Harnessing Genomics for Antimicrobial Resistance Surveillance 2

Genomics for antimicrobial resistance surveillance to support infection prevention and control in health-care facilities

Elita Jauneikaite, Kate S Baker, Jamie G Nunn, Janet T Midega, Li Yang Hsu, Shweta R Singh, Alison L Halpin, Katie L Hopkins, James R Price, Padmini Srikantiah, Beverly Egyir, Iruka N Okeke, Kathryn E Holt, Sharon J Peacock, Nicholas A Feasey, for the SEDRIC Genomics Surveillance Working Group

Integration of genomic technologies into routine antimicrobial resistance (AMR) surveillance in health-care facilities has the potential to generate rapid, actionable information for patient management and inform infection prevention and control measures in near real time. However, substantial challenges limit the implementation of genomics for AMR surveillance in clinical settings. Through a workshop series and online consultation, international experts from across the AMR and pathogen genomics fields convened to review the evidence base underpinning the use of genomics for AMR surveillance in a range of settings. Here, we summarise the identified challenges and potential benefits of genomic AMR surveillance in health-care settings, and outline the recommendations of the working group to realise this potential. These recommendations include the definition of viable and cost-effective use cases for genomic AMR surveillance, strengthening training competencies (particularly in bioinformatics), and building capacity at local, national, and regional levels using hub and spoke models.

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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 Clinical Infection, Microbiology, and Immunology, University of Liverpool, Liverpool, UK** (Prof K S Baker PhD)**; Department of Genetics, University of Cambridge, Cambridge, UK** (Prof K S Baker)**; Infectious Disease Challenge Area** (J G Nunn MSc) **and Drug Resistant Infections** (J T Midega PhD)**, Wellcome Trust, London, UK; Saw Swee Hock School of Public Health** (Prof L Y Hsu MPH, S R Singh PhD) **and Yong Loo Lin School of Medicine** (Prof L Y Hsu)**, National University of Singapore, Singapore; Division of Healthcare Quality Promotion, US Centers for Disease Control And Prevention, Atlanta, GA, USA** (A L Halpin PhD)**; HCAI, Fungal, AMR, AMU, and Sepsis**

Background

Whole-genome sequencing has substantial potential to improve pathogen surveillance. At the health-care facility level, genomics can provide an unparalleled high-resolution picture of the antimicrobial-resistant pathogens associated with outbreaks. However, realisation of this potential requires the rapid generation of actionable information from genomic data that will enable targeted, effective, and timely infection prevention and control measures to be instituted. Although much progress has been made in recent years, fulfilling the promise of genomics for routine antimicrobial resistance (AMR) surveillance remains a major challenge.

To meet this need, the Surveillance and Epidemiology of Drug-resistant Infections Consortium (SEDRIC) working group on genomic surveillance for AMR convened a series of four workshops across different domains, including the use of genomics in health-care facilities (see the first paper in this Series[1] for an overview of the workshops). On March 17, 2022, workshop participants came together to: (1) conduct a situational analysis of the use of genomics for local surveillance of AMR and health-care associated infections; (2) reach a qualified consensus on the value of genomics for AMR surveillance in health-care facilities, including hospitals in different regions of the world; and (3) develop and prioritise recommendations for genomic surveillance to reach its maximum potential benefit in health-care settings. Here, we summarise the discussion from the working group and highlight key findings, including the need to define viable use cases and advocate these to policy makers and funders to stimulate capacity building, to develop new training competencies for the analysis and interpretation of genomic data, and to invest in the development of genomic surveillance innovation in health-care settings. Enacting these recommendations will ensure that pathogen whole-genome sequencing has genuine utility for enhancing infection prevention and control and clinical management.

Advantages and applications of genomics for AMR surveillance in health-care facilities

Health-care associated infections are among the most serious adverse events encountered by hospitalised patients globally, affecting around 7% of patients in high-income countries and around 15% of patients in low-income and middle-income countries (LMICs).[2] Health-care associated infections increase pressures on health-care staff, including infection prevention and control teams, and add a substantial economic burden. For example, health-care associated infections are estimated to cost the UK's National Health Service £2 billion a year.[3] Although health-care associated infections are caused by a diverse range of rare and common bacterial species (which each form complexes of subspecies and strains with varying properties), a relatively small subset of these bacterial subtypes account for a substantial majority of the AMR burden.[4,5] Pathogen surveillance is a key component of infection prevention and control strategy, particularly when detecting and responding to outbreaks. However, at the facility level, the resolution of pathogen identification is typically at species

Division and Antimicrobial Resistance and Healthcare Associated Infections Reference Unit, UK Health Security Agency, London, UK (K L Hopkins PhD)**; Global Health and Infection, Brighton and Sussex Medical School, University of Sussex, Brighton, UK** (J R Price PhD)**; Global Health Division, Bill & Melinda Gates Foundation, Seattle, WA, USA** (P Srikantiah MD)**; Department of Bacteriology, Noguchi Memorial Institute for Medical Research, University of Ghana, Legon-Accra, Ghana** (B Egyir PhD)**; Department of Pharmaceutical Microbiology, Faculty of Pharmacy, University of Ibadan, Ibadan, Oyo State, Nigeria** (Prof I N Okeke PhD)**; Department of Infection Biology, London School of Hygiene & Tropical Medicine, London, UK** (Prof K E Holt PhD)**; Department of Infectious Diseases, Central Clinical School, Monash University, Melbourne, VIC, Australia** (Prof K E Holt)**; Department of Medicine, University of Cambridge, Cambridge, UK** (Prof S J Peacock PhD)**; Clinical Sciences, Liverpool School of Tropical Medicine, Pembroke Place, Liverpool, UK** (Prof N A Feasey PhD)**; Malawi Liverpool Wellcome Research Programme, Chichiri, Blantyre, Malawi** (Prof N A Feasey)

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

For details of the **SEDRIC working group** see https://sedric.org.uk/working-groups/

level only, which offers very limited discriminatory power for epidemiological analysis and little insight into the genetic basis for AMR properties of the pathogen under investigation.

Genomic AMR surveillance of pathogens isolated from health-care associated infections can transform the resolution at which the causative agent of infection is routinely characterised, going far beyond that provided by the species-level identification typically offered by diagnostic laboratories. Isolates can be discriminated at the level of genomic subtypes (eg, multilocus sequence types, or core genome multilocus genome types) to identify facility-level trends, or at the level of single nucleotide polymorphisms to give a fine scale resolution of outbreaks. Owing to the diversity and dynamic nature of the organisms involved in health-care associated infections, applying a one-size-fits-all cutoff (eg, defining a given distance in single nucleotide polymorphisms) to determine the relatedness between isolates has been challenging. Therefore, various approaches have been developed and applied to identify clusters of related cases that consider both the organisms and the context in setting relatedness thresholds, as well as integrating relevant epidemiological data (eg, ward location and patient movement data).[4,6,7] In addition, by characterising the entire genome, genotypic determinants of AMR and virulence can be identified.

Numerous studies have shown the use of genomic approaches to investigate health-care associated infections and outbreaks. However, most of these studies have been retrospective, reporting after the outbreak had ended, and were often dependent on sequencing and analytical capacity confined to research or reference laboratories. As such, despite many reports on the potential benefits of genomics to better understand health-care associated infections, identify sources of infections, and inform specific measures for infection prevention and control, challenges remain before genomic AMR surveillance becomes routine. One of the overarching findings of the SEDRIC working group was the need for the articulation and advocacy of use cases and to that end, we highlight specific applications of genomics in health-care settings.

Facilitating outbreak investigations and supporting infection prevention and control

With current technologies and turnaround times, outbreak investigation and providing support for infection prevention and control is the best use of genomics for AMR surveillance in health-care facilities. The investigation of an outbreak of meticillin-resistant *Staphylococcus aureus* (MRSA) in a neonatal intensive care unit that identified a staff member carrying MRSA as the likely reservoir of a persisting outbreak, and whose treatment terminated the outbreak, provided the seminal demonstration of the use of genomics for infection prevention and control.[8] Subsequent studies have shown that genomic analyses can be essential for both ruling in and ruling out health-care associated infections as part of outbreaks and defining outbreak inclusion criteria, which are vital for deciding whether to execute or withhold costly infection prevention and control measures and, in some cases, determine legal or other penalty ramifications. Genomic analysis of health-care associated infections can elucidate complex epidemiological patterns, including the emergence of new strains, endemic circulation of others that could have been addressed before an outbreak incident, identifying otherwise undetected outbreak events, and the expansion of new multidrug-resistant strains over time.[9–11] Given that most of these studies have been completed retrospectively, their ability to show measurable improvements in outcomes has been limited. However, a recent landmark prospective implementation of genomics for AMR surveillance across multiple hospitals in Australia showed the benefit of real-time genomics for the control of antimicrobial-resistant health-care associated infections.[12,13] This study analysed several thousand organisms and found that a quarter of multidrug-resistant infections were acquired in hospital, that most transmission events would have been missed without the use of genomics, and that the prospective implementation of genomics had a major impact on infection prevention and control measures.[12,13]

Genomics has also been used to identify the sources and transmission pathways of health-care associated infections and the mobile genetic elements carrying AMR. In particular, genomics provides the ability to differentiate between health-care associated infections and community-acquired infections, as well as person-to-person transmission routes versus environmental sources of infection within a facility. For example, studies of vancomycin-resistant enterococci among hospital patients have found a complex mixture of health-care associated infection origins, highlighting both invasive infection with isolates a patient was otherwise carrying asymptomatically (ie, autoinfection) and infections apparently from the environment.[14,15] A recent study in Malawi found largely indistinguishable genetic diversity among community-acquired and health-care associated extended-spectrum β-lactamase-producing Enterobacterales infections, suggesting that autoinfection might be more common than previously thought.[16] Genomics has been similarly instrumental for identifying environmental sources of infection of *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and other bacteria (eg, Enterobacterales), including tracking the movement of AMR genes and resistance plasmids (explored further in the fifth paper in this Series[17]).[9,18–20] Genomics has also been used to explore vertical transmission from mothers to neonates, with multiple pathogens that were thought to be primarily vertically transmitted (eg, Group B *Streptococcus* and organisms causing neonatal sepsis) also found to be health-care associated infections, indicating the need to re-evaluate current intervention practices.[21–24] As such, although the main strength of genomics for supporting

infection prevention and control is the investigation of outbreaks, its application in the longer term and the findings of other focused studies can also inform broader strategy.

Informing patient management

Genomic data are being increasingly used to augment phenotypic antibiotic susceptibility testing for emerging multidrug-resistant pathogens such as *Neisseria gonorrhoeae*[25] and carbapenemase-producing Enterobacterales.[26] However, more work is required to validate, establish, and align bioinformatic predictions between laboratories[26] and create molecular definitions, which will necessitate partnerships between standards agencies, academics, and public health workers (see the third and fifth papers in this Series[17,27]). The diversity of carbapenemase genes in carbapenemase-producing Enterobacterales makes molecular diagnostic testing challenging, with clinical molecular tests targeting common carbapenemase family genes (eg, genes encoding IMP, VIM, OXA-48, NDM, and KPC), while not detecting other genes encoding products with carbapenemase activities (eg, GES-5).[28] Establishing antimicrobial susceptibility profiles of Gram-negative bacteria on the basis of genomic data is thus a challenge and an opportunity. Diagnostic microbiology laboratories have long used predictive rules to help issue phenotypic susceptibility results. The complexity of both resistance determinants and the spectrum of action of new antimicrobial agents or combinations necessitates the use of more complex algorithms to assess whole-genome sequencing data, accelerate the release of user-friendly results, and facilitate the development of antimicrobial prescribing decision support tools for clinical microbiologists and front-line clinicians.

To establish best practice in using genomic data to inform diagnostic testing and infection prevention and control interventions, we can draw on experience gained in genotyping other pathogens for which drug resistance is important in ongoing management of chronic infections, such as HIV and *Mycobacterium tuberculosis,*[29,30] both of which were outside the scope of this working group. We can also consider where genomics has been used to characterise long-term infections with antimicrobial-resistant organisms among patients with chronic health conditions. For example, genomics has been used to study the evolution of AMR in *P aeruginosa* in patients on antimicrobial therapy, which might previously have been considered infection with a new strain,[18,31–33] and similarly elucidated the longitudinal within-patient and transmission dynamics of *Mycobacterium abscessus* among patients with cystic fibrosis.[34,35] With improved interpretability and turnaround times, and for patients with chronic infections, genomics offers the potential to inform clinical management. However, to maintain predictive sensitivity in the face of the emergence of novel resistance variants, genomic surveillance programmes will need to be supported by a degree of ongoing phenotypic testing, which can be quantitatively assessed to remain clinically useful.[36]

Barriers to genomics implementation for AMR surveillance in clinical settings

As already indicated, the barriers to routine implementation of whole-genome sequencing are formidable, especially in LMICs.[37] These barriers include set up and running costs, which are hampered by poor distribution networks and supply chains in many LMICs that might otherwise deploy genomic AMR surveillance as a leapfrog technology to skip over targeted-molecular expansion of isolate-based phenotypic surveillance.[38] Even where supply chain and distribution networks are less of an issue, an absence of demonstrable cost-effectiveness is hampering implementation. A recent literature review identified only nine, poorly harmonised, studies focused on the financial benefits of genomic surveillance in hospitals and for foodborne pathogens in high-income countries, and one upper-middle-income country.[39] As such, there is a clear need to continue to build a holistic evidence base for the use of genomics in clinical settings, which is a policy decision requiring complex, multifaceted information.[40]

There are further substantial challenges in analysing, interpreting, and sharing genomic data, including a shortage of bioinformaticians, delivery of quality assurance processes for laboratory sequencing, and bioinformatic analysis and reporting. Improving the development and delivery of clinically actionable information (including reduced turnaround times and biological interpretability) will also increase enthusiasm for genomic AMR surveillance among health-care professionals. Prolonged turnaround times associated with isolate-based sequencing might eventually be overcome through the development of clinical metagenomic approaches, where microbial genomic data is generated directly from complex patient samples, usually with some form of enrichment. Such approaches have the potential to be transformative for the diagnosis and management of complex, polymicrobial infections, but remain some distance from implementation in the clinic (see the fifth paper in this Series[17] for further details).

Recommendations from the working group

To address the challenges described, the working group proposed a series of recommendations to facilitate genomic AMR surveillance as part of clinical diagnostics, health-care associated infection and outbreak investigation, and to inform real-time infection prevention and control measures.

Define a framework for use at all levels

There is a continued need to strengthen, disseminate, and advocate the evidence base for genomics implementation to support infection prevention and control in health-care facilities. The communication of guidelines and viable use

cases for implementing genomics for AMR surveillance will be key to widespread uptake and there is some promising practice in this area.[41] Wider discussion and coverage of implementation experiences in the public domain will accelerate momentum for the application of genomic AMR surveillance in the clinic and help practitioners to convince policy makers in other settings. To this end, there is also a need to further develop the economic case through both retrospective and prospective cost-effectiveness evaluations, for which little information is currently available.[39] Economic case studies are necessary to persuade health-care decision makers of the long-term benefits of genomic AMR surveillance while acknowledging that start-up costs are high, so returns on investment are only likely to be realised in the medium to long term. The identification of priority pathogens (ie, those identified by WHO and the Global Antimicrobial Resistance and Use Surveillance System pathogen lists) in local health-care settings should be used as case studies to show the effectiveness of genomic surveillance in control and demonstrate improvements in patient management and care.

Cooperation and communication among all of the relevant groups involved with delivering health care (ie, clinicians, microbiologists, infection prevention and control teams, and public health practitioners) will strengthen the political case for adopting routine genomic AMR surveillance by showing that data generated by implementation at one level (eg, for clinical microbiology or infection prevention and control support) will also serve functions at other levels of delivery (eg, for public health surveillance; see the third paper in this Series[27] for further details). Notably, a range of innovations in microbial genomics are in development that would substantially increase the richness of information generated and potentially reduce costs of AMR genomic surveillance data for a variety of functions (see the fifth paper in this Series[17]), including clinical decision making and for action at a public health level. Ultimately, a combined advocacy approach using evidence from various levels of health provision will strengthen the case to health ministries for further investment in these technologies.

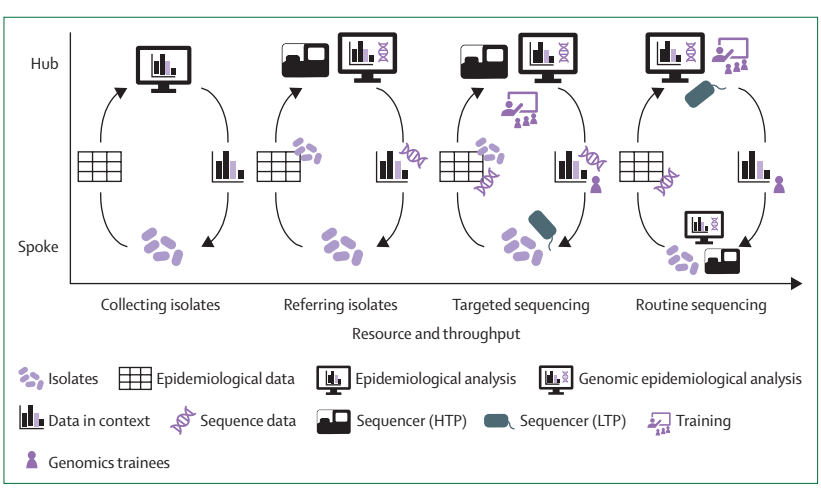

Figure: **Proposed frameworks for the implementation of genomics in hub and spoke models, scaled to increasing resource and throughput**
The role of the hub would transition over time from being a centre for sequencing to becoming a provider of training and other services (eg, analytical services and external quality assessment) as the system grows. LTP=low throughput. HTP=high throughput.

Develop new training competencies

Across all workshops, the working group identified a shortage of appropriately trained individuals as a substantial barrier to the uptake of genomics for AMR surveillance. This is particularly the case for bioinformaticians, where both development and retention of individuals in the sector are key challenges. Current best practice in microbial genomics delivery in health-care facilities is often supported by academic partnerships or functional relationships with reference laboratories, which should continue and be encouraged. However, longer term implementation supported by health-care budgets will require a substantial increase in bioinformatic analytic capacity, which should be addressed in several ways. There is a need to substantially increase bioinformatics training at both undergraduate and postgraduate levels, highlighting the need to rally policy makers, educational leaders, and funders to the cause of genomic health-care surveillance. This should be complemented by the development of training for existing workforces through the development of additional training competencies for diagnostic microbiology laboratory staff to generate, process, analyse, and quality assure genomic data. There is also a need to develop training for clinical microbiologists to interpret genomic data in laboratory outputs and develop reports containing actionable information for infection prevention and control teams. Furthermore, as sequencing technologies and analytical tools continue to rapidly evolve, developing and maintaining continuing professional development will be as important as any initial training programmes.

Analytical bioinformaticians in infection prevention and control teams will need to be supported with relevant training and access to validated, automated pipelines developed and maintained through public health laboratories partnered with specialist academic groups (figure; for more details see the third paper in this Series[27]). This model of pipeline execution and interpretation in local laboratories will deliver timely generation, analysis, and sharing of whole-genome sequencing outputs to aid clinical management and infection prevention and control. However, this model also requires substantial training and strengthening of the bioinformatic workforce at the regional public health or reference laboratory level, who would need different technical competencies (eg, pipeline development, methodological benchmarking, automation, software engineering, and health informatics). A substantial body of work is required to define and map the optimum skills and competencies across these health-care roles (rather than merging all individuals in a general

bioinformatician category), and this will differ by facility and national setting. In some settings, there is an opportunity to draw on current practice in other areas of medicine (eg, paediatrics and oncology) where the use of validated human genomic data is more common. Bioinformatic technical competency mapping, development, and delivery will be key to driving success and workforce capacity building and could be led by national and regional reference laboratories (for more details see the third paper in this Series[27]).

Build capacity with hub and spoke models

Establishing microbiological isolate-based AMR surveillance is a crucial preceding step to integrating genomic approaches as routine. This represents a key barrier given that many areas still do not have appropriate clinical microbiological expertise and facilities. Momentum in this area is building through AMR national action plans and global initiatives and is an initial essential area for investment (figure).

Most health-care facilities do not have the personnel and resources for genomic sequencing. Centralising sequencing services in a hub (eg, national or regional reference laboratory) as part of a hub and spoke model would allow benefits from economies of scale, although this could also lead to extended turnaround times compared with local sequencing. Concentration of sequencing operations in fewer laboratories increases throughput and strengthens the negotiation position with industry to obtain better pricing for service contracts and consumables. This is particularly important in LMICs where, despite improvements in the availability of platforms and supply chains during the COVID-19 pandemic, the cost per genome is substantially higher—in large part owing to highly variable reagent and maintenance costs. Notably, in many high-income countries, clinical microbiology and other diagnostic pathology services are often already centralised in hubs, sometimes run by the private sector. Developing and articulating clear use cases and benefits of genomics for AMR surveillance will be vital in incentivising these stakeholders to invest in genomic technologies and share their data with public health providers. Hub laboratories might also act as analytical hubs, hosting computational or web-based platforms that allow other laboratories undertaking genome sequencing to submit data to conduct their own analyses or receive an output that places their data into context.

Advocating for hub and spoke models is not intended to stifle front-line laboratories from adopting genomics platforms (figure). While recognising the role of the hub as the putative lead entity, generation and analysis of genomic data at spoke facilities serves different valuable functions to analyses undertaken at a regional or national level, both of which are important (see use cases outlined in the previous section, and those in the third paper in this Series[27]). Crucially, local sequencing can improve turnaround times, which might be essential for realising potential improvements in clinical outcomes at the patient level. Whether individual laboratories send isolates for sequencing by hubs or submit locally generated genome sequence data for hub-level analysis (eg, public-health-level surveillance, see the third paper in this Series[27]) will depend on the needs and resources of the system (figure). The use of a hub and spoke model will vary by setting and successful implementation of genomics will depend on developing good relationships between hub and spoke laboratories based on mutual benefit and exchange of expertise and materials. As such, there is a need for continued investment in mechanisms that strengthen and maintain these relationships so that hub laboratories can incentivise the submission of materials and data through advocacy of the utility of the data and the provision of useful information to submitting laboratories. Equally, spoke laboratories will need to show adherence to programmes of recognised standards, such as those for quality assurance and laboratory accreditation. For example, hub laboratories could provide monthly reporting summaries, presentation of the data in the regional or national context, and advice on interpretive criteria based on data received. Ultimately, hubs could take on centralised analytical and training roles. Owing to the increased turnaround times in a centralised model, feedback from hubs to spokes will need to provide benefit outside of the timeframes of patient management, and so should instead be focused on infection prevention and control and longer term concerns.

Conclusions

The barriers and solutions to implementation of genomics in health-care settings highlighted here indicate the need for a holistic solution, with the maximum benefit being achieved by a cooperative and healthy system of supported delivery in individual health-care settings and upward referral to regional, national, and global health-care networks. Training of the workforce in sequencing and bioinformatic techniques and overall capacity building to analyse and interpret data within hospital settings was highlighted as a particular need. There is also a need to engage multiple stakeholders to develop validated protocols, and for quality assurance processes for sequencing and bioinformatics. Finally, the working group recognised the need for improved clarity and advocacy of use cases for genomics implementation within the individual settings.

Contributors

SJP, NAF, KSB, EJ, JGN, and JTM conceptualised the paper. KSB, EJ, and JGN curated all data. KSB, EJ, and JGN did the formal analysis. SJP, NAF, JGN, and JTM did the funding acquisition. SJP, NAF, KSB, EJ, JGN, and JTM did the investigation. SJP, NAF, KSB, and EJ contributed to the methodology. SJP, NAF, KSB, EJ, JGN, and JTM did the project administration. SJP, NAF, KSB, and EJ supervised the project. KSB prepared the original visualisation. KSB, EJ, NAF, LYH, and SRS wrote the original draft. All authors reviewed and edited the manuscript, and engaged and participated in the workshops.

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