

The value of local use cases for expanding pathogen genomics in resource-limited settings

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Locally relevant use cases can maximize national support for genomic sequencing in low- and middle-income countries.

The COVID-19 pandemic elevated pathogen genomics as a routine tool for disease surveillance and outbreak investigation. Sequencing enables high-resolution subtyping of pathogens, inference of phenotypes such as antimicrobial resistance (AMR), streamlined laboratory workflows and improved biosafety. Furthermore, the technology is evolving rapidly, with costs continuing to fall and platforms increasingly automated.

Although genomics may be useful across public health, its utility is not uniform. Low- and middle-income countries (LMICs), where genomics is relatively new outside of research, must prioritize those use cases that drive national decisions and outcomes rather than diffuse, predominantly global benefits.

Recent reviews^{1–3} have focused on developing genomic capacity in low-resource settings, especially to support research. This paper focuses on the use of pathogen genomics operationally – as a routine public-health or clinical tool to inform decision-making in real time for specific populations or patients – rather than as a tool to advance science. Importantly, we emphasize identifying and implementing use cases (Box 1) with clinical, public health or commercial utility to the country generating the data. We believe this emphasis increases sustainability while also yielding global benefits.

For genomics to have an impact, sequencing and bioinformatics capacity by themselves aren't enough: genomics activities need to be well targeted and inform decision-making.

Considerations in the choice of use cases

Historically, the application of genomics in LMICs has been driven by external priorities, which have primarily emphasized use cases with global benefits. For sustainability and equity, genomic sequencing should also generate national benefits – aligning with country priorities and contributing towards decisions or outcomes. Regardless of whether the impact is primarily national or global, the driving consideration in the choice of use cases should be the potential health impact.

The central question in choosing appropriate use cases is whether genomic data will influence decision-making. Diseases with a high burden or high visibility are often the first considered, but they might not be ideal targets if genomic information cannot directly inform action. The most impactful use cases are those with clearly articulated objectives and pathways to influence (Fig. 1).

During the COVID-19 pandemic, many LMICs developed genomics capacity for the first time, typically limited to tracking SARS-CoV-2 variants. Many have since begun to explore wider applications of pathogen

genomics and to assess which use cases offer the greatest national value, what is required for meaningful implementation, and where genomics should reside among competing health priorities. For health systems in LMICs to be genuinely empowered, they must identify and test those use cases that are most relevant to their contexts. Practical experience remains the best guide.

Example 1: malaria genomic surveillance to monitor drug resistance. Routine malaria molecular surveillance (MMS) using dried blood spots has the potential to serve several use cases simultaneously^{6,7}, particularly monitoring antimalarial resistance and detecting *hrp2/3* deletions. Resistance monitoring through amplicon sequencing can inform empirical treatment policies at national or sub-national levels, and knowledge of *hrp* deletions can guide diagnostics policy decisions. Demonstration projects in low-resource settings have shown the feasibility of sequencing key genes, including resistance and the circumsporozoite protein vaccine target⁸, with per-sample costs as low as US \$35.

Example 2: genomic drug-susceptibility testing in tuberculosis treatment. Whole genomic sequencing (WGS) or targeted next-generation sequencing (tNGS) of *Mycobacterium tuberculosis* (MTB) has replaced traditional drug-susceptibility testing in several high-income settings⁹. With high accuracy in detecting drug resistance¹⁰ and faster turn-around times, this approach is mainly constrained by cost. World Health Organization (WHO) analyses suggest that tNGS is already less expensive than current practice in India and would be cost-effective elsewhere under certain assumptions¹⁰. As sequencing costs fall, genomics may replace traditional methods globally as the primary technology for inferring drug susceptibility. Given the magnitude of the global TB burden, this use case could catalyse genomics capacity across LMICs.

An additional use case involves using MTB phylogeny to identify transmission clusters for targeted public-health interventions. This could make use of WGS or leverage data generated through tNGS-based drug-susceptibility testing. Although this use case has traditionally been considered less relevant in high-burden countries, wider availability of MTB genomic data may change that¹¹.

Technical considerations

The requirements stack. Genomic surveillance capacity encompasses far more than sequencing equipment and technical expertise. Having an impact requires a full 'stack': obtaining representative specimens with relevant clinical or epidemiological data; conducting sequencing and bioinformatic analysis; integrating genomic sequences with appropriate metadata and contextual information

BOX 1

How a use case achieves public health impact

A use case refers to a specific application of nucleic acid sequencing for a defined pathogen (for example, *Plasmodium falciparum*) or pathogen group (for example, bacterial agents of foodborne disease) for a discrete purpose (for example, detection of outbreaks of bacterial foodborne disease).

Sequencing for a single pathogen may support multiple use cases. For MTB, sequencing can allow clinicians to infer drug susceptibility to guide treatment¹⁰, identify transmission clusters and high-risk settings, or investigate those clusters. These are distinct objectives — distinct use cases — even if the same specimens are sequenced.

There are several ways in which a use case might have impact. The six categories in the framework below often overlap. The impact of a particular use case can often be explained by answering two or more of the questions posed. Although it might be possible to answer several of these questions for a particular use case, the simplest, most succinct statements of impact are generally the most compelling.

- **Clinical decision support.** Do sequencing data change individual patient management? For example, genomic sequencing of MTB might allow faster and more accurate detection of drug resistance, thereby enabling prompt, effective therapy.
- **Public-health decision support.** Does sequencing inform programme or policy decisions? For example, sequencing of SARS-CoV-2 during the COVID-19 pandemic provided useful context for decision-making. In late 2021, knowledge that the Omicron variant was spreading globally better prepared ministries of health for the consequent rise in cases; this knowledge averted unproductive and potentially distracting investigations into the cause of the increase.
- **Product development.** Does sequencing inform product development? Sequencing of seasonal influenza viruses and SARS-CoV-2, for example, informs the development of vaccines, diagnostics and therapeutics.
- **Preparedness.** Does sequencing improve readiness for emerging threats? Arguably, most use cases improve preparedness, as sequencing is useful in the investigation of and response to outbreaks of infectious disease, including outbreaks of unknown aetiology.

- **System efficiency.** Does sequencing reduce costs, delays or workload relative to standard methods? Health systems have finite resources. Interventions that improve the efficiency of the system, freeing up those resources, necessarily have a positive impact. For example, the use of genomic sequencing to identify MTB drug susceptibility may eventually be less expensive and more timely than traditional drug-susceptibility testing.

- **Pre-requisite intelligence.** Does sequencing provide essential antecedent information? Determining the serotype diversity of pneumococcus in a country might inform the decision about whether to adopt the pneumococcal vaccine and which vaccine to adopt. Similarly, knowledge of the pre-existing genetic diversity of a pathogen informs interpretation of genomic epidemiologic trends after vaccination has begun.

Almost all use cases, including those below, provide at least some degree of both national and global benefit. Nonetheless, it is important to be clear and realistic about the expected beneficiaries and not to presume that benefits will be universal.

- **Examples of use cases with national benefit.** Examples include outbreak detection and investigation or genomic determination of antimicrobial resistance to guide therapy in a specific patient. Similarly, genomic surveillance for resistance can inform presumptive therapy recommendations at a national or subnational level.
- **Examples of use cases with global benefit.** Examples include genomic surveillance of SARS-CoV-2 and seasonal influenza to inform the development of diagnostics, vaccines and therapeutics, and research to advance general scientific knowledge (as opposed to research to guide local actions). There are arguably multiple use cases for genomic surveillance of SARS-CoV-2 or seasonal influenza: (1) to inform the development of vaccines, therapeutics and diagnostics; (2) to detect clusters and provide other situational awareness; (3) to investigate clusters of disease. The first provides primarily global benefits and the latter two primarily national benefits.

into interpretable formats (for example, dashboards or visualizations); and ensuring that disease-control staff can interpret and apply results. Effective implementation requires a clear vision of how genomic surveillance for a particular pathogen can inform decision-making and policy.

Sequencing. For experienced, well-functioning laboratories, establishing sequencing capacity can be straightforward. However, laboratories in LMICs face specific challenges. The first is equipment installation and maintenance, which can require flying in a technician at considerable

cost and delay. Even when the sequencing companies support first-line local technicians, equipment outages can still be lengthy and expensive if specialized technical support is needed or parts are unavailable locally. Supply chain is a second problem, with long delays in delivery, challenges with importation regulations and taxes, and the receipt of supplies with little time remaining before expiration^{1,5,12,13}. The final problem is unreliability of utilities, particularly electricity, which necessitates the addition of uninterruptible power supplies or generators^{1,12}. All of this increases the costs of sequencing in LMICs relative to those in larger economies.

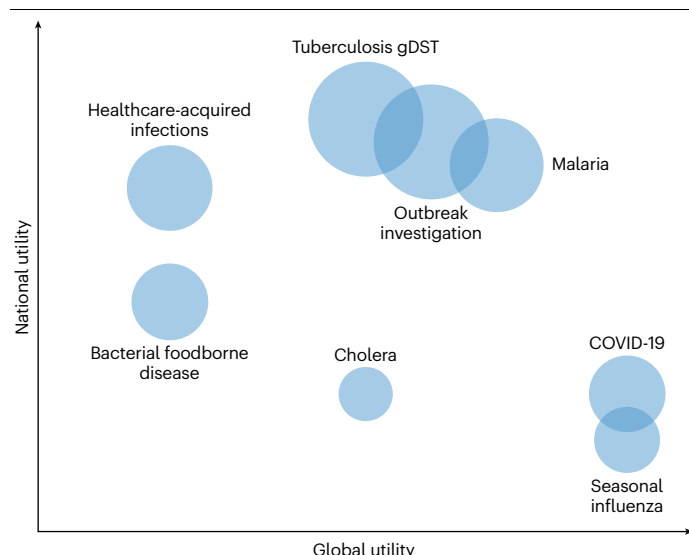


Fig. 1 | Potential impact of pathogen genomics in a hypothetical LMIC.

Use cases are displayed according to national and global utility (vertical and horizontal axes) and potential impact (represented by bubble size). The values here are for a hypothetical LMIC; in any real country, the values will be different, often markedly so, depending on the national context. The placement and size of these bubbles could vary substantially between countries and over time. For example, the 'Bacterial foodborne disease' bubble would be larger and higher in a country with wide food distribution and where large foodborne diseases outbreaks have occurred. The national utility for 'COVID-19' would be higher in a country that is using genomics to investigate clusters of disease, but lower if the country is not able to use the vaccines that benefit from this surveillance. The 'Outbreak investigation' bubble represents a diverse use case, in which genomics can have a variable impact both nationally and globally. Tuberculosis gDST (genomic drug susceptibility testing of MTB) represents sequencing of MTB in clinical settings to determine drug resistance and thereby inform treatment (another common use case for mycobacterial genome sequencing, not shown here, is to detect or investigate clusters of disease).

Computing and bioinformatics. Analytic requirements are more challenging in LMICs than 'wet lab' requirements (such as sequencing) because of the novelty of bioinformatics, the scarcity of bioinformaticians, a lack of computational capacity and scant experience with computationally intensive disciplines. Fortunately, bioinformatics services are relatively easy to outsource, and laboratories moving into pathogen genomics may opt to outsource initially and develop in-house expertise later. Although cloud computing offers scalable bioinformatic solutions, it depends on stable high-speed internet^{1,12}, cloud-management expertise and an appropriate budget.

Data privacy, security and sovereignty. Privacy and data-governance restrictions may limit the use of cloud-based resources for sensitive health data, particularly when those resources are physically located abroad. Cyber-security expertise is expensive and scarce. Although most pathogen-genomic data is not considered sensitive, clinical and epidemiologic data are. Moreover, host sequence data often contaminate raw, unprocessed pathogen genomic data, especially with metagenomics, and theoretically may present a privacy risk.

There are equally complex issues around data ownership and sovereignty, given the potential value of the data in developing commercial

products such as diagnostics and vaccines¹⁴. All of these considerations must be weighed against the global benefits of open data access.

Translating genomic data into impact. A phylogenetic tree by itself isn't useful. For genomic data to have a public-health impact, they must be analysed, integrated with relevant epidemiologic or clinical data, summarized (visually or in writing) and then translated into public health action. This requires specialized expertise in genomic epidemiology that is often scarcer than bioinformatics expertise. The impact also requires the broader public-health workforce to understand when genomic information is useful and how to apply that information.

Clinical use cases. Applying next-generation sequencing in clinical medicine (that is, for individual patient management) will demand rigorous quality assurance, reproducibility and compliance with regulations or ISO standards. Dedicated equipment, automation and validated 'push-button' analysis pipelines are typically required to ensure consistency and reliability.

Economics and sustainability

Sustainability is achievable when perceived benefits exceed costs. Traditional cost-effectiveness analyses are difficult for genomics, because the benefits are diffuse and hard to quantify. Although sequencing and analytics costs can be estimated¹⁵, calculating benefits requires assumptions about disease burden, the fraction that can be prevented by public-health interventions and the impact of genomics on those interventions. There are usually few plausible estimates for any of these. Nonetheless, costs (total costs or costs per sample) by themselves can be informative and worth documenting. In addition, if a monetary estimate of disease burden is available, the 'break-even proportion' – the proportional reduction in disease needed to offset the costs of the sequencing – can be calculated. Such an estimate, particularly if very small (that is, showing that even a small proportional impact on disease results in cost savings), can be useful for advocacy.

Multi-pathogen approaches enhance sustainability. In general, the same or similar equipment, supplies and processes are used across various pathogens, enabling centralization of lab processes. Batching of specimens for pathogen sequencing almost always lowers costs. Taking advantage of these efficiencies requires traditionally vertical programs to work together or to consider how developing genomic capacity within their silo can benefit other programs⁵.

Novel sustainability models for genomic surveillance should also be considered, including leveraging the potential for direct support from industry for product development in the diagnostic, therapeutic and vaccination spaces and leveraging resources in place for human genomic sequencing.

Collaboration with academia

In many countries, genomics capacity now resides in academic institutions, focused on research⁵. Genomics is most impactful when integrated into disease control programs – the public health infrastructure – which generally sit in ministries of health. Strengthening collaboration between academia and public health can accelerate adoption and ensure that investments in genomics yield long-term benefits and find practical applications in health. As countries develop national genomics strategies, inclusive stakeholder engagement and alignment of genomics with broader health system goals are essential for maximizing impact and sustainability.

Summary

Pathogen genomics is becoming indispensable for infectious disease surveillance and control. In high-income settings, years of experience have clarified use case priorities. In low-resource settings, the emphasis should be on identifying locally relevant applications with tangible impact.

Global utility is a less important consideration where a particular pathogen (for example, seasonal influenza) is of relatively low priority and there is limited access to interventions (for example, influenza vaccines) that benefit from genomic surveillance. Nonetheless, support from high-income countries for such global priorities can increase genomic capacity and sustainability in LMICs. The resulting in-country expertise, equipment and supplies can facilitate the application of genomics to other, more locally impactful use cases.

Outbreak investigation is an important, oft-cited application of genomics. Since the COVID-19 pandemic, the world expects rapid genomic characterization of outbreak pathogens and the use of genomics to inform response measures. The onset of a public health crisis is the wrong time to stand up new genomic capacity. Prompt application of genomics can be assured only if public health systems are using genomics routinely for pathogens of importance to them and are ready to apply their know-how to the crisis at hand. As with other aspects of public health, genomic preparedness benefits from having a ‘warm base’ to call on.

Future advances in sequencing, networking and computing will amplify the value of current investments. Declining costs will extend the range of potential applications. Local sequencing can also enhance biosafety by reducing the need to ship live pathogens. The integration of artificial intelligence will further enhance data interpretation and decision support. Experience gained now in bioinformatics and cloud computing is likely to have applications in other computationally intensive areas of public health and science. Together, these trends argue for sustained, well-targeted investment in genomic applications that deliver both national and global benefits.

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