Comment

https://doi.org/10.1038/s41467-024-53057-z

Time to define One Health approaches to tackling antimicrobial resistance

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Recent data re-affirm antimicrobial resistance (AMR) as a One Health problem, particularly in low- and middle-income countries. Transdisciplinary and intersectoral collaboration are required if we are to improve environmental hygiene, addressing both AMR and a range of aligned development challenges.

Antimicrobial resistance (AMR) has been described as "the quintessential One Health problem" and it is believed that any meaningful effort to ameliorate this global public health challenge will require transdisciplinary and intersectoral collaboration to improve health for humans, animals and the environment[1]. There is not, however, enough evidence describing how antimicrobial resistant bacteria flow between different ecological compartments, or precisely what form One Health solutions to the problem of AMR should take. The complex and tightly correlated landscape of AMR transmission in the ecosystem means that results from studies powered to examine one particular aspect are likely affected, or even biased, by dependencies on other aspects. This lack of clarity poses serious challenges for selecting and balancing interventions to control AMR, especially as strong, potentially competing cases can be made to focus resources on antimicrobial stewardship and/or infection, prevention and control (IPC) practices in health care facilities on one hand, and water, sanitation and hygiene (WASH) practices in community settings on the other hand. Filling this evidence gap has become more pressing given that several recent studies, mostly from high-income settings, have shown limited evidence of a role for animal and environmental reservoirs in the human acquisition of key AMR pathogens.

Limited evidence for AMR as a One Health problem in high-income countries

A study of extended spectrum beta-lactamase (ESBL) producing *E. coli* by Public Health England (now UK Health Security Agency) compared isolates from human faeces, sewage, farm slurry, and retail foodstuffs to human bloodstream infection (BSI) isolates and found little overlap between non-human reservoirs and isolates from invasive human disease[2]. Similarly, a genomic surveillance of *E. coli* in the UK found distinct lineages and mobile genetic elements of *E. coli* between human BSI and livestock samples[3]. A recent study of *Klebsiella pneumoniae* from a wide range of clinical, community, animal and environmental settings in Italy, described by the authors as "a hotspot for hospital-acquired carbapenem non-susceptible *Klebsiella*", found no genotypic or phenotypic evidence for non-susceptibility to carbapenems outside the clinical environment[4]. In these studies, a lack of relatedness between bacterial isolates found in human infection samples and isolates from other ecological sources may not equate to a lack of transmission between ecological compartments. The sampling strategies employed including sampling animals from closed farms alongside unlinked humans from a large geographical area, may have influenced the ability to detect significant or potential transmission events[5].

Emerging data re-affirm AMR is a One Health problem in LMICs

On the other hand, some studies have shown evidence for a strong association between poor environmental health infrastructure and AMR, particularly affecting the most vulnerable populations in the world[6]. The Drivers of Resistance in Uganda and Malawi (DRUM) study, collected demographic, geospatial, clinical, animal husbandry and environmental health (including WASH infrastructure and practice) data from households in urban, peri-urban and rural settings in Uganda and Malawi[7]. Longitudinal human, animal and environmental sampling at each household was used to isolate ESBL *E. coli* and ESBL *K. pneumoniae*. Multivariable models illustrated that human ESBL-producing *E. coli* colonisation was associated with the wet season and close animal interaction, and that without adequate efforts to improve environmental health, ESBL-producing Enterobacteriaceae transmission is likely to persist in these settings[8,9].

E. coli is a highly diverse species, and the resolution offered by whole genome sequencing (WGS) reveals that sub-groups of *E. coli*, even at the level of discrimination offered by multi-locus sequence typing are generally distinct in different ecological sources. Despite this, there is flow of antimicrobial resistant strains or AMR genes between one health compartments. This is particularly evident in sub-Saharan Africa (sSA), where analysis of *E. coli* genomes from the UrbanZoo study in Kenya demonstrated that although transmission of the general *E. coli* population is often within host species[10], there is significant flux of accessory genes on mobile genetic elements (MGE), especially AMR genes, between humans and animals[11,12]. Sharing of the accessory genomes across different sources was also observed among *K. pneumoniae* isolates from clinical, environmental, and animal sources in Ghana, an indication of transmission of *K. pneumoniae* between the different compartments[13].

In Malawi and Uganda, comparison of *E. coli* genomes revealed high diversity of *E. coli*, MGE and ESBL genes that were distributed independent of ecological compartments[14]. Detailed lineage level SNP analysis of these genomes further indicated putative transmission events of ESBL-*E. coli* between humans, animals and the environment[14]. Outside sSA and Europe, evidence of phylogenetic intermixing and sharing of AMR genes between humans, animals and soil has been reported in Bangladesh[15]. Similarly, in Ecuador, significant clonal and AMR gene sharing of third generation cephalosporin resistant *E. coli*

was observed between children and animals, suggesting interlinkage of AMR in animals and humans[16]. The degree of sharing of bacteria strains and AMR determinants between different ecological compartments reported in studies such as these is certainly underestimated. This is particularly the case because carriage studies involving isolate WGS do not fully account for within sample diversity. Nevertheless, even without capturing that full diversity, the available evidence suggests exchange of AMR bacterial strains and AMR determinants between the different ecological compartments is common, particularly in low- and middle-income countries (LMICs).

WASH systems and the spread of AMR across ecological compartments

Detection of closely related ESBL-producing Enterobacteriaceae in humans, animals and the environment within LMICs not only illustrates the relevance of the One Health paradigm to key AMR human pathogens, but is also a manifestation of the poor environmental health standards and practices combined with the close interactions between humans, animals and the environment. Although not a surprise to the WASH community, the prominence of AMR as a global health issue can be used to shine new light on the urgency to address Sustainable Development Goal 6: ensuring the universal and equitable access to WASH for all. This could be effectively utilised to catalyse renewed enthusiasm and commitment for investment in WASH infrastructure, with aligned effective social and behaviour change programmes to reduce the interactions between these different ecological sources. On the other hand, the fact there is limited evidence for ESBL-*E. coli* and *K. pneumoniae* transmission between humans, animals and the environment in settings such as Europe where WASH infrastructure is strong, highlights the central role context appropriate approaches to improving environmental hygiene must play. The presence of these bacteria in healthcare settings informs us that IPC strategy in these settings is failing, placing patients at risk of adverse outcomes. Indeed, a high prevalence of healthcare associated infection, in part, illustrates a failure of environmental hygiene measures and practices in healthcare settings[17]. The response to AMR must not only be contextually appropriate, but also take a whole system approach, understanding that infection prevention is broader than the practice of IPC in healthcare facilities, and should embrace WASH infrastructure and practice in domestic, public and institutional settings. Indeed, to prevent severe bacterial infection from ESBL-*E. coli*, asymptomatic transmission of ESBL-enteric bacteria needs to be interrupted. AMR does not recognise the disciplinary silos in which we typically operate and the presence of widespread ESBL-enteric bacteria indicates that we are failing to create effective, equitable and sustainable access to basic WASH infrastructure and services for the most vulnerable populations in the world.

Conclusion

Evidence for a One Health Framework for AMR remains incomplete. While some studies have provided evidence of the need to take a One Health approach to AMR, such approaches will differ according to setting. Acknowledging however, that environments in LMIC are commonly contaminated by AMR bacteria such as ESBL–producing *E. coli* and *K. pneumoniae* and therefore unsafe, is a critical starting point. It demonstrates the need for a whole system approach to environmental hygiene, in which we will see catalytic and reinforcing advantages from transdisciplinary working to develop context appropriate and sustainable solutions that tackle global public health, economic development, dignity and wellbeing simultaneously by improving WASH infrastructure and practice. Bacterial populations must be segregated by introducing transmission bottlenecks between human, animal and environmental compartments to reduce overall AMR transmission rates. To achieve this, there is an urgent need for designing, validating and understanding how best to implement such approaches in the face of competing public health priorities in all societies, and especially in LMICs.

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Received: 16 November 2023; Accepted: 26 September 2024;
Published online: 10 October 2024

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Author contributions

P.M. and N.A.F. conceived this work. P.M., T.M., C.P.J., and N.A.F. wrote the manuscript, with critical revision by D.C. and L.M. All the authors read and approved the final version of the manuscript.

Competing interests

The authors declare no competing interests.

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Peer review information *Nature Communications* thanks the anonymous reviewer(s) for their contribution to the peer review of this work.