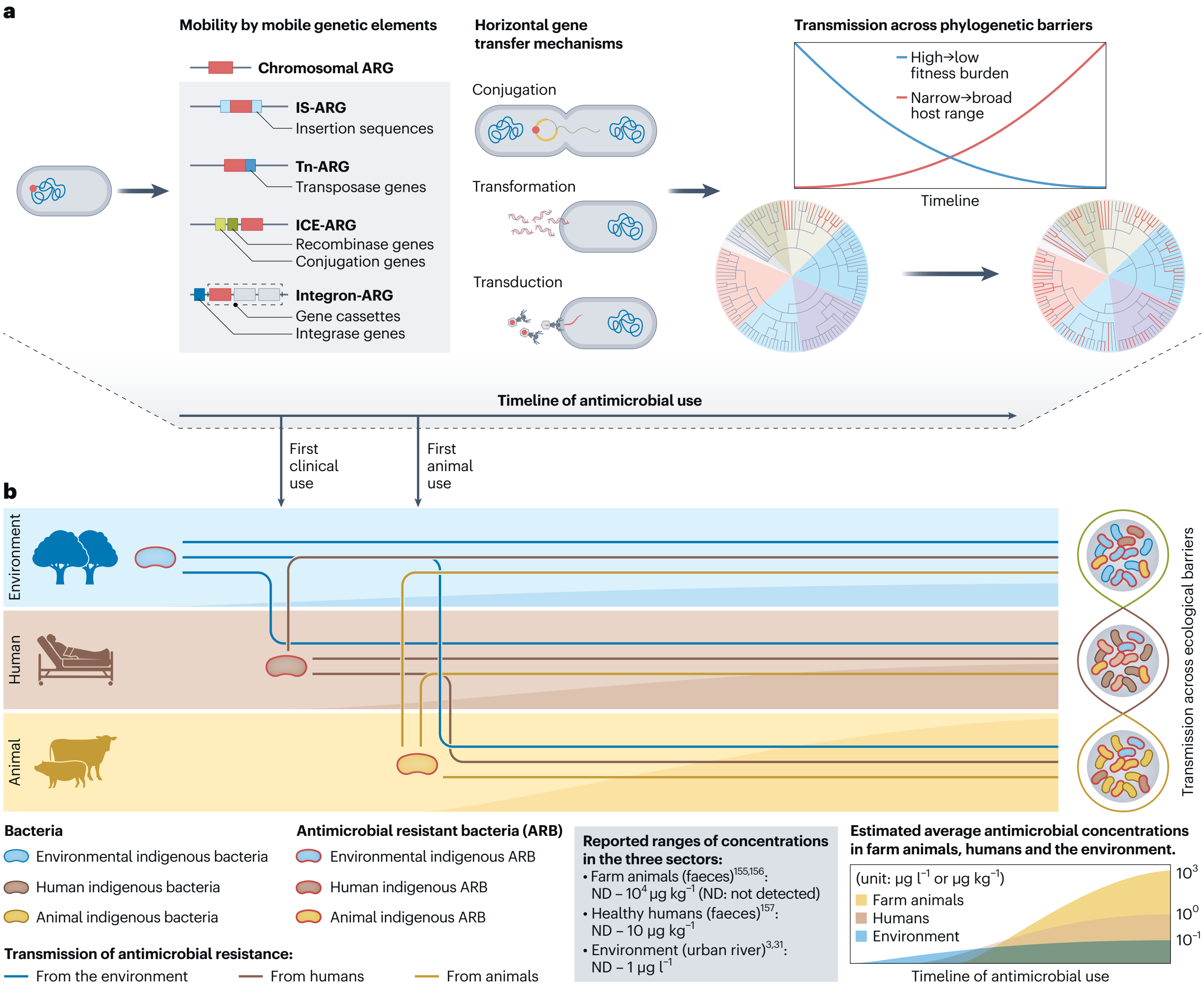

Fig. 1 | Development of AMR connectivity between the sectors of humans, animals and the environment. a, Evolution and transmission of ARGs along a simplified model timeline of the antimicrobial era. ARGs acquired high mobility potential through association with mobile genetic elements. IS, insertion sequence; Tn, transposon; ICE, integrative conjugative element. They achieved low fitness cost by selection for compensatory mutation, and broad host ranges through transmission to and interaction with a diversity of bacteria. **b**, Pathways of AMR connectivity among the three sectors under selective pressure. The selective pressure increases over the model timeline of antimicrobial use, as indicated by the shaded areas in the blocks of each sector and further explained in the bottom-right panel. In this panel, the recent concentrations (at the time of publication) were sourced from previous studies[3,31,159–161]. To simplify ARG transmission between sectors over time, the pathways are illustrated based on the assumptions that the first clinical use of antimicrobials initiated the transmission of ARGs between humans and the other sectors; the first animal use of antimicrobials initiated the transmission between animals and the other sectors. Created with BioRender.com.

loss whereby microbial communities become increasingly similar over time[56–58], mean that diverse ARB and ARGs are more likely to be connected in time and space (Fig. 1b).

The WHO initiated a Global Action Plan in 2015[59] that advocated for AMR surveillance within each sector, while also seeking the means of achieving an integrated understanding of the transmission and connectivity of AMR across humans, animals and the environment. Since then, 121 countries have formulated national action plans, including high-income countries (HICs) and LMICs in Africa, Asia and South America[60]. However, disparities in the approaches of these countries are evident, especially regarding understanding AMR in non-human sectors and its cross-sector connectivity[13]. For example, many HICs have made substantial efforts to curb the flow of ARB and ARGs by promoting awareness of AMR, introducing and improving antimicrobial stewardship programmes, implementing stringent infection and prevention practices, restricting routine uses of medically important antimicrobial agents for livestock, and developing strong financial provisions to encourage and support the implementation of One Health management of AMR. In contrast, LMICs face systematic barriers. In most LMICs, securing reliable access to clean water and food as well as high-priority antimicrobial agents, and reducing hospital-acquired resistant infections remain substantial challenges. The focus in many LMICs is predominantly on the sector of human health[61]. The Tracking Antimicrobial Resistance Country Self-Assessment Survey (2023) reported that, despite the desire for One Health approaches, only 20 of 177 countries have available coordinated mechanisms and integrated approaches for implementing national action plans to tackle AMR across sectors[62].

Despite its critical importance, AMR connectivity—particularly cross-sector transmission within the One Health frameworks—remains poorly understood. Yet, characterizing these interactions is essential to developing effective strategies to manage AMR, which cannot be tackled by focusing on any single sector. Through the lens of connectivity, we can determine the extent to which ARGs have been disseminated across sectors, identify key sectoral interactions, track their dynamics over time, and ultimately devise targeted interventions to tackle AMR.

Definition of AMR connectivity

Despite the critical role of cross-sector connectivity in One Health, a systematic scientific definition of AMR connectivity remains lacking. Clarifying what constitutes connectivity and identifying which habitats and pathways should be included in AMR connectivity assessments are essential for developing targeted interventions against AMR spread.

Connectivity at ecological, microbial and genetic levels

ARGs are generally carried by bacteria within microbial communities in a range of ecosystems. In this Perspective we therefore define connectivity at three levels: ecological, microbial and genetic (Fig. 2a). In addition to the classical ecological connectivity—here adapted as the ability of ARB and ARGs to move between physically connected places—we extend the concept of connectivity to examine microbial and genetic homogenization across both connected and disconnected habitats.

Ecological connectivity is a concept derived from classical ecology and refers to ARB and ARGs transport between physically connected habitats across humans, animals and the environment. The spread of ARGs relies on either the movement of host bacteria or contact of recipient cells with donor cells (for example, conjugation) or DNA fragments (for example, transformation and transduction)[63]. ARB and ARGs in different sectors are ecologically connected and can be transported between habitats either directly or indirectly through pathways driven by geographical/physical connectivity, animal migration and anthropogenic systems and processes. For example, a livestock farm represents a system in which humans, animals and the surrounding environment are closely linked through activities such as feeding, slaughter, waste management and cleaning[64]. Informal urbanization, especially with poor hygiene infrastructure, may create strong ecological connectivity[48,65], and wastewater treatment systems, while engineered to eliminate contaminants as barriers between humans and the environment, can also create opportunities for ARG exchange among bacteria of human, animal and environmental origins[12,66]. Also, increasing international travel, immigration, and global feed and food exchange create historically unprecedented long-distance connectivity[26,67,68]. Under sustained anthropogenic interference and selective pressure, such ecological connectivity drives complex ARG transmission events, resulting in novel ARG–host combinations[69]. Moreover, antimicrobial selective pressure in various habitats provides both ARB and ARGs the opportunities to fix compensatory mutations and co-opt mobile genetic elements for further dissemination[37,70].

Microbial-level connectivity refers to the potential for bacterial taxa to establish and proliferate in habitats across humans, animals and the environment. Microbial-level connectivity can be quantified based on the genetic distance, being directly proportional to similarity levels in the overall community profiles or to phylogenetic relationships of specific taxonomic groups from different habitats. By comparing the overall community structures, the similarity of microbial abundance and diversity between different habitats can be considered at several taxonomic levels depending on the employed sequencing platforms and bioinformatic tools. Phylogenetic resolution at the genus or species levels can be obtained by metagenomic sequencing, particularly using long-read platforms[71]. Strain-level resolution can be achieved by genomic mining and single-cell sequencing, either of whole genomes or key loci (for example, essential single-copy genes)[72–74]. Significant correlations between microbial communities and ARG profiles in the environment have been identified by multivariate analysis[14,75,76], indicating the possibility of inferring ARG-level connectivity (defined in the next paragraph) from microbial-level connectivity. However, this approach, especially when involving normalization and correlations that are non-causation-based, is not yet robust[77]. The main problem of community-level analysis is often insufficient sequencing depth to capture rare taxa. Moreover, single species surviving in different habitats despite dissimilarity of the overall communities can contribute to AMR connectivity. ARGs, especially those of clinical importance, are more likely to associate with specific groups of human pathogens than common environmental bacteria[78]. Connectivity of these pathogenic groups across sectors may have greater implications for human health than the overall profile-based community connectivity. Limits of detection/quantification may hinder our capacity to identify the specific taxa, which can be overcome through enrichment with different media[79]. *Escherichia coli* is a taxonomically and functionally important bacterial group in human and environmental health, serving both as a well-established indicator organism for tracking faecal contamination[34,80] and a major hub for horizontal gene transfer[81]. Genomic analysis of *E. coli* strains from differing habitats has revealed resolvable phylogenetic clusters among them[82,83]. Therefore, the phylogenetic relatedness of ARG-carrying *E. coli* strains across sectors can provide a window into the connectivity of potential antimicrobial-resistant pathogens.

Genetic-level connectivity refers to the potential for specific genes to occur and be horizontally transferred in habitats across humans, animals and the environment. Like microbial-level connectivity analysis, connectivity at the ARG level can be assessed either by community-wide profiling or targeted examination of individual ARGs. Although common ARGs are ubiquitous and are not very informative in inter-habitat comparisons, the profile similarities based on overall ARG abundance and diversity still provide a measure of connectivity[76]. A high degree of similarity might reflect the sampling of similar ecosystems or the existence of direct ecological connections between habitats with distinct resistomes (that is, a collection of characteristic ARGs occupying a habitat[84]). For example, the high similarity of resistomes between wastewater and the environment downstream from the discharge point could be evidence of direct connectivity or pollution, because the ARG profiles in community wastewater differ significantly from those of environmental origins[85]. For connected habitats, ARGs can be spread by the dispersal of host bacteria or by horizontal gene transfer. Examining correlations between the connectivity profiles of ARGs and those of microbial communities can indicate whether ARG dissemination may be caused by community migration or genetic exchange. However, due to its low resolution, the overall ARG profile has limited use in deciphering the underlying connection in scenarios where there is either little pollution or multiple similar pollution sources[34]. By examining specific groups of ARGs, better estimates of connectivity could provide insights into the proliferation of specific ARGs across sectors[30]. This requires studies to pinpoint high-resolution marker ARGs. Together with improved technologies, especially long-read sequencing, deep tracking of these marker ARG sequences and their genetic context (especially association with mobile elements and host genomes) is becoming readily available, with the potential to detect weak or complex connectivity among habitats[86–88]. This can also enhance accurate source tracking and pollution management.

Habitats and pathways in connectivity assessment

The One Health framework for tackling AMR has often been depicted as a three-way connection between humans, animals and the relevant environments. The high diversity of habitats within the One Heath framework and the often limited research resources call for the prioritization

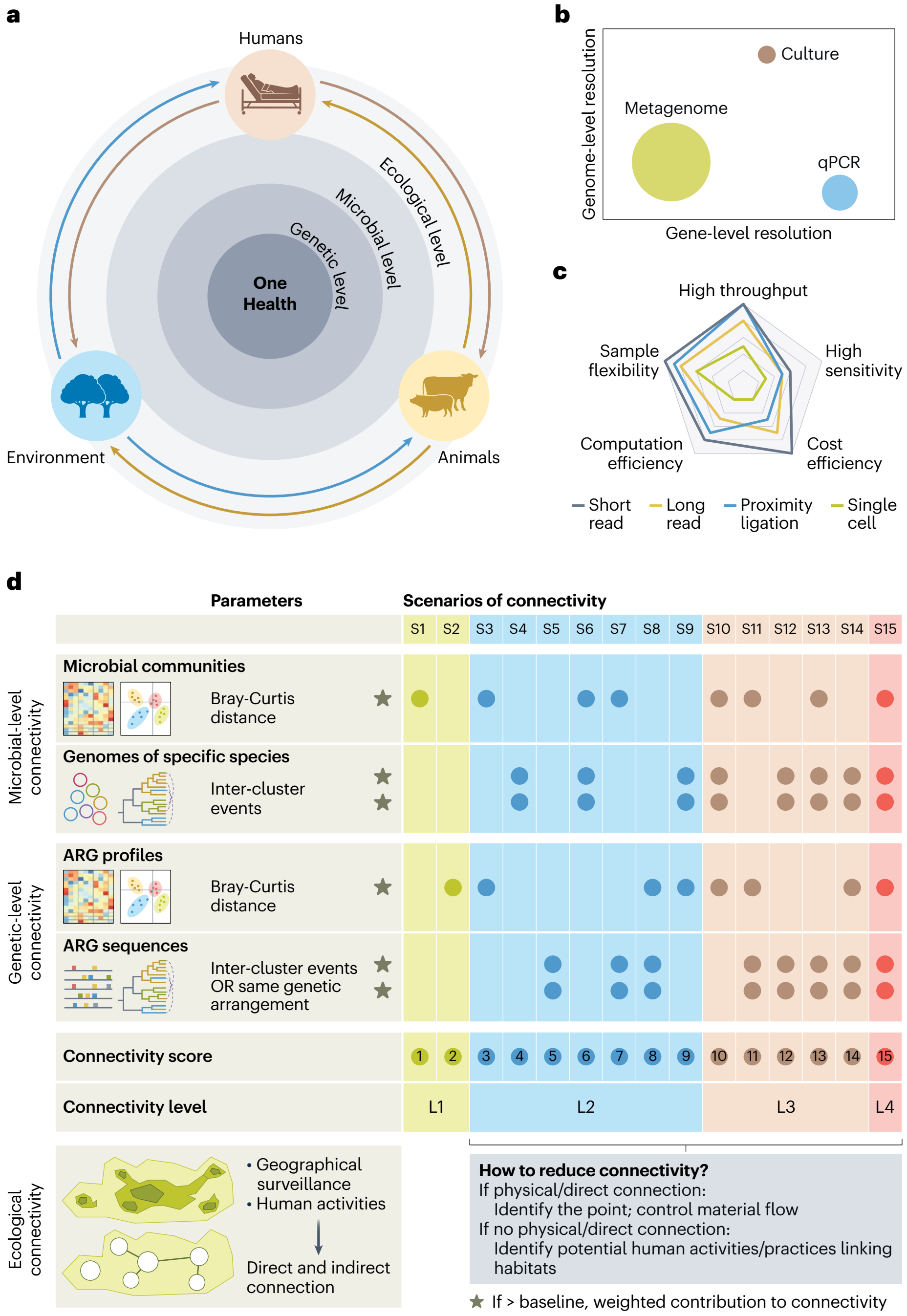

Fig. 2 | Approaches to assess AMR connectivity at different levels. **a**, Ecological-, microbial- and genetic-level connectivities under the One Health framework. **b**, Resolution of metagenomics, quantitative PCR (qPCR)-based methods and culture-based genomics at the gene and genome levels (genome- and gene-level resolution: ability to accurately retrieve the full genome and gene sequence; circle size: diversity of ARGs that can be retrieved). **c**, Comparison of metagenomic sequencing techniques based on throughput, sensitivity, cost, computational demand and sample flexibility. **d**, Assessment of microbial-, genetic- and ecological-level connectivity, and evaluation of overall connectivity levels. Microbial-level connectivity is examined by looking at the profile similarities of microbial communities and the phylogenetic relationships of full genomes, which are quantified by Bray–Curtis distances and the number of inter-cluster events, respectively. Genetic-level connectivity is examined by looking at the profile similarities of the ARG profiles and the identity of the ARG sequences, which are quantified by Bray–Curtis distance and the number of inter-cluster events/shared genetic arrangement, respectively. Regarding their contributions to connectivity, the weights for parameters based on genomes and ARG sequences are double those based on community and ARG overall profiles. Parameter combinations of microbial- and genetic-level connectivities are summarized into 15 scenarios (S1–15), based on which connectivity is classified into four levels (from weak to strong: L1→L2→L3→L4). Ecological connectivity may assist in designing the control strategies for connectivity at relatively high levels (for example, L2, L3 and L4).

of habitats to be included in connectivity studies. To determine priority habitats, we propose focusing on the criteria of high AMR development potential, close connection to humans, and minimal resource requirements for connectivity studies.

Humans. AMR in humans has been widely studied across various body sites, including the gut, oral cavity, respiratory tract and skin[89]. Among these, the gut microbiome—and its associated resistome—has received the most attention[90–92], particularly regarding its environmental connectivity[76,93,94]. The gut microbiome probably has the highest potential for the development of AMR compared to other body sites[91], primarily due to the oral administration of most antimicrobial agents, the high numbers and densities of actively growing microbes with a large nutrient supply, and direct connection with the environment and animals via food and drinking water. Discharge and reuse of residential/urban wastewater containing gut-derived microorganisms and ARGs, as well as land application of associated sludges or biosolids, contribute to the connectivity between humans and the environment[95,96]. The extent of this connectivity depends, among other factors, on the resilience of the associated environments and the treatment efficiency of wastewater systems.

Animals. Environmental studies on AMR in animals have primarily focused on the gut, with less attention on other body sites. Multiple animals have been examined for their potential as hosts or vectors transmitting AMR, including ARG exchanges between birds and their terrestrial or aquatic habitats[83,97], and also the role of insects such as houseflies and cockroaches in spreading AMR within food farms[98–100]. However, most studies focus on livestock animals, which are more likely to develop infectious diseases and require antimicrobial therapy under intensive animal husbandry practices[101,102]. Although many countries have banned the prophylactic and routine use of antimicrobial agents in animal production, implementing such restrictions has been incomplete[6,103]. Animal husbandry is a substantial contributor to cross-sector AMR connectivity, especially in LMICs, where humans often live in close proximity to animals, and access to veterinary resources is limited[15,104]. ARB and ARGs may be transferred directly from animals to humans by consuming meats and other products[105]. Livestock manure application is commonly practised, providing nutrients to agricultural production across HICs and LMICs[106]. Such application creates a potential transmission pathway for ARB and ARGs from animals to soil and plants[107]. With the growing global demand for animal protein, aquaculture farms are emerging as another critical AMR transmission source[108], especially those with minimal regulatory oversight of antimicrobial use and location downstream of community/industrial wastewater treatment plants.

Environment. Given the broad range of habitats in this sector, each with distinct connections to humans and animals, as well as varying potential as reservoirs or hotspots for ARG development, we focus on four key categories: water, soil, plants and air. (1) Wastewater from communities, hospitals and farms has been studied extensively, as it is closely related to the AMR burden in human and animal sectors[109]. Wastewater discharge and reuse are potential routes for promoting AMR spread in downstream environments[110,111]. (2) Soil holds a stable, diverse and predominantly intrinsic resistome[42,112–115], which can be significantly promoted by human activities such as various field applications[116,117]. (3) The use of antimicrobial agents and other pesticides in the management of plant diseases started in the 1950s[118] and has progressively increased ever since[55,119]. Through gene transfer and co-selection, resistance to both similar and dissimilar compounds may occur in crop products[120–122], possibly providing a direct link to humans[123–125]. (4) The atmosphere has recently been recognized as a potentially important route for the dissemination of ARB and ARGs[126,127]. The potential of transmission by air has mainly been examined at livestock farms[128], wastewater treatment plants[129], landfill sites[130] and hospitals[131], among others[132]. ARGs released from these environments can become aerosolized, travel long distances, and expose humans and animals over a wide spatial scale[127].

In view of the above, we suggest studies to include diverse habitats across the One Health sectors to best evaluate the magnitude of AMR connectivity. Priority should be given to specific 'hotspot' habitats, especially when available resources are limited. AMR in the human and animal sectors can be directly estimated from faecal samples, which constitute the primary reservoir of ARB and ARGs in humans and animals, or investigated by raw wastewater monitoring if faecal samples are unavailable[109]. In the environmental sector, AMR can be evaluated from commonly studied and easily accessible habitats, such as wastewater from communities, hospitals and farms; waste sludge for discharge; surface water upstream and downstream from pollution sources; farm and urban soil with and without obvious pollution; and airborne particulate matter from specific environments such as farms and landfills. Surveys of ARB and ARGs on leafy and root vegetables, especially those eaten raw, would be a valuable adjunct to the connectivity, as consuming these foods provides a direct route for environmental ARGs to enter the human gut. The selection of habitats for connectivity studies may vary depending on factors such as area characteristics (for example, urban environment or livestock farm), scope (for example, general human–animal–environment or specific human–environment connectivity) and available resources (for example, financial and technical support).

Approaches to examine connectivity

In recent decades, extensive research employing culture-dependent and -independent methods has been conducted to investigate microbial communities and AMR in humans, animals and the environment[3,15,22,92]. Sequence-based methods continue to develop, with substantially reduced costs and rapidly evolving bioinformatic pipelines, and are preferred when examining AMR connectivity[133]. Nevertheless, traditional PCR-based and culture-based methods play a crucial role in recovering targeted genomic information from complex microbiomes and resistomes[82,134,135].

Comparing approaches for AMR studies

Metagenomics has become one of the most promising methods for examining connectivity at both the microbial and genetic levels in environmental studies[76,94,115,136,137]. Among metagenomic sequencing technologies, short-read sequencing remains the most mature and cost-effective approach, although it cannot resolve proximal genetic elements. However, these genetic contexts are essential for evaluating ARG-associated health risks, including mobility potential and host pathogenicity. Advanced technologies, such as proximity-ligation sequencing[138], long-read sequencing[139] and single-cell sequencing[73] can partially overcome these limitations by reconstructing genetic linkages and recovering genomic information.

Despite these advances, emerging technologies face limitations for connectivity assessment, particularly in LMICs (Fig. 2b,c), due to the issues of cost, throughput, flexibility, sensitivity and the computational resources required. Short-read sequencing remains the most economical approach, with other advanced sequencing technologies still being expensive. Scaling these advanced sequencing platforms is costly and technically challenging. Their limited flexibility and stringent sample preparation requirements further restrict their applicability. Sensitivity remains an issue, in that emerging technologies are often less effective in detecting rare species or events. Compared with mature short-read metagenomics, data analysis for other technologies requires more computational resources and bioinformatic expertise.

Unlike high-throughput metagenomics, quantitative PCR (qPCR)-based methods quantify target genes using primer-based amplification. Due to its simplicity and high sensitivity, qPCR has been extensively applied for quantifying specific bacteria and ARGs[135,140]. Culture-based methods, although limited to a small fraction of culturable species, provide critical host–ARG information, and many of these species are of clinical or veterinary importance. Whole-genome sequencing of isolated hosts helps trace potential transmission pathways among humans, animals and the environment[15,82,141]. However, although PCR- and culture-based methods focus on specific targets, they lack the breadth of non-targeted sequencing.

In spite of the availability of the above tools to profile AMR in various habitats, connectivity studies, especially of cross-sector connectivity, remain rare[13–15]. Such research is inherently complex and costly, posing challenges for evaluating connectivity across regions and designing One Health-based control strategies. Nevertheless, the short-read metagenomics approach—with its cost-effectiveness, technical maturity and robust bioinformatics support—offers a practical framework for integrative cross-sector connectivity studies at regional and global scales.

Methods to assess connectivity

Profile-based connectivity. Connectivity assessment based on abundance and diversity profiles can be approached through various comparative analyses. The most straightforward method employs shared elements as connectivity indicators, although this approach has significant limitations due to biases inherent in detection methods themselves. For instance, the high sensitivity of qPCR may introduce false positives, whereas false negatives are typical of metagenomic sequencing[142]. The method, which relies soly on commonly present elements, fails to account for the differential contributions of low- versus high-abundance elements, thereby overlooking crucial indicators of profile (dis)similarity. More robust evaluations can be achieved through statistical methods that incorporate both abundance and diversity, such as correlation-based approaches or distance metrics (for example, Bray–Curtis dissimilarity). The availability of well-developed pipelines and packages has facilitated the widespread adoption of these methods for analysing connectivity of microbial and genetic profiles. However, due to the extensive data processing hiding behind the statistical methods, the connectivity can be obscured by spurious correlations between two independent variables that arise due to complex and ambiguous biological events or by normalization that can change the strength of identified correlations between variables[143].

Phylogeny-based connectivity. Genome or gene alignments can provide a high-resolution picture of phylogenetic diversification and similarity between bacterial strains' genomes or gene variants, and are particularly valuable for studies focusing on specific bacteria or ARGs. This is especially helpful for understanding microbial flow and genetic dynamics. Phylogenetic cluster and genetic arrangement are thus recommended for phylogeny-based connectivity analysis. For example, in-depth genomic analysis for specific bacterial groups can provide insights into their diversity in different habitats and potential transmission pathways[144]. For specific ARGs, gene variants together with genetic context from assembled fragments are valuable for tracking gene transfer[88]. This genetic context approach is especially powerful for environmental samples characterized by high microbial diversity, where target ARG sequences often occur in low abundance. Although direct recovery of those rare ARG sequences from metagenomic datasets remains challenging, assembly of flanking regions proves feasible[145], enabling more robust connectivity assessments in complex environmental matrices.

Integrated assessment of connectivity. We propose an integrated assessment of AMR connectivity by coupling profile- and phylogeny-based analyses (Fig. 2d), thus providing a comprehensive picture of connectivity. This approach leverages the strengths of both methods, with greater emphasis placed on genome and gene sequence data, as these provide more definitive evidence of connectivity than community and ARG profiles. We acknowledge the fact that ecological and phylogenetic barriers to the connectivity will identify certain connectivities (for example, human–animal) with greater proximity than others (for example, human–soil)[75,78,146]. This, in fact, can be considered by including connectivity 'baselines' of corresponding habitat pairs. The connectivity 'baseline' is set based on the sites where pollution or interference is minimal. Moreover, the baseline approach enables discrimination between connectivity arising from natural exposures versus anthropogenic pollution. The proposed framework assesses the related parameters of microbial- and genetic-level connectivity by comparing with the baseline, then summarizes into 15 risk scenarios. We classify the connectivity of the 15 scenarios into four levels (L1–L4, from weak to strong) and suggest appropriate control strategies for those with relatively high connectivity (L2-L4). Ecological connectivity identified through surveillance, including direct and indirect connections within and between habitats, may assist in designing the intervention strategies.

Proposing a standard approach to study connectivity

Connectivity studies will provide a valuable approach for understanding and potentially managing the AMR crisis. Considering that faecal pollution is a major driver of widespread ARG transmission in most environments[93], we propose that connectivity studies start through analysis of *E. coli* isolates in various compartments. As the most extensively characterized intestinal bacterial species, *E. coli* has been widely adopted for regional and global AMR studies[82,147]. With appropriate parameters, such as single-nucleotide polymorphism thresholds, *E. coli* genomic surveillance can effectively assess cross-source linkages across the One Health continuum[148,149]. Although no single bacterial species can fully represent AMR patterns for all other bacterial species or specific environments, *E. coli* surveillance through a One Health lens offers many benefits, particularly in regions where the implementation of complex or expensive investigation methods may be challenging[150,151]. As a classical indicator of faecal pollution, isolating *E. coli* strains requires minimal technical demand. Standard experimental workflows for *E. coli* culture and susceptibility testing have been followed for decades for the surveillance of faecal pollution in the environment and AMR in the clinic[152]. This makes it easy to integrate *E. coli*-based connectivity studies into existing monitoring systems. The tracking of *E. coli*, as an opportunistic pathogenic species, could also provide clues about how clinically relevant ARB and ARGs are disseminated in the environment. The well-developed sequencing technologies and bioinformatic tools, along with the extensive public databases of *E. coli* genomes[153,154], enable deep genomic exploration for downstream connectivity analysis. Archived *E. coli* strains support valuable retrospective studies and allow tracking and comparing *E. coli* isolates over time series and geographical regions, aiding in deciphering connectivity trends in the future and in unstudied areas. This can be further facilitated by collecting metadata associated with *E. coli* samples, especially when attempting to understand the causal factor that may influence connectivity. The systematic collection of additional metadata, such as pollution status (for example, selective and co-selective agents) and environmental context (for example, geographical location and climate variables), will facilitate the establishment of coordinated databases to aid multi-scale (local to international) efforts to reduce the connectivity of AMR across sectors.

Although information from *E. coli* as an indicator of faecal contamination is of high concern for public health, *E. coli* forms only a minor part of the human microbiome and is not expected to proliferate in the environment. Therefore, we recommend metagenome-based profiling as a complementary approach for those regions with the necessary resources. However, it is important to prioritize equitable access to such technologies so that all regions can benefit from these advancements. Based on the above considerations, we propose an implementation roadmap with the following procedure for assessing AMR connectivity by *E. coli* characterization and metagenomic analysis (Fig. 3):

1. Baseline establishment and pollution identification:

- Survey of environmental pollution and geographical features to identify possibly polluted sites that should be included in connectivity studies of a specific area, as well as minimally polluted/impacted sites for setting connectivity 'baseline';

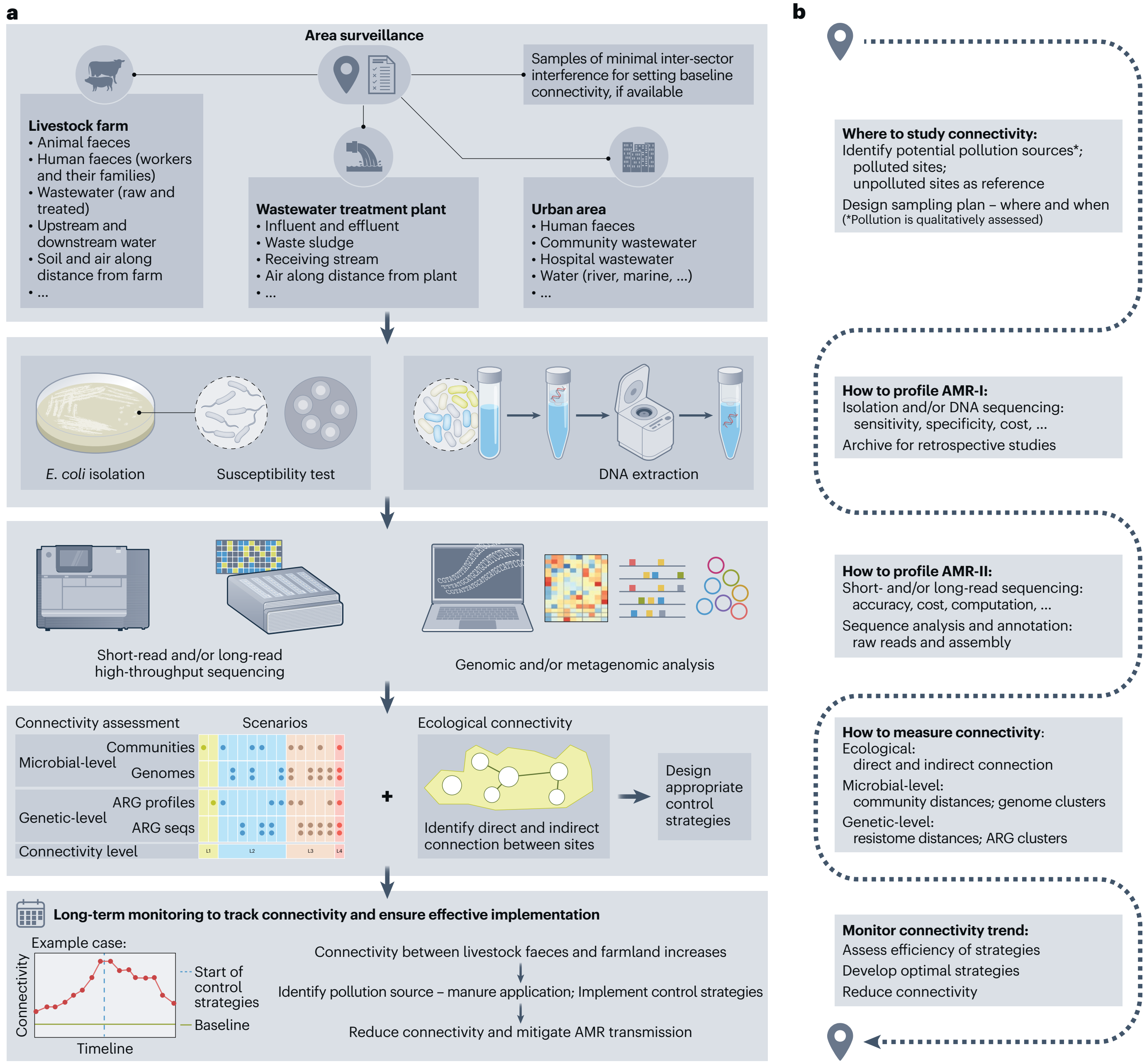

Fig. 3 | Examining AMR connectivity within and between habitats. **a**,**b**, The proposed standard approach (**a**) and implementation roadmap (**b**) for examining AMR connectivity within and between habitats. Connectivity studies begin with surveillance to characterize the area in terms of pollution types and loads. The sampling scheme (for example, sample types and time) depends on the characteristics of the area (for example, potential pollution sources and geographical features). It couples culture-independent and -dependent methods to assess microbial- and genetic-level connectivity. Genomic and metagenomic analyses provide perspectives of microbial- and genetic-level connectivity at different resolutions. By tracking connectivity over time, we may identify the optimal control strategies to mitigate AMR connectivity across sectors. Created with BioRender.com.

- If unavailable in the studied area, 'baseline' samples from other areas or relevant high-quality datasets in public databases are an option;

2. Sampling strategy design:

- Developing sampling plans to determine sampling method and frequency, including when and how to perform sampling (for example, any control-strategy implementations during the period need to be considered);

3. *E. coli*-based connectivity analysis:

- Having many *E. coli* isolates thus providing sufficient depth to capture genomic variation;
- Sequencing and genome assembly to obtain complete or near-complete genomes, including chromosome and plasmid sequences;
- Genomic analysis to examine connectivity at the genomic and genetic levels, which can be indicated by phylogenetic clusters and genetic arrangements.

4. Metagenome-based connectivity analysis:

- DNA extraction and sequencing of appropriate depth—it is suggested to have spike-in cells before extraction for absolute quantification[155] and reference samples included for benchmarking variability[156];

- Metagenomic analysis of community and ARG profiles, and assembly tools to recover long genetic fragments;
- Assessment of microbial- and gene-level connectivity, including (i) overall profile-based connectivity, which is based on the similarity of whole community and ARG profiles; (ii) connectivity of assembled high-quality genomes of specific taxonomic groups, which is evaluated by phylogenetic clusters; (iii) connectivity of particular ARG sequences, which can be learned from phylogenetic clusters and genetic arrangements;

5. Source identification and intervention planning:

- Comparison with the baseline to identify the level of connectivity and critical points for initiating control actions. Time-series studies might help identify connectivity trends, and with the rapid development of machine-learning tools, possibly define how connectivity evolves under different implementations of control strategies.

Summary and perspectives

The world has never been more deeply connected than it is today, and it will be even more so in the future, from macro-scale material flows to micro-scale microbial interactions[157]. Indeed, unprecedented levels of pollution and global mobility have facilitated the movement of microorganisms and their genetic elements within and between humans, animals and different environments. This is demonstrated by the global-scale dissemination of AMR. Despite extensive studies on this leading public health threat, efforts to examine AMR profiles under the holistic human–animal–environment framework and to consolidate current knowledge on AMR across sectors remain challenging. Nonetheless, understanding cross-sector connectivity is essential for managing AMR, as the global threat cannot be simply addressed in any single sector or country today[9].

The 2024 United Nations General Assembly High-level Meeting on Antimicrobial Resistance was a crucial milestone in strengthening global, regional and national cross-sectoral efforts to combat AMR[158]. AMR presents a rising global threat to human, animal and plant health, to food and water security, and to achievement of the Sustainable Development Goals (particularly SDGs 1–3, 8, 12, 14 and 15). The meeting was a critical opportunity for political leaders to consider measurable targets and practical steps to address AMR. Key commitments included increased investments to ensure equitable access to antimicrobial agents and promote their appropriate use, alongside enhanced cross-sectoral AMR surveillance and data-reporting mechanisms. However, although action plans are available for most countries to achieve these goals, the capacity for implementation is not ready. This is mainly due to lack of a clear roadmap to understand and manage AMR connectivity across the sectors of humans, animals and the environment. We propose concentrating initial efforts on addressing AMR connectivity within and between high-priority habitats as a fundamental component of AMR management. Progress in three key areas—advancing our scientific understanding of connectivity patterns, developing standardized detection and quantification methods, and establishing uniform assessment frameworks—would enable more accurate evaluation of AMR connectivity pathways. This may facilitate identifying the most optimal and comprehensive control strategies to reduce AMR connectivity across sectors. If translated into appropriate actions, these will substantially slow the process of AMR transmission, even though may not reverse the trend. However, failure to act will inevitably lead to an increase in AMR connectivity over time, consequently exacerbating AMR (Fig. 4). We must therefore understand the factors driving AMR connectivity, establish measurable targets, assess the connectivity in a quantitative way, and develop and implement control strategies to efficiently decrease the connectivity.

Recognizing AMR as a complex global crisis, governments must implement coordinated interventions across the human, animal and environmental sectors. The challenges to tackling AMR and the role of cross-sector connectivity vary greatly by region, necessitating tailored control strategies. For example, in regions banning the routine use of antimicrobial agents in farmed animals, like the EU, control priority should go to humans (for example, judicious use and development of rapid diagnostic tools) and the environment (for example, improving waste management and treatment technologies). In regions with poor infrastructure, their major effort should be to establish basic wastewater treatment and sanitation systems, as well as increase public hygiene awareness, instead of setting strict discharge standards, which may be a priority in HIC settings. Therefore, priority control strategies should be designed based on local situations, and connectivity studies proposed in this Perspective are intended to guide efforts to the key aspects, especially the inter-sector points, to mitigate AMR connectivity.

Regionally tailored strategies—encompassing both sector-specific and cross-sector approaches—can be developed through routine monitoring of AMR connectivity patterns over time. Along with methodology standardization and data integration, it is possible to establish global and regional surveillance databases of cross-sector connectivity, driving regional, national and international efforts in combating AMR. The measured cross-sector connectivity, by integrating monitoring data from healthcare, agriculture and the environment, will create channels for efficient communication between sectors. Such an integrated AMR connectivity surveillance programme has been considered by the Quadripartite bodies at UN General Assembly 2024[158]. We underline the urgency of addressing AMR connectivity in a global context by noting the linkages with broader development issues, including pandemic preparedness, universal health coverage, sustainable food systems and environmental protection.

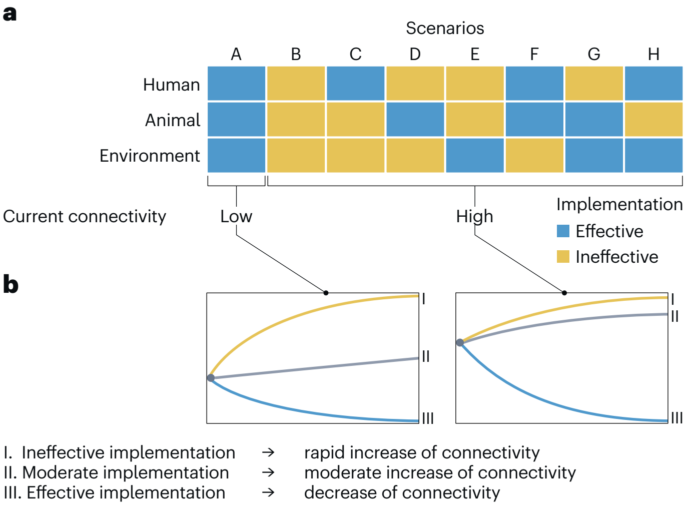

Fig. 4 | AMR connectivity between humans, animals and the environment and trends over time under different scenarios of the control strategy implementation. **a**, Current low and high connectivity levels shaped by implementing control strategies with different effectiveness. **b**, Future development of connectivity level over time as a function of implementing control strategies with different effectiveness (that is, ineffective, moderate and effective implementation).

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T.Z., L.L., B.L., X.Y. and E.T. conceptualized the study. T.Z. provided supervision and guided the overall direction. L.L. designed the figures and wrote the manuscript, with input from all authors. Y.X., Y.Y. and X.X. contributed to visualization. M.R.G., W.G., M.J.B., C.M.M., D.G., K.S., S.P.D., A.P., P.V., E.C., E.D., N.A., G.C., D.F.-K., F.W. and T.U.B. contributed to discussion of the content, and writing and editing of the manuscript. P.J.J.A., M.v.L., P.H.N., R.H., B.F.S., D.F., T.T.-Y.L., K.M.Y.L., F.X., X.Z., J.G., H.S., G.D.W., J.M., C.B., R.C.P., S.Z.A., C.-J.C., G.Y., Y.L., Y.W., J.S., Y.Z., M.Y., X.L., B.H., L.Z., Y.W., S.T., B.K. and Y.-G.Z. commented on the paper. All authors read and approved the final version of the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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