Harnessing Genomics for Antimicrobial Resistance Surveillance 4

Exploiting genomics for antimicrobial resistance surveillance at One Health interfaces

Dishon M Muloi, Elita Jauneikaite, Muna F Anjum, Sabiha Y Essack, David A Singleton, Mitchelle R Kasudi, Matthew J Wade, Beverly Egyir, Jamie G Nunn, Janet T Midega, Sharon J Peacock, Nicholas A Feasey, Kate S Baker, Ruth N Zadoks, for the SEDRIC Genomics Surveillance Working Group

The intersection of human, animal, and ecosystem health at One Health interfaces is recognised as being of key importance in the evolution and spread of antimicrobial resistance (AMR) and represents an important, and yet rarely realised opportunity to undertake vital AMR surveillance. A working group of international experts in pathogen genomics, AMR, and One Health convened to take part in a workshop series and online consultation focused on the opportunities and challenges facing genomic AMR surveillance in a range of settings. Here we outline the working group's discussion of the potential utility, advantages of, and barriers to, the implementation of genomic AMR surveillance at One Health interfaces and propose a series of recommendations for addressing these challenges. Embedding AMR surveillance at One Health interfaces will require the development of clear beneficial use cases, especially in low-income and middle-income countries. Evidence of directionality, risks to human and animal health, and potential trade implications were also identified by the working group as key issues. Addressing these challenges will be vital to enable genomic surveillance technology to reach its full potential for assessing the risk of transmission of AMR between the environment, animals, and humans at One Health interfaces.

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Animal and Human Health Department, International Livestock Research Institute, Nairobi, Kenya (D M Muloi PhD, M R Kasudi BVM); **Institute of Infection, Veterinary and Ecological Sciences, University of Liverpool, Liverpool, UK** (D M Muloi); **Department of Infectious Disease Epidemiology, School of Public Health, Imperial College London, London, UK** (E Jauneikaite PhD); **NIHR Health Protection Research Unit in Healthcare Associated Infections and Antimicrobial Resistance, Department of Infectious Disease, Imperial College London, Hammersmith Hospital, London, UK** (E Jauneikaite); **Department of Bacteriology, Animal and Plant Health Agency, New Haw, UK** (Prof M F Anjum PhD); **Antimicrobial Research Unit, University of KwaZulu-Natal, Durban, South Africa** (Prof S Y Essack PhD); **Clinical Infection, Microbiology, and Immunology, University of Liverpool, Liverpool, UK** (D A Singleton PhD, Prof K S Baker PhD); **Data Analytics and Surveillance Group, UK Health Security Agency, London, UK** (M J Wade PhD); **School of Engineering, Newcastle University, Newcastle-upon-Tyne, UK** (M J Wade); **Department of Bacteriology,**

Background

In 2022, the Surveillance and Epidemiology of Drug-resistant Infections Consortium (SEDRIC) convened a series of workshops on the applications of genomics for the surveillance of antimicrobial resistance (AMR) in bacterial pathogens (see the first paper in this Series[1]). The third SEDRIC workshop was held on April 20, 2022, and focused on surveillance at One Health interfaces. During the workshop, participants from a diverse range of settings and sectors (see full authorship in the first paper in this Series[1]) conducted a situational analysis on the use of genomics for surveillance of AMR at One Health interfaces. The diversity in national, disciplinary, and professional backgrounds of participants and in socioeconomic drivers across their countries and sectors contributed to a qualified consensus on the value and utility of genomics for AMR surveillance at One Health interfaces and enabled the group to propose recommendations for stakeholders to realise the full potential benefit of genomics implementation. The workshop considered One Health interfaces primarily through the prism of human health risks from other One Health domains. However, to build intersectoral collaboration, the needs and drivers of other sectors will need to be considered, including, for example, economic justification, commercial confidentiality of data, and risks to consumer perception or global trade.

The use of genomic AMR surveillance at One Health interfaces

One Health is broadly recognised as a multidisciplinary approach to explaining the interactions and interfaces between human, animal, and ecosystem health, for which AMR is a shared challenge.[2] This is reflected at the global level in the quadripartite collaboration between WHO, the World Organization for Animal Health, the Food and Agriculture Organisation of the United Nations, and the UN Environment Programme, which collectively represent many aspects of human, livestock, crop, wildlife, water, and other environmental components of One Health (albeit with limited representation of companion animals). During the workshop, One Health interfaces were considered as points of interaction between humans, animals, and the environment, for example through consumption of crops or food of animal origin, shared use of water, shared environmental space, or the use of human or animal waste as feed or fertiliser (figure).

Although the working group agreed (in common with other workshops described in the second and third papers in this Series[3,4]) that the granular resolution afforded by genomics had unprecedented potential to support enhanced surveillance of AMR transmission across One Health interfaces, a substantial amount of work remains to be done before this potential is realised. Work is needed in methodology development and standardisation, quality assurance, inference of directionality of transmission, intersectoral agreement on potential implications of surveillance, and cost–benefit evaluation of the use cases for genomic AMR surveillance. This work will also require justification of study populations, sample types, target organisms, and sample sizes; harmonisation of genomics protocols;[5] the development of better tools to interpret surveillance

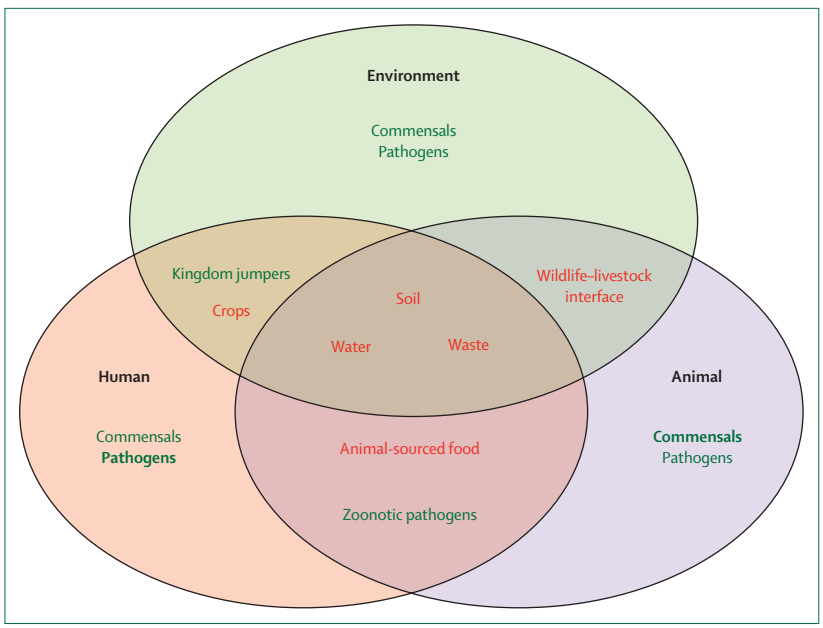

Figure: **Conceptual representation of One Health realms**
One Health realms include humans, animals, and the environment. The figure shows potential interfaces (red text) and organisms of concern (green text). In current antimicrobial resistance surveillance, genomic surveillance tends to focus (shown in bold) on clinical isolates from humans and commensal isolates from animals.

Noguchi Memorial Institute for Medical Research, University of Ghana, Legon-Accra, Ghana (B Egyir PhD)**; Infectious Disease Challenge Area** (J G Nunn MSc) **and Drug Resistant Infections** (J T Midega PhD)**, Wellcome Trust, London, UK; Department of Medicine** (Prof S J Peacock PhD) **and Department of Genetics** (Prof K S Baker)**, University of Cambridge, Cambridge, UK; Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, UK** (Prof N A Feasey PhD)**; Malawi Liverpool Wellcome Research Programme, Chichiri, Blantyre, Malawi** (Prof N A Feasey)**; Sydney School of Veterinary Science, Faculty of Science, University of Sydney, Camden, NSW, Australia** (Prof R N Zadoks PhD)**; School of Biodiversity, One Health and Veterinary Medicine, University of Glasgow, Glasgow, UK** (Prof R N Zadoks)

Correspondence to:
Prof Kate Baker, Department of Genetics, University of Cambridge, Cambridge CB2 3EH, UK
kb827@cam.ac.uk

results in terms of exposure pathways and interventions, which might be unknown or highly context dependent;[6–8] and consideration of potential trade implications of detection of multidrug-resistant organisms in animals or crops. On this point, it is worth noting that the World Trade Organization allows member countries to define an appropriate level of protection to manage biosecurity risks from imports and is becoming increasingly cognisant of concerns around AMR.[9] The working group raised concern that genomic surveillance outputs in a One Health setting would inevitably depend on the samples selected for analysis, creating considerable potential for bias. Observed associations could be mistaken for causation, especially in the absence of complete information on potential alternative sources or owing to preconceived notions about transmission pathways or risks. For example, AMR surveillance in humans tends to focus on clinical isolates, whereas AMR surveillance in animals often focuses on commensal isolates (figure).[10] When commensal isolates are considered across species, prevalence of AMR might be higher in humans than animals.[11]

There were also a range of views on the importance of transmission at One Health interfaces relative to selection and transmission within the human population or health sector. Indeed, some recent data provide only limited support for AMR as a major One Health problem in either high-income countries[12,13] or low-income and middle-income countries (LMICs),[14,15] although data from LMICs are scarcer. Paradoxically, although genomic surveillance might be the tool needed to establish the importance of One Health interfaces in AMR ecology,[6] its implementation can be difficult to justify without viable use cases providing evidence of its value, especially in resource constrained settings. A similar situation is commonly encountered in surveillance and control of neglected zoonotic diseases.[16]

The working group considered whether and how genomic surveillance could be integrated with existing systems. For example, should genomic surveillance be embedded in existing epidemiological surveillance programmes for AMR in livestock,[10,17] foodborne pathogens,[18] or across species and systems as done in the EU[19] and the USA?[20] Alternatively, should One Health surveillance feed into or sit above human health systems, or encompass the three domains of One Health equally, as in the Global Tricycle Surveillance Protocol?[21] A major recommendation of the working group was that use cases for genomic AMR surveillance be better articulated and advocated. For example, if resources for basic hygiene measures are lacking, it is questionable whether prioritising genomic surveillance would have any benefit for infection prevention and control and reduce risk of AMR transmission.[22]

In addition to the need to identify the anticipated benefits, address privacy issues, and address potential risks associated with the use of genomic surveillance, ethical concerns exist surrounding sharing of genetic and clinical data across institutions and countries where genomic facilities exist. This was the focus of considerable discussion in the workshops summarised in the second and third papers in this Series.[3,4] Although not explicitly discussed, drivers of AMR that need to be considered when designing genomic surveillance studies might need to include antimicrobial use as well as pesticides,[23] heavy metals,[24] disinfectants,[25] and AMR transmission pathways.[26]

AMR genomics at the human–animal interface

Humans and animals interact in myriad ways, both directly and indirectly, via food, human or animal waste, and exposure to shared environments. The degree and patterns of interactions between humans, companion animals, livestock, and wildlife vary widely across urban, rural, and remote areas. For example, direct interactions between humans and animals in high-income urban settings might be dominated by companion animals, who might even pose a greater AMR risk than livestock, as seen in Australia.[27] On the other hand, in informal settlements or on waste dumps in LMICs, humans, dogs, pigs, ruminants and avian, rodent, or carnivorous wildlife all live, forage, and interact.[28,29]

Existing surveillance mechanisms for animal-derived or food-derived antimicrobial-resistant bacteria are still largely based on microbiological and phenotypic assessment and are only supplemented by genomic surveillance to investigate unusual AMR patterns. For example, phenotypic surveillance led to the detection of a

rapid increase in colistin resistance in *Escherichia coli* isolates from livestock in China, and genomic sequencing of a resistant isolate led to the discovery of the plasmid-associated mobile colistin resistance gene (*mcr-1*).[30] Subsequent analyses using whole-genome sequencing data showed a global spread of *mcr-1* across numerous ecological niches and in association with a diverse range of plasmids and bacterial species.[31] These observations informed global intervention efforts, including the ban of colistin use in the livestock sector in China and other countries.[32] Much of the initial work on colistin resistance was based on phenotypic approaches and, of 2824 isolates that were screened using minimum inhibitory concentrations of colistin and PCR to assess the presence of the *mcr-1* gene, only 135 isolates were assessed by whole-genome sequencing. As such, although the value of whole-genome sequencing in understanding the evolutionary origin, global spread, and subsequent containment of the colistin-resistant determinants is undeniable, the use case for routine genomic AMR surveillance was not made by the discovery of *mcr-1*. It is possible that in some countries, genomic AMR surveillance at One Health interfaces can only be justified on such a response-mode basis.[33] Another essential, last-resort antimicrobial used to treat multidrug-resistant bacterial infections is tigecycline. As with colistin and *mcr-1*, resistance against tigecycline was first reported from livestock in China and was found to be encoded by newly recognised *tet*(X3) and *tet*(X4) genes. In the UK, the Animal and Plant Health Agency routinely uses whole-genome sequencing to confirm AMR genotypes in *E coli* isolates obtained from livestock for research and surveillance purposes. Retrospective analysis for nearly 2000 *E coli* and *Escherichia fergusonii* genome sequences from livestock and retail meat, and from more than 90 000 human *E coli* and *Salmonella* spp isolates, showed the presence of the *tet*(X4) plasmid in five isolates, with clear differentiation of the animal isolates and the four human isolates.[34]

Questions remain regarding the diversity, persistence, and dispersal propensity of such newly emerging, increasingly resistant clones, and genomic studies will be essential for answering these questions. Likewise, a growing number of studies have shown presence of human-pathogenic extended-spectrum beta-lactamase (ESBL) resistant clones such as *E coli* ST131 (discussed in the third paper in this Series[4]) in livestock,[10] pets,[35] and wildlife,[36] although the direction of transmission is often unclear. Like other wild birds, gulls of the Laridae family (seagulls) are rarely treated with antimicrobials but feed on or near human waste, meaning that they are likely to be recipients rather than sources of drug-resistant *E coli*. Indeed, proximity to human habitation or wastewater treatment plants is an important predictor of the gut resistome diversity of wild birds[37] and for the prevalence of antimicrobial resistant *E coli* in wild red deer.[38] It is largely unknown which roles birds and other wildlife might have in the transmission and persistence of AMR in an environment, or in its transmission to humans.

The *E coli* ST131 example highlights the need for better tools to model the relative importance of exposure and source attribution pathways to inform potential interventions. Indeed, epidemiological surveys of behaviour and exposure pathways might be needed to complement genomic surveillance to identify and prioritise risk reduction strategies.[39] The examples described here also illustrate the enormous investment required for the detection of rare resistance determinants, and workshop participants recognised that the justification for such investment is highly context dependent.

Integrating environmental dimensions in One Health AMR surveillance

Although examples of integrated AMR surveillance programmes already exist for human, animal, and food sectors, a true One Health approach would require that environmental surveillance also be embedded within these systems.[40] The environment might have an important role as a reservoir for the evolution and dissemination of drug-resistant bacteria and AMR genes, including within and between hosts via direct contact with contaminated interfaces, such as soil, water, human, animal, or plant waste, and airborne particles (figure).[41] There is no clear framework underpinning environmental AMR surveillance, and there is no clarity around which sample types or indicators should be measured (whether drug-resistant bacteria, AMR genes, or mobile genetic elements) for the environmental sector.[42] The use of sentinel organisms, whether animal species such as egrets[43] or bacterial species such as *E coli*,[44] provide one potential pathway for genomic AMR surveillance but might not align well with the focus on WHO priority pathogens as proposed for public health (see the third paper in this Series[4]).

Environmental monitoring might pass over the use of isolate-based bacterial genomics to focus on metagenomics or metatranscriptomics (see the fifth paper in this Series[45]). For example, the Global Sewage Study showed the effectiveness of using metagenomic data to analyse environmental samples and resolve spatial trends of AMR at a global scale.[46] This study found that AMR gene diversity and abundance are highly variable by region and influenced by socioeconomic, health, and environmental factors. At a local scale, other genomic studies have suggested the possibility of using sewage monitoring as a complement to clinical surveillance of resistance by providing community-level AMR readouts,[47,48] particularly in the wake of its application for SARS-CoV-2 surveillance.[49] The use of metagenomics in environmental studies cannot provide species-specific phenotypic data but, when combined with chromosome conformation capture technologies such as Hi-C, metagenomics can provide

fine scale association between AMR genes and host pathogens.[50] Functional metagenomics can also be used to discover novel AMR genes in soils.[51] However, the cost of such technical capability is still very high, putting further pressure on the economic justification and use case.

Although the scientific possibilities are ever-expanding, the examples and applications described here might not constitute surveillance as actionable information. Moreover, we do not need environmental genomic surveillance to know that water, hygiene, and sanitation challenges exist in many countries. As noted by one workshop participant who had studied transmission of multidrug-resistant *E coli* in a neonatal intensive care unit in sub-Saharan Africa where functioning handwashing facilities were not available, prioritisation of investment needs to be considered carefully in such settings.

Barriers to genomics implementation at One Health interfaces

Although there are many examples of insights gained from the implementation of genomics across human, animal, and environmental domains, a scarcity of clear use cases, including cost–benefit calculations and consideration of the opportunity costs of AMR genomic surveillance compared with alternative investments, currently limits the justification for the routine use of genomics in AMR surveillance at human–animal–environment interfaces. The working group highlighted the substantial barriers and a long path to implementation for routine genomic AMR surveillance at One Health interfaces, particularly in areas without sanitation and clean drinking water and where basic animal, and sometimes human, microbiological and phenotypic AMR surveillance is not yet established. The working group identified several barriers (eg, training and evidence of cost-effectiveness) in common with domains covered by previous workshops (ie, hospital and public health surveillance, discussed in the second and third papers in this Series[3,4]). However, surveillance at One Health interfaces has additional complexities, such as the need to consider data sharing arrangements and cooperative funding structures across sectors that include both public and private stakeholders. Furthermore, epidemiological metadata are generally stored in silos that do not have interoperability across One Health sectors, sites, and countries. Fragmented data architectures at local and national levels and an absence of harmonised approaches and ontologies in capturing metadata are additional barriers to rapid and open data integration and sharing (explored in detail in the third paper in this Series[4]).

Recommendations from the working group

The workshop and subsequent stakeholder-focused discussion on how to build on the advantages and overcome barriers of genomics for One Health AMR surveillance led to the following recommendations: (1) defining a framework for use; (2) addressing funding models and evaluating cost-effectiveness; and (3) leveraging existing integrated genomic surveillance activities and integrating of environmental AMR surveillance.

Defining a framework for use at all levels

The working group agreed that there was a strong need to define a use and actionability framework for genomic AMR surveillance in a One Health context owing to: (1) the need to focus resources across the substantial breadth of potential surveillance areas (eg, domestic and wild animals; rural and urban animal populations; waste, marine, and freshwater waterways; and crops); (2) limitations on inference regarding directionality of transmission or risk pathways and behaviours from surveillance data; (3) the potential for risk–benefit imbalance whereby genomic AMR surveillance primarily benefits human health while the costs of surveillance might be borne by other sectors; and (4) concerns about the risk of potential negative surveillance outcomes, such as the stigmatisation of individuals or populations with potential implications for the movement of people and products (as seen for, eg, COVID-19 or cholera). The working group recommended broad consultation to communicate and build trust among stakeholders considering perceived and genuine risks and benefits across groups. This will require consultations with organisations at both national and international levels with regard to defining the implications of surveillance outcomes, for example the World Trade Organization, where AMR is already the subject of substantive discussions.[9]

Addressing funding models and evaluating cost-effectiveness

Genomic epidemiology has had an important role in rapidly uncovering epidemic origins as well as identifying and tracking the spread of variants of concern for public health threats, which has been shown for viral diseases, including severe acute respiratory syndrome, COVID-19, Zika virus disease,[52] Ebola virus disease,[53] and Middle East respiratory syndrome,[54] as well as many foodborne bacterial pathogens (see the third paper in this Series[4]). Genomic surveillance of bacterial pathogens has primarily been used at the national scale—eg, for control of waterborne campylobacteriosis in New Zealand[55]—or across economic and political unions—eg, for control of *E coli* O104:H4 from sprouts,[56] or *Bacillus anthracis* from heroin.[57] The working group agreed that genomics is now at an inflection point that will increasingly allow health outcomes to be informed in real time, at least for human health care in high-income countries, although the examples presented as justification are largely still reactive—ie, in response to outbreaks, rather than based on proactive surveillance.

In discussions around strengthening global health security, the use of genomics and the importance of AMR as a slow pandemic should be considered.[58] However, these conversations need to include the cost of genomic AMR surveillance and the avoidance of a high-income-country bias, especially as the impact of AMR falls most heavily on LMICs. Indeed, anticipated trickle-down effects of whole-genome sequencing are yet to be articulated and realised in many LMICs, which might still have very limited human and animal health-care and surveillance infrastructure. Development and evaluation of metrics that capture the costs of implementation of whole-genome sequencing and the effect of AMR on the health of humans, animals, and their environment are needed to make a strong case for LMICs to invest in genomics. In addition, assessment of opportunity cost might be needed—eg, if funds were not invested in genomic surveillance, how else could they have been used to promote global health surveillance? The working group discussed whether governments in LMICs should be encouraged to invest in genomics. The urgency of AMR is well understood among policy makers and professionals, as reflected in many national action plans on AMR, and there might be an opportunity to leverage existing genomic surveillance activities for COVID-19, tuberculosis, and HIV (see the second paper in this Series[3]). However, for One Health genomic AMR surveillance to be adopted in most LMICs, it will be vital to show clear beneficial use cases, and to consider innovative financing options and improvement of capacity in terms of training (see the second paper in this Series[3]).

Build on existing One Health surveillance activities

Implementation of genomic AMR surveillance activities might be possible within existing national or trans-national public health, AMR, or food safety surveillance systems as outlined in this report (and in the second and third papers in this Series[3,4]). Where systems are not yet in place, or to support harmonisation of approaches and comparability of data globally, participation could be encouraged in the sentinel organism-focused WHO Tricycle protocol.[59] This protocol aims for integrated global surveillance of one indicator, ESBL-producing *E coli,* across the human, animal, and environment compartments and has already been implemented in six LMICs. Existing foodborne disease-focused surveillance programmes could extend to consider AMR[18] or a range of pathogens relevant to human AMR burden. Several programmes, for example led by the Animal and Plant Health Agency in the UK, the European Centre for Disease Control, or the European Food Safety Authority, focus on the major foodborne pathogens (ie, non-typhoidal *Salmonella* spp and *Campylobacter* spp) or on sentinel species such as *E coli*, but do not cover all highly virulent and drug-resistant bacterial pathogens (eg, *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species; see the second paper in this Series[3]). The UK Health Security Agency has shown the benefits of replacing some traditional microbiology methods with whole-genome sequencing for real-time surveillance of AMR pathogens (including foodborne infections), resulting in improved public health and reduced economic costs.[60] Similarly, the UK Animal and Plant Health Agency have implemented sequencing for serotyping *Salmonella* spp and for AMR determination in *E coli* taken from healthy livestock and retail meat products.[61] The USA uses sequencing when conducting integrated surveillance of many foodborne pathogens across the Food and Drug Administration, Centers for Disease Control and Prevention, and Department of Agriculture in the form of the National Antimicrobial Resistance Monitoring System (also known as NARMS).[20] Complete integration of routine whole-genome sequencing into One Health surveillance platforms is still developing. For example, the UK Pathogen Surveillance in Agriculture, Food, and Environment programme (also known as PATH-SAFE) is one of the first initiatives to integrate whole-genome sequencing into routine AMR surveillance across the three One Health sectors. The organisations listed here reflect countries with high wealth and low risk tolerance, emphasising how the use case might not be uniform across the globe.

Conclusions

Genomics can provide an unparalleled high-resolution understanding of the identity and current distribution of resistance genes and AMR bacteria at One Health interfaces. However, the vast scales at which humans, animals, and the environment intersect demand a focused approach when seeking to realise the potential benefits of integrating genomics into AMR surveillance. Without clear use cases where genomic surveillance can provide actionable information for mitigating the risk of AMR spread in and between animal and human populations and the environment, in a manner that is cost-efficient compared with alternative investments, the rationale for establishing genomic AMR surveillance across One Health interfaces will be limited. Identifying and developing suitable economically viable and epidemiologically beneficial use cases, ideally building on existing One Health surveillance activities, is therefore a high priority. Furthermore, although increasing genomic surveillance has the potential for clear benefits in terms of scientific understanding and improving public and animal health, there are potential risks to the movement of people, animals, or products if new types or high levels of AMR are discovered. As such, discussion with relevant stakeholders about cost–benefit calculations and consideration of suitable funding models for genomic AMR surveillance at One Health interfaces will be vital, especially in LMICs.

Contributors

SJP, NAF, KSB, EJ, JGN, and JTM conceptualised the study. KSB, EJ, and JGN curated all data. SJP, NAF, JGN, and JTM acquired funding. SJP, NAF, KSB, EJ, JGN, and JTM did the investigation. SJP, NAF, KSB, and EJ contributed to all methodology. SJP, NAF, KSB, EJ, JGN, and JTM did project administration. SJP, NAF, KSB, and EJ supervised. RNZ contributed to visualisation. DMM, RNZ, MFA, SYE, KSB, and EJ wrote the original draft. All authors reviewed and edited the paper and engaged with and participated in the workshops. All authors had final responsibility for the decision to submit for publication.

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