Overview: Harnessing genomics for antimicrobial resistance surveillance

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Summary

Nearly a century after the beginning of the antibiotic era, which has been associated with unparalleled improvements in human health and reductions in mortality associated with infection, the dwindling pipeline for new antibiotic classes coupled with the inevitable spread of antimicrobial resistance (AMR) poses a major global challenge. Historically, surveillance of AMR bacteria typically relied on phenotypic analysis of isolates taken from infected individuals, which provides only a low-resolution view of the epidemiology behind an individual infection or wider outbreak. Recent years have seen increasing adoption of powerful new genomic technologies with the potential to revolutionise AMR surveillance by providing a high-resolution picture of the AMR profile of the bacteria causing infections and provide real-time actionable information for treating and preventing infection. However, many barriers remain to be overcome before genomic technologies can be adopted as a standard part of routine AMR surveillance around the world. Accordingly, the Surveillance and Epidemiology of Drug-resistant Infections Consortium (SEDRIC; www.sedric.org.uk) convened an expert working group on Genomics Surveillance for AMR to assess the benefits and challenges of using genomics for AMR surveillance. This overview, and the associated four workshop summaries detail these discussions and provide a series of recommendations from the working group that can help to realise the massive potential benefits for genomics in surveillance of AMR.

1. Background

Tackling antimicrobial resistance (AMR) is one of the most important health challenges of the 21st century. AMR already causes substantial morbidity and mortality worldwide, with a recent estimate suggesting that AMR was the attributable cause of death for approximately 1.27 million people in 2019[1]. This toll is expected to rise in the coming decades with estimates that as many as ten million people could die each year as a result of AMR[2]. AMR also carries a substantial economic burden through direct healthcare costs and loss of productivity, with one estimate suggesting that AMR costs >$4.6 billion annually in the United States alone[3].

In 2015, the World Health Organisation (WHO) adopted a Global Action Plan on AMR, which included objectives in areas such as improving awareness of AMR, reducing disease incidence through sanitation, hygiene, and infection control measures, optimizing antimicrobial stewardship and developing sustainable investment models for new medicines, diagnostics, vaccines, and other interventions. One of the key objectives was to strengthen the knowledge and evidence base around AMR through increased research and surveillance (defined here as systematic data collection to inform action)[4]. As a result, there is substantial momentum in building bacterial isolate-based AMR surveillance around the world, including the development of national action plans and submission of global data to the WHO Global Antimicrobial Surveillance System (GLASS) initiated in 2018.

Although GLASS has previously considered the relevance of genomics in AMR surveillance[5], the SARS-CoV-2 pandemic has since transformed the global disease surveillance landscape, particularly with respect to genomic surveillance. The period between March 2020 and December 2022 saw the generation of nearly 14 million publicly available SARS-CoV-2 genomes from 215 countries, which helped to inform global public health responses (https://gisaid.org/submission-tracker-global/). The concept of a “Variant of Concern” is now established in the public lexicon, and health policy makers increasingly appreciate the potential of genomic surveillance to provide a high-resolution picture of the transmission

dynamics and evolution of microbial pathogens that inflict substantial public health burden. Expansion in genomic capacity, combined with evidence for the utility of genomic surveillance of AMR over the last two decades (Figure 1),[5,6] demonstrate the feasibility and timeliness of adopting this technology as an essential part of routine surveillance programmes. The time is therefore right to build on the political and public understanding and willingness to invest in surveillance capacities to tackle the AMR pandemic.

Accordingly, the Surveillance and Epidemiology of Drug-resistant Infections Consortium (SEDRIC; www.sedric.org.uk) convened a working group on Genomics Surveillance for AMR to review the evidence base of the benefits and challenges to using genomics for AMR surveillance, and to generate recommendations that could lead to effective implementation.

2. How was the working group conducted?

The working group held a series of four workshops with nearly 100 international experts from across the AMR and pathogen genomics fields (Appendix pages 1 - 3), which was followed by a broader community consultation through an online survey (Appendix pages 8 – 10). Group members were identified through a combination of searching the SEDRIC membership list, literature survey, other online content (e.g. grey literature, research profiles), and suggestions from the steering group and core members being conscious to attain the required expertise and be diverse with respect to geography, gender, ethnicity, and career stage. A subset of 'core members' with collective expertise across the domains attended all workshops and bookend meetings to shape the conduct and outputs from the workshops (Figure 2, Appendix 1 -3).

The first three workshops were on the application of genomics in isolate-based surveillance across different surveillance domains: 1) hospital-based surveillance; 2) public health and international surveillance; and 3) surveillance at One Health interfaces. The breadth of potential surveillance domains led the group to limit the scope to bacterial AMR surveillance, excluding *Mycobacterium tuberculosis* where genomic surveillance is already comparatively well-established[7]. Workshops 1 - 3 comprised two parts. Part 1 was a landscape analysis of the application of genomics for AMR surveillance, a discussion on the value of genomics in the domain, and the development of rated consensus statements from those discussions (Appendix Pages 4, 11 - 13). Part 2 guided members to develop stakeholder owned recommendations for realising the potential of genomics for AMR in the domain, which were then prioritised by polling (Appendix Pages 5 -6, 11 - 13). A list of stakeholders was predefined for consideration by working group members, with encouragement to include un-nominated stakeholder groups (Appendix page 6). A final workshop considered pre-selected innovations in genomics where surveillance would not be based on the sequencing of individual isolates but implementation is farther from routine. Specifically, these were: 1) clinical metagenomics; 2) environmental metagenomics; 3) gene and plasmid-based tracking; and 4) machine learning. Participants discussed the potential improvements brought by each of these innovations and the vision for implementation, followed by the development of specific recommendations (Appendix page 7).

The outcomes from workshops were then used to develop a consolidated position with the core working group and then broader opinion was invited through a community survey (Appendix page 8 -10). The survey was disseminated electronically via social media channels

and over email within group member networks. In total, 160 professionals from the AMR community completed the survey (Figure 2), and their responses broadly reflected agreement with the working group (Appendix 10 -13). In sum, the SEDRIC working group developed a series of views and prioritised recommendations for the use of genomics for AMR surveillance [8] that captured expert opinion in the field.

3. What did we find?

Nine recommendations for harnessing genomics for AMR surveillance are proposed by the group (Box), which are expanded on in four individual workshop reports in this series (D-23-00144, D-23-00145, D-23-00146, D-23-00147). While we have endeavoured to avoid repetition across the four reports, some common themes emerged in terms of advantages and challenges for genomic surveillance of AMR across the workshops and these are summarised below.

3.1 Advantages

Genomic AMR surveillance was considered to offer many advantages over current approaches. Genomics enables finely resolved tracking of AMR pathogens at the individual strain level, while the electronic nature of most of the analytic processes downstream of sequencing offers advantages for many aspects of data handling, including sharing, storage, and quality assurance. Although these features are common to genomic surveillance of all pathogens, there are several advantages that are distinct for genomic surveillance of AMR bacteria. These include the ability to assay for genotypes relating to resistance against multiple classes of antimicrobial in parallel; the ability to determine whether AMR has emerged in a previously circulating lineage or represents expansion of a new lineage; and the ability to determine the genetic basis of resistance. Determining the genetic basis for resistance is important as it can support outbreak linkage and has future potential to predict the capacity for AMR spread (e.g., whether the resistance is encoded by chromosomal mutations or by acquired resistance genes). Furthermore, establishing and strengthening an adaptable genomic AMR surveillance infrastructure contributes to pandemic preparedness efforts both by monitoring for new microbial threats and ensuring that adequate facilities and a trained pathogen genomics workforce are available should a new pandemic pathogen emerge.

3.2 Applications

The applications for genomic AMR surveillance differed by domain. Briefly, a growing evidence base exists for the use of genomics for AMR surveillance in hospital settings to support the detection of outbreaks and provide actionable information to infection prevention and control (IPC) teams. Genomic insights can also inform clinical decision making at a patient level, although this aspect is comparatively less well developed at present and many challenges remain (e.g. cost-effectiveness evaluations, reductions in turn-around times (Workshop 1, D-23-00144). At a public health level, the detection of emerging threats and the design and assessment of suitable interventions, particularly around supporting treatment recommendations and shaping vaccine formulations, has been well demonstrated (Workshop 2, D-23-00145). The use of genomics for AMR surveillance at One Health interfaces has similar applications and is already operating effectively for foodborne diseases in some regions (Workshops 2, D-23-00145, and 3, D-23-00146). However, further applications in transmission risk assessment frameworks, and exploiting environmental monitoring were also

identified in the One Health surveillance domain (Workshop 3, D-23-00146). A major finding of the group was the need to define a framework for the application of genomics in AMR surveillance and to identify and advocate for potential use cases. Each workshop report therefore highlights some of the key applications relevant to each domain.

3.3 Challenges

The common framework used for each workshop enabled the group to reflect on the shared and distinct barriers to the use of genomics for AMR surveillance. Common issues included a lack of resources and political will, underlining the importance of clear use cases and advocacy in parallel with robust cost effectiveness studies, and the need for more training, particularly around bioinformatics. The Hospital & IPC workshop explored many of the basic practical barriers associated with establishing genomic surveillance; including a lack of meaningful epidemiological surveillance or microbiology infrastructure, poor supply chains and pricing structures, and issues around cooperating effectively in hub and spoke models. Major difficulties in the Public Health and International sphere were the need to build trust and cooperation among stakeholders and work toward harmonised surveillance underpinned by strong data governance. And finally, the challenges facing surveillance at One Health interfaces reflected the even more complex set of relationships required to define common goals and cooperate across national ministries and public and private sectors, which underlined the need to pre-define how surveillance information would be used.

4. Where to from here?

Since the clinical introduction of antimicrobials in the 1940s, it has become clear that we will remain locked in an ongoing arms race with bacterial pathogens indefinitely. The generation of actionable AMR surveillance data, particularly at the resolution offered by genomics, will provide invaluable information to support efforts to limit the spread and impact of AMR.

Many of the recommendations made by the working group overlap between isolate-based AMR surveillance and pathogen genomic surveillance more generally (e.g. Recommendation four; Harmonise and standardise surveillance), highlighting the interconnected nature of this work and the areas from which common solutions to harnessing genomic surveillance for AMR might be drawn. For example, similar themes around Recommendation five (Agree equitable data governance and sharing) are seen in the recent WHO recommendations on pathogen genomic data sharing that were released during the conduct of the working group[9] (and see further in Workshop 2, D-23-00145).

Ultimately, the working group recommends these nine activities as central to achieving the potential of genomics for AMR surveillance. Their relative ordering and importance differed by domain and geographical setting, which is further elaborated on in individual workshop reports (see Box). These recommendations should guide ongoing and new discussion among stakeholders in the AMR genomic surveillance space, including those in genomics and AMR research, technology development, bioinformatics, clinical and public health roles, funding, education, and policy (Appendix page 6). We are on the cusp of realising the full potential for genomics in tackling AMR, but much work is still needed.

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Figure legends

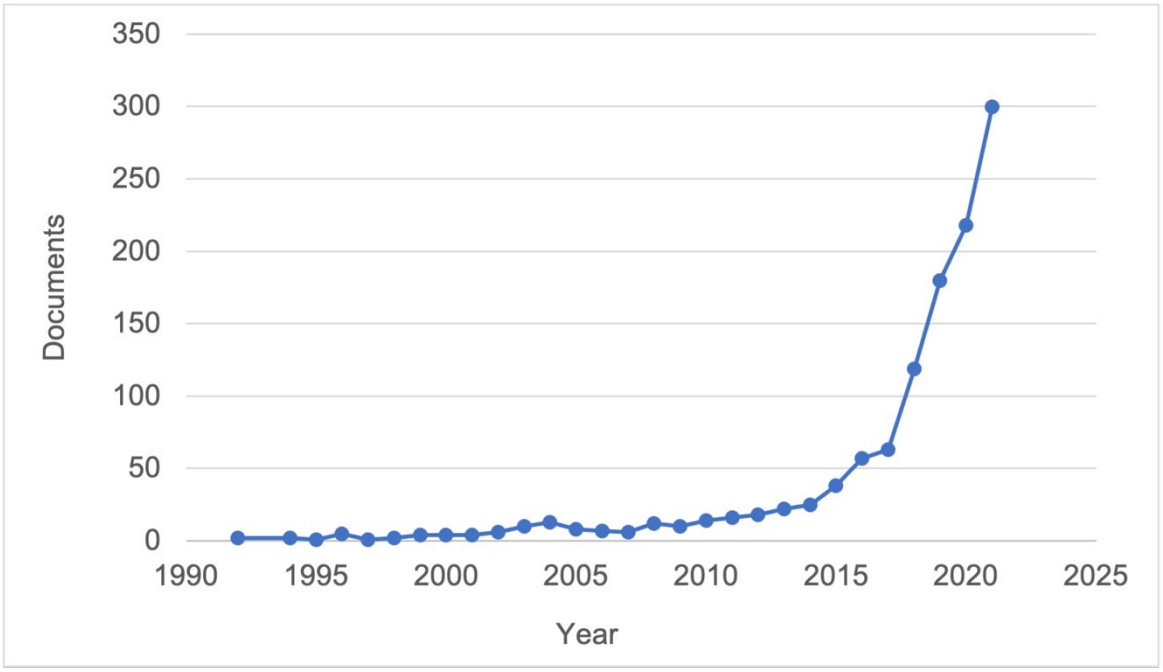

Figure 1. The building evidence base for the use of genomics in surveillance of antimicrobial resistance. The release date of 1,162 publications between 1992 and 2021 retrieved by the following search terms in SCOPUS: (TITLE-ABS-KEY (amr OR antibiotic AND resistan* OR antimicrobial AND resistan*) AND TITLE-ABS-KEY (genomic*) AND TITLE-ABS-KEY (surveillance OR monitoring).

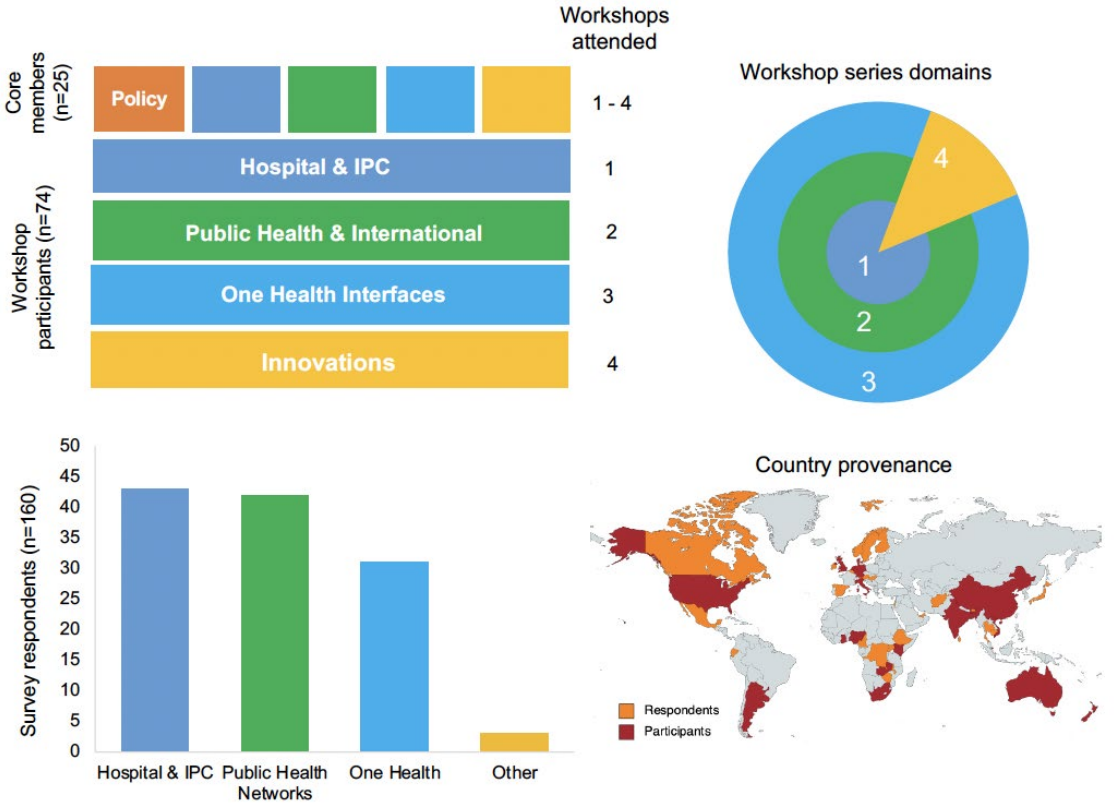

Figure 2. Composition and workflow of the working group. The core working group (mixed expertise) and workshop participants (drawn on for domain expertise) **(upper left)** participated in a series of three nested workshops relating to those domains (1 – 3), and one cross-cutting, workshop (4) **(upper right)** coloured according to the inlaid labels. Consensus statements and recommendations developed from the workshops were then put to a larger set of members of the AMR community with similar domain expertise **(lower left)**. Expertise was drawn from a diverse geographical range **(lower right)**.

Box. Prioritised recommendations from the working group*

1. **Define a framework for use at all levels**
   The aims, actions, and outcomes of genomic AMR surveillance data need to be clearly defined at all levels; for example, clinical applications rely on robust inference of phenotype from genotype, while clearly defined risk mitigations are needed for One Health.

2. **Build capacity, including in hub and spoke models**
   The cost-effectiveness of genomics improves with throughput but differs markedly by geographical region. These barriers can be partly overcome by initiating genomics in regional hub and spoke models to centralise training, infrastructure, and supply chains.

3. **Develop new training competencies**
   Competencies in genomic epidemiology are required for health scientists conducting genomic AMR surveillance either as a new workforce or developing/delivering training for existing staff categories.

4. **Harmonise and standardise surveillance**
   Agree a common, abbreviated list of bug/drug combinations also informed by local needs; develop clinical standards; support pathogen-specific expert review groups for interpretation guidelines; and develop a single access user portal. Agree sampling frameworks for One Health.

5. **Agree equitable data sharing and governance**
   Benefits are maximised with open, immediate data sharing, but concerns exist around stigmatisation and inequitable data contribution and use. Robust governance is critical, and should be based on lessons from SARS-CoV-2 and in line with the WHO global genomic surveillance strategy.

6. **Improve stakeholder interactions and relationships**
   Improved trust, communication, and partnerships among stakeholders are particularly important for network and One Health surveillance. Policy makers need to define key questions. Researchers and health deliverers should consolidate and advocate clear use cases.

7. **Address funding models and evaluate cost effectiveness**
   Funding models are needed for research and capacity-building programmes, surveillance implementation, and continuous improvement, particularly for One Health surveillance with a breadth of stakeholders. Real-time cost-effectiveness studies are needed.

8. **Invest in AMR genomic surveillance innovations**
   Genomic surveillance innovations (clinical and environmental metagenomics, gene/plasmid tracking, and machine learning) offer advantages, but research to address the common barrier of an uncharacterised association with health outcomes is needed.

9. **Better integrate environmental surveillance**
   The environment is an under-surveyed potential source of AMR genes. Examples from agriculture where a direct impact of AMR surveillance and interventions have been characterised need to be built upon and expanded.

* Although many of these themes are cross-cutting across domains, each is given focus in one or more subsequent workshop reports which should be accessed for more information. Specifically, D-23-00143 focuses on recommendations 1 -3, D-23-00144 on

recommendations 2 and 4 – 6, D-23-00146 on recommendations 1 and 7, and D-23-00147 on recommendations 8 and 9.

References

1. Antimicrobial Resistance Consortium. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet* 2022; **399**(10325): 629-55.
2. O'Neill J. Tackling drug-resistant infections globally: final report and recommendations United Kingdom: Wellcome Trust HM Government, 2016.
3. Nelson RE, Hatfield KM, Wolford H, et al. National Estimates of Healthcare Costs Associated With Multidrug-Resistant Bacterial Infections Among Hospitalized Patients in the United States. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2021; **72**(Suppl 1): S17-S26.
4. World Health Organisation . Global Action Plan on Antimicrobial Resistance, 2016.
5. World Health Organisation. GLASS whole genome sequencing for surveillance of antimicrobial resistance, 2020.
6. Kwong JC, McCallum N, Sintchenko V, Howden BP. Whole genome sequencing in clinical and public health microbiology. *Pathology* 2015; **47**(3): 199-210.
7. The Cryptic Consortium. A data compendium associating the genomes of 12,289 Mycobacterium tuberculosis isolates with quantitative resistance phenotypes to 13 antibiotics. *PLoS biology* 2022; **20**(8): e3001721.
8. The SEDRIC genomics working group. Harnessing Genomics for AMR surveillance, 2022.
9. World Health Organisation. Global genomic surveillance strategy for pathogens with pandemic and epidemic potential 2022 - 2032: World Health Organisation, 2022.