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Perspective

National investment case development for pathogen genomics

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SUMMARY

Sustaining and expanding genomic surveillance capacity requires broader investment in genomics that target both novel and pandemic pathogens. Currently, there is no standardized methodology to evaluate the cost and benefit of a multi-pathogen surveillance system. We propose a framework for pathogen genomic surveillance that links public health and systems considerations to a stepwise approach.

OVERVIEW

Sustaining and expanding the genomic surveillance capacity built during the COVID-19 pandemic requires broader investments in genomics that target both novel and endemic pathogens. To promote these investments, national communicable disease control programs require estimates of the costs associated with next-generation sequencing (NGS) alongside its potential contribution toward enhancing early detection and response capacity. However, weighing the costs and benefits of a multi-pathogen surveillance system is not straightforward. Currently, there is no standardized methodology to evaluate the economic returns for a multi-pathogen surveillance system, given rapid advances in sequencing technology, the complexity of health services infrastructure, local epidemiology of disease burdens and risks, and the wider societal benefits that are contextual and complex to quantify. To weigh factors underpinning investments in pathogen genomics, we propose a framework for pathogen genomic surveillance that links public health and systems considerations to a stepwise approach that includes pathogen prioritization, an assessment of genomic utility, estimating the costs of genomic sequencing, and robust multi-pathogen planning that responds to wider system requirements. This complements the World Health Organization (WHO)'s global genomic surveillance strategy for pathogens with pandemic and epidemic potential that aims to guide countries accordingly. We profile a number of considerations that aim to inform a cost-sensitive system design of a well-integrated genomics platform to enable timely public health action.

BACKGROUND

In 2022, the WHO released its global genomic surveillance strategy for pathogens with pandemic and epidemic potential.[1] This high-level framework is a recognition of the growing importance of genomic surveillance in detecting, monitoring, and responding to public health threats. Much of the recent upsurge in pathogen genomic capacity was built during the COVID-19 pandemic, where it enabled early identification and tracking of SARS-CoV-2 variants and informed timely public health action to prevent further spread.[2] However, genomic characterization of several other high-risk pathogens is also beneficial. Respiratory pathogens, such as influenza virus, are well recognized to pose a high pandemic risk due to antigenic shift and drift. Genomics has played an important role in characterizing the transmission risk and consequences of highly pathogenic avian influenza (H5N1) during recent outbreaks in the United States.[3] Genomics for arboviral disease is essential for understanding the transmission risk, linking serotypes and lineages, identifying locally acquired vs. imported infections, enhancing diagnostic test accuracy, and helping to better design and target public health interventions.[4,5] Mpox, which is endemic in the African region, has recently seen a global resurgence, being declared a public health emergency of international concern (PHEIC) in 2022 and 2024. Genomic surveillance is useful where routine diagnostic testing is unable to differentiate pathogen subtypes, where certain clades are linked to greater transmission risk and mortality.[6] Genomics has been recently recommended by WHO as a

cost-effective strategy for the early diagnosis and treatment of drug-resistant tuberculosis (TB) to circumvent challenges resulting from the timeliness and accuracy of conventional tools.[7,8] Finally, genomics can provide more detail on pathogen antimicrobial resistance (AMR), a growing global health threat, informing infection control efforts, antimicrobial stewardship, and clinical decision-making.[9] The demonstrated benefits of genomic surveillance for AMR in healthcare institutions already exist.[10]

Investments in pathogen genomics can yield public health, clinical, and commercial benefits even in settings with limited resources.[11] While the contribution of genomics to enhanced surveillance is crucial, pathogen genomic information on emerging disease threats has accelerated the development of diagnostics, therapeutics, and vaccines. Furthermore, countries where NGS systems have been established to respond to endemic pathogens have already proved capable of pivoting this capacity in response to emerging threats.[12]

The WHO genomics strategy is a timely blueprint for action. However, countries will require guidance to inform national planning and budgeting. A recent assessment across 13 countries in Asia highlighted that despite existing genomics capacity, few have national strategic plans that integrate pathogen genomics within wider communicable disease control efforts.[13] There remains a heavy reliance on external resources, highlighting gaps in domestic financing that will be crucial for sustainability. While the case for investing in pathogen genomics is compelling, NGS technology does require substantial start-up and recurring costs. Budget holders and program managers will be required to make careful decisions about how to balance cost-sensitive system design with public health impact.

WEIGHING THE COST AND BENEFITS

The development of investment cases is commonly used to advance the introduction of high-impact interventions in public health. Investment cases have recently been applied in maternal, newborn, and child health and HIV/AIDS to inform national planning and resource allocation.[14,15] Typically, an investment case includes an economic analysis to investigate the cost effectiveness of different health interventions.[16]

However, the case for investing in pathogen genomics requires a somewhat different approach. Estimating the cost of pathogen genomics is complex for several reasons. NGS technology is dominated by a few manufacturers whose list prices, distribution and service charges, taxes, and end-user costs are opaque and/or vary considerably between countries. As a result, while the price of sequencing has declined substantially in recent years,[17] it remains relatively expensive. In addition, the market environment is highly dynamic, with frequently updated equipment and reagent kits from established manufacturers, new market entrants, and third-party suppliers that can be complex to compare. Finally, end-user prices are heavily shaped by the design of surveillance and laboratory systems, with delays in sample transport, inefficient batch processing, and reagent wastage driving up costs.

Defining the benefits of pathogen genomics is equally challenging. Conventional cost-benefit and cost-effectiveness analyses have been used in the health sector to position investments against forward-looking cost savings or standard metrics such as disability-adjusted life years. These approaches assist policymakers in assessing interventions with well-defined health impacts, often generated by combining findings from controlled trials with prospective implementation assessments and modeled estimates. There is a strong case for consideration of pathogen genomics to prevent, prepare, and respond to disease outbreaks as a common good for health (CGH), as it is non-rival (one person's use does not reduce use by others), generates large social externalities (benefits extend beyond immediate users), and has the potential to improve human lives.[18–20] However, evaluating the cost effectiveness for CGHs associated with infectious disease control interventions is difficult due to dispersed benefits and dependence on disease epidemiology, health services infrastructure, and local context.[20]

Despite these limitations, the morbidity, mortality, and economic consequences of disease outbreaks have been well documented. Economic losses from the influenza pandemic have been estimated at $570 billion/year globally[21] and from the COVID-19 pandemic at $16 trillion in the US alone.[22] Historically, economic analyses of disease surveillance have shown economic benefits and value. For example, enhanced meningococcal disease control efforts in Africa showed cost savings of up to $80 to prevent a case and up to $263 to prevent a death due to meningococcal meningitis.[23] However, such analyses in the literature are generally disease specific, and there is currently no standardized approach to assess the benefits of global and regional efforts to enhance infectious disease surveillance more broadly,[24] particularly because investments benefit not only human health but also animal health and other sectors, such as international trade and tourism. A recent systematic review indicated that evidence of cost effectiveness for pathogen genomics surveillance remains insufficient.[25] It found that only specific pathogens have been studied for surveillance cost effectiveness and were mostly assessed during outbreaks in clinical settings without national surveillance data. A 2016 economic evaluation of PulseNet, a surveillance system to identify and respond to outbreaks caused by foodborne pathogens, came closest to a multi-pathogen analysis. It measured cost effectiveness using the reduction of reported illness and savings on medical costs and productivity losses averted in the United States. From 1994 to 2009, it showed that medical costs and productivity losses were reduced by up to $507 million, and the direct effects of improved recall of tainted food products saved another $37 million.[26] This approach could potentially be expanded to include more disease surveillance programs and provide a better understanding of the economic benefits of a multi-pathogen genomic surveillance system.

Meanwhile, the benefits of surveillance systems extend beyond a health perspective and include wider societal and economic benefits. For example, zoonotic diseases disproportionately affect poor populations in resource-constrained countries; strengthening disease surveillance among both humans and animals should improve livelihoods and increase economic output in such contexts.[27] While these economic analyses of surveillance systems are complex and further studies are required, they provide useful material for advocacy to gain political support and national commitments for investments in surveillance.[28]

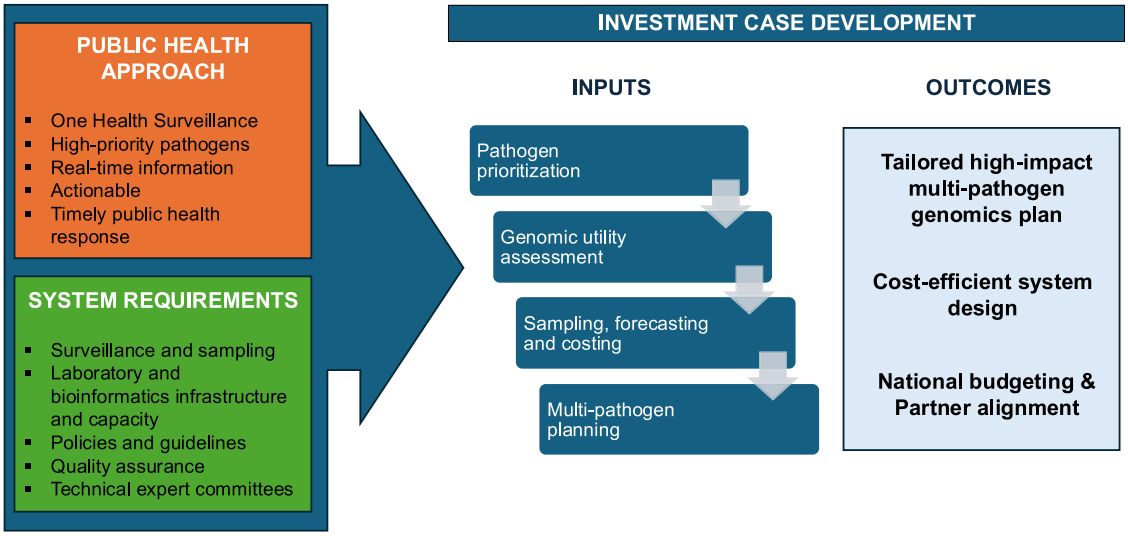

Figure 1. Investment case framework for pathogen genomics surveillance

Notwithstanding these challenges and uncertainties and in keeping with the WHO genomics strategy, we believe establishing sustained genomic surveillance capacity is imperative for all countries.

PUBLIC HEALTH AND SYSTEMS APPROACH

We propose an alternative investment case framework for pathogen genomics that considers important public health objectives and systems requirements. Such an approach would aim to optimize public health benefits, provide real-time, actionable information for prioritized pathogens and emerging threats, broadly strengthen relevant systems components, and be sustainably affordable (Figure 1). We highlight a number of considerations and inputs/steps to inform this process.

System requirements

Decisions regarding the adoption and scale of pathogen genomics should be informed by a readiness assessment of national surveillance and laboratory systems. Key parameters include the robustness and coverage of existing laboratory and public health surveillance systems, including conventional and molecular diagnostics; turn-around times between sample collection and sequencing; bioinformatics and computing infrastructure; the existence of appropriate workforces, policies, and procedures; laboratory accreditation and independent quality assurance; and national technical expertise to advise public health professionals and policymakers on the interpretation of pathogen genomic data.

The value add of pathogen genomics is likely to be greatest where local surveillance and laboratory systems have a basic level of coordination and functionality and where the capacity to respond to genomic data exists. In severely resource-constrained settings, such capacity will likely need building across multiple areas, with sustained external support, before in-country pathogen genomics can feasibly be adopted and deliver impact.

The identification of major SARS-CoV-2 variants of concern illustrates the importance of having a basic level of genomic capacity. Variants including the Alpha (B1.1.7), Beta (B1.351), Gamma (P1), Delta (B.1.617.2), and Omicron (B1.1.529) were all detected through increased reporting of clinical cases, unusual PCR results, and routine genomic surveillance.[29–34] Beyond COVID-19, genomic surveillance has been applied to other diseases. In Canada, for instance, pathogen genomics has been used to investigate TB transmission, characterize carbapenemase-producing Enterobacteriaceae, and support food safety measures during *E. coli* outbreak.[35,36] The response to the Ebola and Zika epidemics has also demonstrated the importance of genomics in understanding and controlling emerging diseases.[37]

Therefore, a strong laboratory and surveillance structure being integrated within a broader adoption of multi-pathogen genomic sequencing is crucial for effective surveillance. It facilitates the prompt detection and tracking of new variants, supports comprehensive public health responses to various pathogens, and ensures readiness for future pandemics and epidemics.

Pathogen prioritization

Within each context, the prioritization of pathogens for genomic surveillance should be informed by the biological characteristics of pathogens alongside the epidemiological and clinical characteristics of the associated disease.[38] Epidemiological parameters include local disease burden (e.g., incidence and case-fatality rates), the mode and intensity of local transmission, population immunity, and the rate and relevance of genetic mutations vis-à-vis pathogenicity, transmission, immune escape, and drug resistance. In Asia, a hotspot for infectious disease outbreaks, weighing national and local risks will be essential for prioritization. For example, the burden of TB and drug-resistant disease in Indonesia and the Philippines is among the highest in the world.

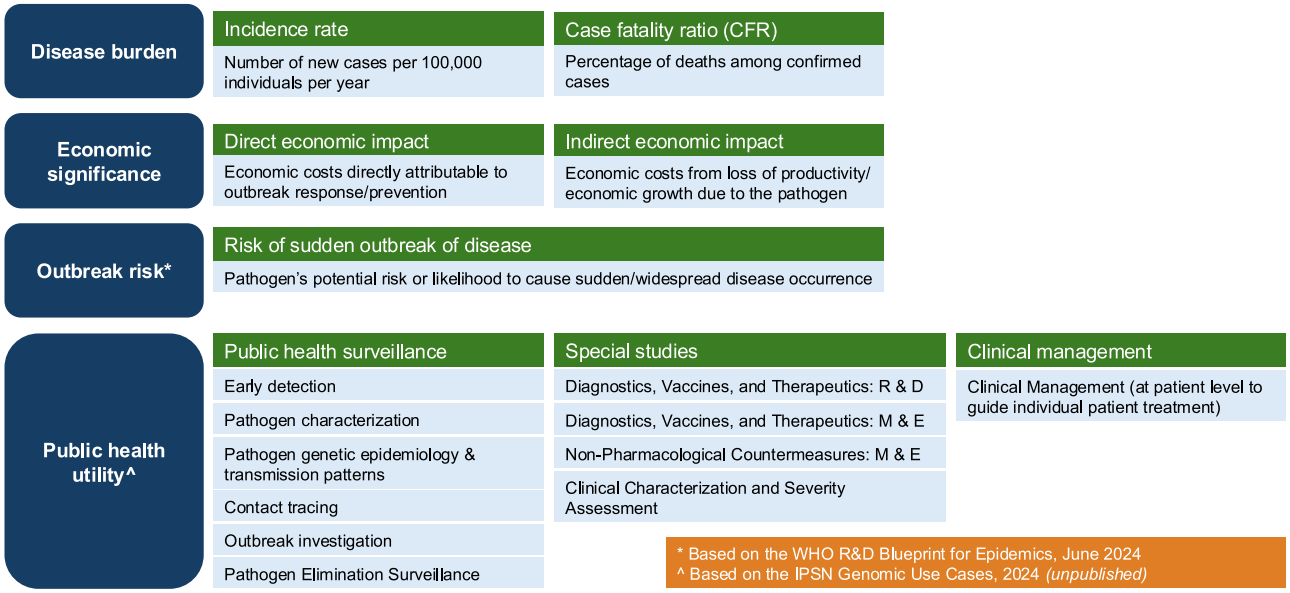

Figure 2. Pathogen prioritization and genomic utility assessment components

In northern areas of Southeast Asia, zoonotic spillovers are common due to exposures at the human-animal interface resulting from climate stress, biodiversity loss, agricultural activities, and deforestation. In these settings, country- and context-specific risk assessments will inform decisions regarding pathogen prioritization. The WHO bacterial priority pathogens list demonstrates the importance of pathogen prioritization. This document lists carbapenem-resistant *Acinetobacter baumanii* as having critical priority due to its ability to transfer resistance genes and fluoroquinolone-resistant *Salmonella typhi* as high priority due to its high burden of disease in resource-constrained settings.[39] In another example, the SAR-CoV-2 virus has evolved tremendously since its emergence, with increased transmissibility due to changes in its functional properties and antigenicity, giving the virus the ability to evade the immune response. Such characterization would be important to consider in a prioritization exercise to ensure future variants can be detected early and mitigate the spread of the virus.[40]

In developing the list, WHO undertook a global pathogen prioritization process to develop a list of priority pathogens to enhance outbreak preparedness by advocating for investments in research, development, and innovation in medical countermeasures.[5] This list serves as a starting point for selecting pathogens for genomic surveillance. However, among currently prioritized pathogens, only a subset will likely be prioritized for genomic assessment based on national priorities and country context. It will also be deployed in tandem with existing conventional or molecular testing. For new variants or novel pathogens, additional decision-tree models have been developed to inform public health risk based on genomic characterization through metagenomics.[41]

Genomic utility assessment

A national expert consultation is essential to inform genomic surveillance planning. Findings will support countries in identifying pathogen groupings where genomics would yield the greatest public health impact in their context. The public health utility for genomic surveillance includes (1) infectious disease control; (2) the development of outbreak mitigation or prevention tools, such as diagnostics, therapeutics, or vaccines through research and development (R&D); and (3) patient care and management.

There is high public health utility where genomics enables early detection and identification of high-risk settings, guides antimicrobial stewardship, assesses vaccine or diagnostic tool effectiveness, informs the introduction of pharmacological and non-pharmacological interventions, and enhances contact-tracing efforts.[11] The COVID-19 Genomics UK Consortium, formed in 2020, demonstrated the value of pathogen genomics for public health. It leveraged a network of academic and research institutions and public health and other agencies to provide data for public health decision-making, policymaking and evaluation, and development of COVID-19 therapeutics and vaccines.[42]

The utility of genomics for contact tracing or clinical decision-making would be high for diseases and in areas where the turn-around time between specimen collection and sequencing can be short. Moreover, while commercial utility may be highest in countries with more established R&D or manufacturing capacity, even low-resource countries can benefit from data sharing.

Figure 2 profiles the components of pathogen prioritization and its genomic utility. These components should be evaluated at a national level to guide decision-makers on the priority pathogens for genomic surveillance. The list of public health utility corresponds to the International Pathogen Genomic Surveillance (IPSN) genomic uses, which is under development.

Costing of genomic sequencing

The pathogen prioritization process and utility assessment can inform more detailed costing analyses. As genomic

sequencing platforms rely upon high throughput to keep costs down, multi-pathogen approaches that leverage integrated laboratory networks are crucial. This pivot toward the cost-sensitive design of national systems for multi-pathogen genomics is an important departure from the application of genomics as a single-pathogen research tool.

Once priorities have been defined, questions about where to sample alongside the frequency and quantity of sequencing will inform national equipment and reagent forecasts, which play a major role in determining costs. With the exception of SARS-CoV-2, guidance on how to approach sampling of priority novel and endemic pathogens remains largely absent. Defining the objective of genomic sequencing for each pathogen grouping will be crucial, as sampling strategies may differ for monitoring pathogen incidence or predominant circulating variants, detecting new pathogens or zoonotic spillover, or assessing the impact of public health interventions such as vaccine introduction or antimicrobial stewardship.

Making the best use of existing sequencing platforms is an important first step. Notably, the type of sequencing has important forecasting and cost implications. Targeted NGS, whole-genome sequencing, or metagenomics each respond to different questions and carry cost implications that can vary widely.

Despite these challenges, national multi-pathogen estimates for genomics equipment and reagent requirements are essential. In many countries, national forecasts are absent, with procurement orders remaining in the hands of individual laboratories. Major cost reductions are achievable through more effective coordination and batched procurement. Genomics equipment and reagents have recently been listed on global supply catalogs, creating opportunities for price reductions and market shaping. Additional cost reductions could be achieved through the use of low-cost third-party reagents, targeted NGS, or the use of multi-pathogen panels.

To facilitate national budgeting, the WHO recently released a tool to assist with commodity forecasting and costing for pathogen genomics.[43] The first version of the tool is limited to SARS-CoV-2 and two manufacturing platforms, but during the recent IPSN Global Partners Forum in November 2024, the tool was updated and includes a broader range of pathogens. Importantly, the WHO tool does characterize the full system costs of introducing NGS. It advocates for a more detailed budgeting exercise that includes costs associated with bioinformatics, human resources, facilities, sample transport, additional costs from importation taxes, and costs for accreditation and external quality assessments.

However, there are wider barriers related to the costs of NGS-related equipment when implementing genomic surveillance programs. Genomic analysis requires high computing power and advanced software tools, often limiting access and driving up costs. Cloud computing has gained more traction as genomic datasets grow, allowing flexibility in analytic tools and freeing users of hardware maintenance.[44] As costs are incurred, financial sustainability can pose a challenge in resource-constrained settings. The lack of a reliable supply chain of NGS-related equipment continues to pose a major barrier, with countries in South and Southeast Asia reporting long resupply periods and delays in repair times.[13] The lack of access to training programs to build capacity and retain a skilled workforce can hinder implementation.[43,45] Mitigating these challenges through market-shaping activities to reduce prices of NGS-related equipment, improve supply chain resilience and efficiency, and ensure the capacity of the new and current workforce is essential to the sustainability of a genomic surveillance system.

Multi-pathogen planning

An investment case developed with the above considerations should yield a costed multi-pathogen genomics plan. The utilization of laboratory equipment for simultaneous sequencing of multiple priority pathogens is likely to be most cost efficient. The plan should include a strategy for optimizing genomics infrastructure while upscaling a wider suite of system-wide improvements. Attention should be given to addressing capacity gaps in laboratories and bioinformatics, data sharing and information technology infrastructure, and accreditation and quality assurance mechanisms.

Planning should also include how to best position genomics capacity within a national context. In some instances, centralizing capacity with efficient sample collection and transport may be optimal, whereas in areas with localized disease risk, establishing decentralized capacity may be more appropriate. Furthermore, as capacity is often divided between national public health institutions, the private sector, and academic/research entities, establishing public accountability for pathogen genomics is critical for protecting national public health.

To illustrate an example of how the components in Figure 1 can be applied, a genomic sequencing capacity landscape assessment at the national level can be a starting point to assess the system requirements.[13] Indicators of laboratory and bioinformatics infrastructure, supply chain resiliency, data sharing and reporting, and broader related issues, such as financing, policy and guidelines, and partnerships, will provide a comprehensive picture of the capacity and readiness of the surveillance system. Understanding the capacity will guide the prioritization of pathogens based on the components described above. For example, in certain Asian countries, TB and influenza could be prioritized due to the high case burden, endemicity and its genomic utility for early detection, development of vaccines, and clinical management. Understanding the priority pathogens will inform the number, frequency, and type of sampling required. A costing assessment using the WHO costing tool can be done to decide on building or expanding the appropriate laboratory and infrastructure capacity. The genomic surveillance of these prioritized pathogens should be integrated into the wider existing surveillance system in a multi-pathogen approach to further take advantage of the economies of scale and reduce costs. Following this process allows a genomic surveillance system to have a high impact on early detection and clinical management of TB and influenza cases, as well as contribute to vaccine development. This approach could also be used for national budgeting for other pathogens and aligning on resource contributions from external partners.

Figure 3 depicts the key components of an integrated multi-pathogen surveillance system. An example of a set of prioritized pathogens is central to the model, and this is nested within

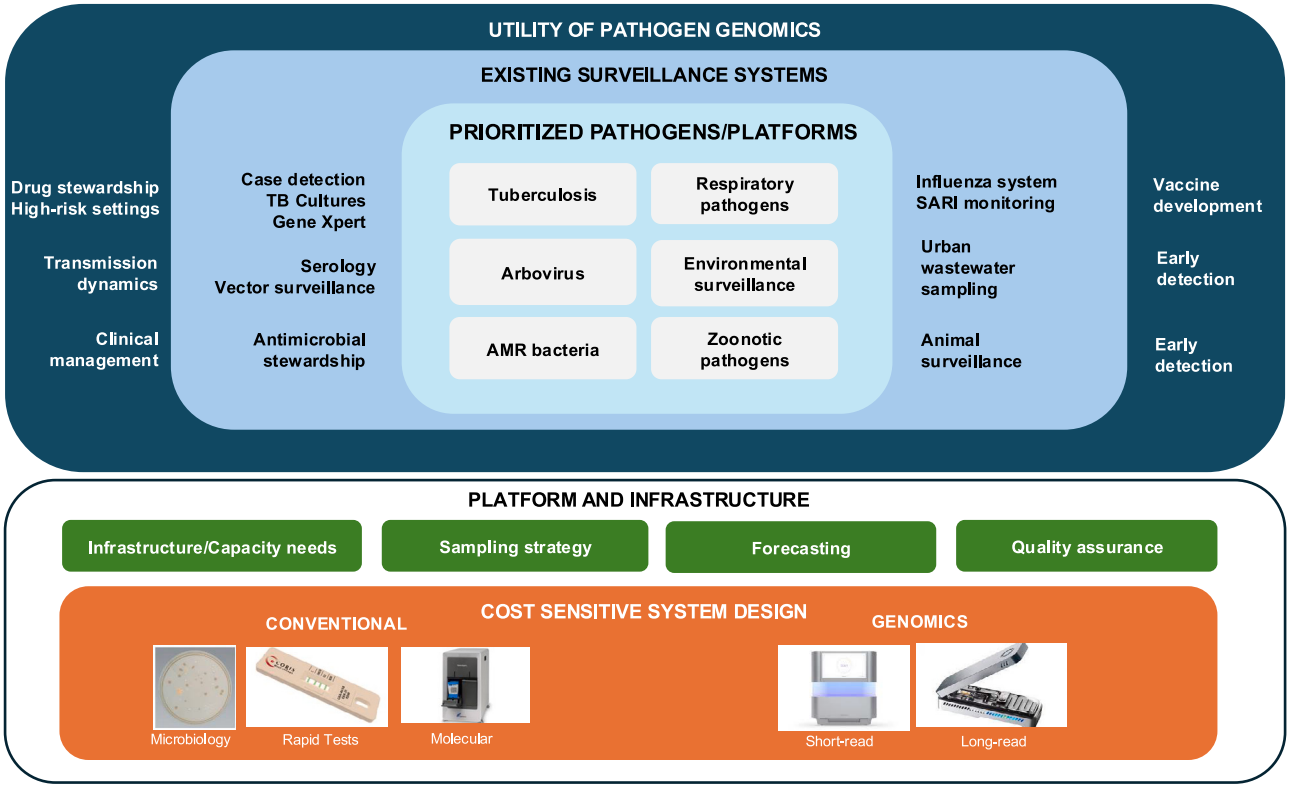

Figure 3. Interaction between prioritized pathogens and existing surveillance systems to inform national planning on platform and infrastructure needs

existing disease-focused surveillance systems. Pathogen genomics is integrated into this system with a clear articulation of the value add of genomic surveillance for each pathogen. This informs a national-level plan on infrastructure and capacity needs, sampling strategies, sequencing forecasting volumes, and quality assurance mechanisms. Defining where genomics complements conventional diagnostic methods in a particular context informs cost-sensitive system design.

As genomic surveillance grows in scope, the associated legal, policy, and ethical challenges must be carefully addressed to ensure responsible use of data introduced by large-scale genomic data collection. Legal frameworks often lag behind the rapid advances in genomic technologies, creating a fragmented regulatory landscape where data ownership, access, and cross-jurisdictional sharing are inconsistently governed. This leads to significant bottlenecks in responding to public health threats, particularly in time-sensitive emergencies.[46] These gaps can exacerbate global inequities, particularly where genomic data from low-resource settings are utilized by high-income countries without a guarantee of equitable benefits or compensation.[47] Besides pathogen access and benefit sharing, which is a key issue in the draft pandemic treaty negotiations,[48] other ethical concerns from increased genomic data collection range from issues of data ownership to balancing public health needs with national sovereignty and individual privacy.[49,50]

Finally, the efficient use of genomics requires leveraging existing disease surveillance and laboratory system capacity. Sustainable genomic surveillance heavily depends on ongoing support and domain expertise from other laboratory services and researchers, especially in microbiology, virology, and data analytics. For example, WHO's Global Influenza Surveillance and Response System can potentially be leveraged to characterize the burden of non-influenza respiratory pathogens.[51] Additionally, with wastewater sampling emerging as an important early warning tool, polio surveillance systems can be deployed for multi-pathogen surveillance in a strategic low-cost manner.[52] By combining different capacity, datasets, programs, and networks, a multi-pathogen approach will be strengthened through collaborations between stakeholders.[53]

Increasing and sustaining genomic surveillance capacity in lower-resource settings also benefit the wider global community, including higher-income countries. Stronger surveillance capabilities enable quicker pathogen detection to mitigate the international spread of the virus and guide public health interventions. When genomic sequencing data are shared on international databases, other countries are able to develop and update medical countermeasures such as diagnostics, therapeutics, and vaccines. While these are likely to be developed in wealthier nations, lower-income countries could also profit from a benefit-sharing mechanism that promotes fairer access to these advancements. Enhancing genomic surveillance capacity also aligns with the core requirements of the International Health Regulations for detecting and evaluating public health events.[54] This,

in turn, fosters improved cross-border information exchange, strengthens international collaboration, and reinforces global health security.

CONCLUSION

In conclusion, the absence of a well-defined methodology to evaluate the costs and benefits of pathogen genomics highlights the need for an investment case framework that emphasizes timely public health response and benefits. Assessing the system requirements for genomic surveillance can guide national planning of a multi-pathogen approach for optimal efficiency, resource allocation, and partner alignment. To facilitate this process, a set of considerations, including pathogen prioritization, genomic utility, and cost of NGS, has been proposed. This approach has the dual purpose of enhancing national communicable disease surveillance for endemic pathogens while establishing in-country capacity to detect and respond to emerging threats.

AUTHOR CONTRIBUTIONS

Y.K.K. drafted the original manuscript and contributed to conceptualization. P.M.P., D.H., and R.d.A. contributed to conceptualization and the reviewing, editing, and writing of the manuscript. S.W., M.G., and L.M. contributed to analysis and visualization. S.S.K., E.J.L., Y.S., J.P., S.M., H.C., B.M., and V.S. contributed to the reviewing, editing, and writing of the manuscript. All authors read and approved the final version of the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

SUPPLEMENTAL INFORMATION

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