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Bridging the implementation gap: Challenges and opportunities for integrating whole genome sequencing in tuberculosis surveillance in low-resource settings

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ABSTRACT

Introduction: Tuberculosis (TB) remains a major global health concern, particularly in low-income countries where the impact is greater. The lack of proper surveillance tools in these countries is a big impediment to effective TB control. Whole-genome sequencing (WGS) has successfully been integrated into routine TB programs in high-income countries and transformed disease surveillance by providing rapid, high-resolution transmission insights, drug resistance profiling, and outbreak detection. However, its uptake in resource-limited settings where TB burden is most prevalent remains limited.

Methods: This review examines how WGS is currently being utilised for TB surveillance and highlights the main obstacles to its adoption in limited-resource settings as well as the strategies that could improve its uptake. A literature search was conducted in PubMed, Google Scholar, and the World Health Organisation (WHO) databases with keywords "whole genome sequencing," "tuberculosis," "surveillance," "transmission," and "drug resistance." Studies published between 2015 and 2025 were prioritised, with a focus on applications in high-burden settings.

Results: Key challenges identified include infrastructural issues whereby 78% of high-burden countries lack adequate sequencing facilities according to WHO 2023 data; financial barriers, with recurring costs surpassing $150 per sample in low-resource settings as compared to $80 in high-income countries, and a shortage of trained personnel with only 2.3 bioinformaticians being available per African country. Other hurdles involve concerns over data sovereignty, weak regulatory frameworks, and ethical dilemmas surrounding privacy and equitable data usage, with only 31% of low-resource countries having genomic data policies. Nevertheless, promising innovations like portable sequencing devices which have a sensitivity of up to 92% and cloud-based platforms that reduce computational needs by 70% offer scalable opportunities for equitable integration. We also highlight partnership models that blend WHO technical guidance, Global Fund financing, and South-South collaborations that could enhance sustainability.

Conclusion: To realise the full potential of WGS in TB-endemic regions, a coordinated approach that combines technical advancements with policy changes, ethical data governance, and sustained investment is needed. Tackling these challenges is essential in achieving equitable, genomics-informed TB control that aligns with global TB elimination goals.

List of abbreviations: HICs, High income countries; IP, Intellectual property; LMCIs, Low and middle income countries; MDR-TB, Multidrug resistant tuberculosis; MTB, Mycobacterium tuberculosis; TB, Tuberculosis; tNGS, Targeted next generation sequencing; WGS, Whole Genome sequencing.

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1. Introduction

Tuberculosis (TB) is an ancient communicable disease that continues to pose a major global health challenge, particularly in low- and middle-income countries (LMICs) (1,2). Despite notable strides in lowering global TB incidence, prevalence, and mortality over the years, the World Health Organization (WHO) End TB Strategy vision to eradicate TB remains elusive. There was an increase in new TB cases globally in 2022, with approximately 10.6 million cases being reported by the WHO, up from 10.3 million in 2021, the vast majority being recorded in LMICs (1). This upward trend continued in 2023, with 10.8 million cases being recorded, making it the highest number recorded since the initiation of global TB surveillance in 1995 (1,3). While mathematical models suggest that we could eradicate TB by 2050 using a comprehensive approach that includes advanced diagnostics, effective treatment regimens, vaccines, and improved detection of latent and active infections (4), the current trajectory makes such predictions appear overly ambitious.

Whole-genome sequencing (WGS) is a tool that has revolutionized TB surveillance, offering incredibly detailed insights into how the disease spreads, its drug-resistant patterns and outbreak detection (5–7). This tool has transitioned from a pure research tool to a Clinical Laboratory Improvement Amendments (CLIA) - approved tool for TB screening, diagnosis, and clinical management, as well as public health surveillance. Unlike traditional genotyping methods that only analyze a tiny fraction of <1% of the *Mycobacterium tuberculosis* (MTB; the causative agent for TB) genome, WGS examines over 90% due to its high resolution power (7,8). In high income countries, WGS has seamlessly been integrated into standard TB surveillance and diagnosis. For instance, the Centre for Disease Control and Prevention rolled out the use of WGS for all culture-confirmed TB cases in the United States in 2018, leading to improved detection of drug-resistant strains that impacted public health responses (9). The same has been carried out in the United Kingdom, where WGS has been used to investigate and contain TB outbreaks (10). The implementation of WGS in real time in these regions has demonstrated its capability to revolutionize TB control efforts through a rapid, precise, and comprehensive analysis of TB pathogens. However, its implementation in low-resource settings where TB is endemic remains limited. There is only 50% of African countries have in-country sequencing capacity, an expansion catalysed by the COVID-19 pandemic, highlighting significant potential to strengthen TB surveillance and control (11). However, this achievement may underscore the urgency to capitalise on these gains so as to enhance equitable TB detection and timely access to care. In this review, we evaluate the utility of WGS for TB surveillance and the main challenges of integrating it in low-resource settings for TB surveillance. We also highlight various ways we can advance an equitable and sustainable scale-up.

2. Utility of WGS in TB surveillance

The high resolution power of WGS allows for precise and timely surveillance of TB transmission, accurate detection of drug resistance and informed public health interventions. Unlike the traditional genotyping approaches like MIRU-VNTR and Spoligotyping, WGS can detect single-nucleotide polymorphisms that differentiate even closely related MTB strains (12,13). This level of precision allows for the construction of precise phylogenetic trees that reveal hidden transmission pathways that are often missed by traditional methods and could be used to not only locate transmission hotspots but provide necessary data which health experts could employ for various TB interventions. Studies in Taiwan and Italy, for instance, successfully detected transmission clusters using WGS that would have otherwise gone undetected, prompting timely public health interventions (14,15). In Gambia, WGS was used to reveal that many cases previously thought to be new infections were actually reactivation of latent TB infections, prompting a change in control strategies (16). Similarly, WGS helped uncover localized community transmission clusters in Vietnam, resulting in focused contact tracing and vaccination campaigns (17,18).

The WGS has significantly enhanced real-time TB outbreak detection and containment in resource-limited and high-transmission settings. For instance, in KwaZulu-Natal rural hospital, WGS uncovered an outbreak of extensively drug-resistant TB that was driven by a single super-spreading strain, triggering immediate infection control measures including better ventilation, patient isolation and enhanced staff training (19,20). Similarly, genomic analysis in Eswatini revealed previously unrecognised transmission hotspots in households and social gatherings, challenging the assumption that TB transmissions mostly happened in clinical settings thus prompting community-based interventions (21). In Myanmar, portable nanopore sequencing enabled rapid detection of a multidrug-resistant TB (MDR-TB) outbreak in a refugee camp, facilitating timely isolation and tailored treatment that curbed further spread (22). In the Czech republic, WGS helped trace MDR-TB transmission among displaced populations and pointed gaps in healthcare access, leading to the deployment of mobile clinics and telemedicine services (23).

In addition to human-to-human transmission, WGS has played a vital role in shedding light on zoonotic and cross-border TB spread. A study along the Botswana–South Africa border identified similar MTB strains among miners across both countries and linked transmission to labour migration. This prompted a coordinated binational screening and treatment initiatives (24,25), a crucial public health approach to mitigate the spread of TB infection across countries while cutting diagnostic costs associated with migration dynamics. In Ethiopia, WGS linked bovine strains (*Mycobacterium bovis*) to human patients and connected these infections to the consumption of unpasteurised dairy products (26) resulting in authorities initiating cattle vaccination programs and public awareness campaigns on safe milk practices. WGS has also proven indispensable in distinguishing between relapse and reinfection, information that is critical in TB-endemic areas where recurrent cases are common. In Peru, WGS revealed that approximately 30% of TB recurrent cases were due to reinfection rather than relapse, thus influencing changes in treatment policy and drug susceptibility retesting protocols (27). Similarly, a study in South Africa's high HIV-prevalence regions discovered that many suspected relapses were actually reinfections, indicating continued community transmission (28) leading to the implementation of post-treatment follow-up and household contact screening.

Furthermore, WGS has improved clinical management by providing comprehensive and rapid drug-susceptibility profiles. In South Africa, WGS accurately detected drug resistance patterns with over 90% sensitivity and specificity, enabling faster and more effective treatment modifications (20). Evidence from the CRyPTIC consortium in India further demonstrates that WGS detects resistance to both first- and second-line anti-TB drugs, including bedaquiline (29). Practical implementation in LMICs is increasingly feasible, as shown by Namibia's successful use of small-scale Illumina iSeq100 platforms further demonstrate that targeted investments can enable successful WGS implementation in resource-constrained settings (30). WGS can also swiftly predict resistance to other treatments once rifampicin resistance is detected, allowing clinicians to optimise treatment regimens faster than with phenotypic drug-susceptibility testing alone. However, for newer drugs such as bedaquiline and pretomanid, incomplete understanding of genotype–phenotype relationships and evolving resistance mechanisms means WGS should be utilized to make judgements, rather than solely dictate, clinical decision-making. Effective clinical integration therefore requires not only laboratory and bioinformatics expertise, but also genomics-literate clinicians and well-designed workflows that account for turnaround times, data governance, and seamless integration of genomic testing into routine TB services.

Direct sputum sequencing has emerged as a promising culture-free alternative. By extracting and sequencing DNA directly from patient sputum, this approach eliminates weeks of culture and reduces exposure

to live TB in the lab (31) A 2018 study demonstrated that direct sputum WGS performed directly on sputum could deliver a comprehensive drug-resistance profile within 5 days, approximately three weeks faster than sequencing from mycobacterial growth indicator tube (MGIT) cultures or phenotypic drug susceptibility testing (32) allowing earlier initiation of effective treatment. Direct sequencing also captures within-sample genetic diversity including mixed infections and minority resistant variants that can be lost during culture. However, technical challenges remain, notably low mycobacterial DNA abundance and high human DNA in sputum samples, often necessitating targeted DNA enrichment or ultra-deep sequencing. Continued improvements in sample preparation including better pathogen DNA capture and host DNA depletion are needed to make direct sputum WGS as robust as culture-based approaches. Despite these limitations, direct sputum sequencing offers a viable pathway for low-resource settings by reducing reliance on complex lab infrastructure. With optimized protocols, WGS could be performed using basic molecular laboratories and benchtop sequencers, thereby avoiding the need for expanded BSL-3 facilities. Emerging targeted sequencing technologies exemplify this shift. For instance, the Deeplex Myc-TB assay uses a single-tube multiplex PCR to amplify multiple genomic targets directly from sputum, enabling species identification, genotyping, and resistance detection for several anti-TB drugs under BSL-2 conditions (33). Collectively, these innovations illustrate how TB WGS is being re-engineered for low-resource settings by simplifying workflows, reducing biosafety requirements, and accelerating turnaround times.

3. Challenges of integrating WGS in TB surveillance in low-resource settings

Despite the great impact of WGS application in TB surveillance, its implementation in low-resource settings, where the burden of TB is high, faces significant hurdles, some of which we explore below.

3.1. Infrastructural barriers

The implementation of WGS in LMICs is hindered by multiple interrelated infrastructural challenges, including limited laboratory facilities, inadequate digital and logistical capacity. Traditionally, WGS is performed on cultured MTB isolates, which demands Biosafety Level-3 (BSL-3) laboratory facilities. BSL-3 labs have resource-intensive features (such as negative airflow and specialized waste handling) and scarce in many high-burden countries. The need to culture infectious TB organisms also raises biosafety risks for laboratory personnel and requires robust containment protocols (34). Shipping samples to distant reference labs for culture/WGS further introduces logistical challenges, from cold-chain requirements to sample degradation and biohazard risks during transport. All these factors underscore substantial infrastructure and safety barriers when relying on traditional culture-dependent WGS.

Most LMICs lack access to high-throughput sequencing facilities and continue to depend on traditional diagnostic methods like sputum smear microscopy, Xpert MTB/RIF, and phenotypic drug susceptibility testing. These conventional tools are not only less accurate but also time-consuming, and they lack the resolution that WGS provides (35). Additionally, techniques like spoligotyping and MIRU-VNTR are still commonly used to investigate TB transmission in low-resource settings, even though they offer much lower resolution compared to WGS (13). Even in settings where sequencing platforms are available, the high operational costs associated with procurement of reagents and equipment maintenance only widen the gap in access, leaving these countries reliant on international collaborations and external funding (35). A recent assessment of East African countries starkly highlighted this reliance with approximately 97% of all bacterial WGS data from the region being generated by external labs (primarily in Europe or North America), with minimal in-country sequencing happening in a few countries (36). Tanzania led in-country sequencing efforts, followed by Kenya and Uganda, while other countries had to send all their samples abroad. This reliance on external sequencing not only creates delays but also means that local capacity building is lagging. A parallel barrier lies in the digital infrastructure that is required for processing and interpretation of WGS data. Many laboratories in low-resource settings lack the bioinformatics capacity, high-performance computing systems, and secure data storage essential for genomic data analysis (4,30,37). Poor internet connectivity and limited access to cloud computing solutions further constrain the use of WGS, especially where data-intensive processing and remote collaboration is needed (37,38). The absence of region-specific genomic databases as well as underrepresentation of local *Mycobacterium tuberculosis* genetic resources in public repositories also hampers meaningful interpretation of results limiting their usefulness in clinical and epidemiological contexts (6,39).

Beyond the laboratory itself, critical infrastructural challenges also include logistics and supply chains. Stable electricity, consistent cold-chain storage for samples and reagents, and efficient specimen referral networks are often lacking in resource-limited settings, further constraining WGS adoption and integration to national TB programs (40, 41). Many low-resource settings rely on centralised sequencing hubs, normally located within national reference laboratories, requiring shipment of samples. Such shipping introduces biosafety risks, risks of sample degradation and long turnaround times, often compromising sequencing quality (30,42,43). These logistical complexities, coupled with poor road infrastructure and disrupted supply chain collectively hinder the quality and timeliness of sequencing outputs, ultimately limiting the practical impact of WGS on TB control in resource-constrained settings.

3.2. Financial constraints

The high cost of WGS remains a major impediment to its widespread adoption in low-resource settings. Although WGS cost per sample has decreased from $10,000 in 2001 to approximately $50-100 in 2023 due to technological advancements (44–46), the initial capital investment remains prohibitive for most TB-endemic countries. Setting up a basic WGS facility requires substantial capital investment, often ranging between $200,000 and $500,000, excluding annual maintenance costs of up to 10-15% of the initial investment (44). For instance, a WGS implementation project in the Kyrgyz Republic cost over $230,500 for startup, with $98,000 going to the Illumina equipment, $42,000 to bioinformatics infrastructure, and $35,000 to staff training (41). Notably, 87% of these costs were covered by donor funding, underscoring the sustainability challenges many low-resource settings face in independently establishing and maintaining sequencing capacity. This is exacerbated by high recurrent costs ranging from $150 to $300 per TB sample, mainly due to import tariffs, fragmented supply chains, and inadequate local production capacity (35,45). In contrast, high-income countries benefit from established infrastructure, streamlined logistics, and lower per-sample costs of $80–120. These financial pressures are worsened by significant gaps in health infrastructure, as exemplified by Kenya's National Tuberculosis, Leprosy, and Lung Disease Program, which reported chronic stock-outs of genotypic drug susceptibility testing reagents and critical shortages of trained laboratory personnel in 2023 (47). Table 1 shows a comparison of a typical WGS-related costs across different income settings and the key challenges faced by LMCIs.

Beyond these constraints, a lack of cost-effectiveness studies in low-resource settings make it difficult for policymakers to justify investments in WGS over conventional methods in such settings. This compels most low-resource countries to prioritise on expanding access to basic TB diagnostics such as GeneXpert (47) which costs $9.98/sample, forcing over 73% of TB reference labs in such countries to rely on short-term grants to keep their WGS operations running, which puts them at risk of halting programs when funding runs out (26,46). Despite some modelling studies suggesting that WGS could be cost-saving in

Table 1
A comparison of WGS-related costs across different income settings and key challenges faced by LMCIs.

Cost Component	High-Income Countries (HICs)	Low- and Middle-Income Countries (LMICs)	Key Challenges in LMICs	Data Source
Startup costs (equipment & Setup)	$150,000 - $300,000	$200,000 - $500,000	High import taxes, lack of local service contractors	(30,41, 44–46)
Recurring Cost per Sample	$80 – $120	$150 – $300	Reagent stock outs and cold chain requirements	(35,44, 45)
Annual maintenance costs	10–15% of capital cost	20–35% of capital cost	Limited local technical support	(35,44, 45)
Personnel Training	$5,000–$10,000 per lab	$15,000–$25,000 per lab (including overseas training)	Brain drain, lack of standardized curricula	(17,45, 48)
Bioinformatics Setup	Often integrated	Up to $77,000	Poor network coverage	(20,44, 45)
Hidden Costs	Minimal	30–50% (sample transport, power backup, data bundles	Infrastructure gaps increase operational burden	(30,41, 44–46)
Funding Source	Government, institutions	73% rely on short-term grants	Inadequate funds	(5,17, 41)

high-burden settings through targeted interventions that reduce transmission, real-world data from LMICs is scarce (26). Without clear demonstration of long-term economic benefits of WGS like reduced disease burden due to targeted interventions, many governments and donors will remain reluctant to allocate sufficient funding.

3.3. Technical and workforce challenges

The integration of WGS into TB surveillance in low-resource settings is impeded by a shortage of skilled trained personnel (42,48). Unlike conventional TB diagnostics, WGS requires expertise in sequencing protocols, data analysis, and interpretation, all of which are in short supply in many low-resource settings (42). A 2019 survey by the WHO and the Global TB Programme showed that over 70% of laboratories in African countries lack trained personnel capable of handling WGS data and integrating it into public health decision-making (49). This scarcity of skilled bioinformaticians and molecular microbiologists severely limits the scalability of WGS in low-resource settings. Furthermore, genomic literacy among frontline clinicians and TB program managers remains low, often resulting in sequencing results being underutilised or misunderstood in operational contexts (50).

Several pilot initiatives, such as the CRyPTIC consortium and the SEQAFRICA have attempted to bridge this gap by providing training on genomic data interpretation and bioinformatics workflows tailored to TB and antimicrobial resistance (29). However, these efforts often rely on short-term funding and have limited geographic coverage, leaving many high TB-burdened countries without consistent access to capacity-building programs. In Kenya, for example, a pilot WGS-based TB surveillance project faced delays in implementation due to a lack of local bioinformatics expertise, requiring collaboration with international partners for data analysis and interpretation (51). To fully leverage WGS for public health impact, there is an urgent need to invest in sustainable, regionally led training programs in genomic epidemiology that combine theoretical knowledge with practical skills in sequencing, data analysis, and public health integration. Even when genomic epidemiology training programs are available, many low-resource settings persistently experience a challenge of brain drain of skilled personnel due to better opportunities abroad (52).

Many trained bioinformaticians, molecular microbiologists, and laboratory scientists often leave for higher-paying jobs or more research-enabling environments in high-income countries, which leaves many laboratories dependent on external collaborators for bioinformatics support (52). For instance, a regional capacity-building program conducted in East Africa in 2020 reported that nearly 40% of the trainees moved to institutions outside the region within 18 months of completing their training (53). This continuous loss of skilled human resources severely undermines efforts to build sustainable, locally driven genomic surveillance systems. As a result, many laboratories in low-resource settings end up relying heavily on external partners for sequencing, data analysis, and interpretation (52–54). For instance, in Uganda, a WGS-based TB project that initially had shown promise was delayed due to the departure of key staff trained in bioinformatics, necessitating reliance on collaborators in the UK for genome assembly and variant calling (34). This dependency introduces delays, limits local ownership of genomic data, and hampers the development of contextually relevant public health responses. Without deliberate strategies such as competitive remuneration, institutional support, and career development pathways, efforts to integrate WGS into TB surveillance in low-resource settings will remain vulnerable to disruption and external dependence.

3.4. Data-sharing concerns

The global nature of TB transmission warrants international data sharing to support effective surveillance and coordinated public health responses. However, significant technical and ethical barriers hinder the seamless exchange of genomic data between countries. The lack of standardised data formats and interoperable platforms complicates the integration of genomic data from diverse sources (55,56). Many laboratories in low-resource settings often operate with limited technical capacity and incompatible data systems, which makes it difficult to align with global data sharing standards (39). As a result, the fragmentation of data reduces the utility of shared datasets and creates inefficiencies in global TB monitoring efforts. Furthermore, data sovereignty and equity concerns present a significant hurdle to effective data sharing. Many LMICs are understandably hesitant to share genomic data without clear agreements on its use, ownership, and the distribution of benefits arising from downstream research (39,56,57). Past experiences with biopiracy and unfair research partnerships erodes trust, particularly when data from LMICs is used to generate publications or patents with little or no recognition of local contributions. These concerns are exacerbated by the absence of stringent legal and ethical frameworks to govern data sharing and protect national interests (57). In many existing international agreements, researchers from low-resource settings are treated primarily as data suppliers rather than equal partners, further deepening inequalities in global health research (39).

While frameworks like the Nagoya Protocol and FAIR (Findable, Accessible, Interoperable, Reusable) data principles are designed to promote equitable and transparent data sharing, their implementation remains uneven and technically demanding for low-resource settings (58). This is further compounded by the technical and financial challenges accompanying data sharing. Uploading and managing large genomic datasets requires reliable broadband, secure storage, and high computational power resources that are often scarce in low-resource settings (20,55). Moreover, many cloud-based solutions often come with ongoing subscription fees that many institutions in resource-limited settings cannot afford (45). On top of that, many current data sharing platforms are tailored for high income countries, making it hard for low-resource countries to access them (39,56). Tackling these issues calls for investment in locally suited data

infrastructure and the creation of fair data sharing frameworks that acknowledge the contributions of resource-limited countries. Engaging with communities and the local ethics review boards is crucial for ensuring responsible implementation of WGS.

3.5. Ethical concerns

The implementation of WGS for TB surveillance in resource-limited countries brings up some serious ethical questions that need thoughtful consideration. A major issue is patient privacy since genomic data hold extremely highly sensitive information that could be misused if not safeguarded properly (59). In many low-resource settings, the lack of strong data protection laws and poor digital security systems heightens the risk of unauthorised access or breaches, which could lead to discrimination in areas like employment or insurance (56). Moreover, getting an informed consent can be tough in populations with low literacy, where the idea of sharing genomic data might not be fully grasped (59).

Another ethical concern is the potential stigmatisation of communities or ethnic groups that are identified as hotspots for certain TB strains with genomic surveillance unintentionally labelling certain populations as "reservoirs" of drug-resistant TB, resulting in social marginalisation or travel restrictions (37,59). This is more concerning for indigenous communities, where historical mistrust of public health initiatives is greatest. The ethical principle of reciprocity often gets overlooked in current WGS implementation models. Furthermore, the collection and storage of biological samples raise important questions about ownership and future use, particularly when samples are shared with international researchers without clear agreements on benefit-sharing (56,60). While low-resource settings provide samples and data, the benefits of research such as new diagnostics or treatments often tend to flow disproportionately to high-income countries. This "parachute research" approach exacerbates global health inequities and undermines local trust in genomic surveillance programs (61). To tackle these ethical challenges, we need to develop ethical frameworks tailored to the specific contexts of these communities' engagement, transparent benefit-sharing mechanisms, and strong data governance structures.

3.6. Policy and regulatory gaps

The rapid advancement of WGS technology has outpaced the development of suitable policies and regulations in many resource-limited settings. In many of these countries, the absence of specific legal frameworks governing the collection, storage, and use of genomic data presents significant challenges for public health practitioners (57, 62). National TB programs often miss out on policies that would help integrate WGS into surveillance systems. In the absence of clear national guidelines, TB programs are often forced to piece together ad hoc solutions or adopt regulations intended for other purposes, like HIV testing policies, which may not adequately address the unique challenges posed by genomic data. This creates potential legal and regulatory risks for both healthcare providers and patients. Furthermore, regulatory challenges such as delays in adopting WHO-recommended sequencing protocols makes implementation even harder (2,58).

Successful stories like South Africa's use of WGS for tracking MDR-TB underscore how crucial it is to align local policies with global standards (63). The cross-border nature of TB transmission highlights the urgent need for harmonized international policies, yet progress on this issue has been slow. Different national regulations governing data sharing, sample transport, and diagnostic approvals continue to create significant bottlenecks for multinational surveillance efforts (42,57,60). Furthermore, many existing international health frameworks such as the International Health Regulations (2005), were not designed with genomic surveillance in mind, resulting in critical governance gaps. Addressing these challenges will require coordinated, multisectoral collaboration across health, science, and justice ministries, alongside meaningful engagement of the affected communities so as to ensure ethically sound and context-appropriate policy.

Intellectual property (IP) issues present another significant policy gap. Currently, there is no internationally accepted way for managing IP rights related to TB genomic data, which can easily spark disputes over how research findings are to be commercialized (64,65). In many low-resource settings, there is inadequate legal expertise to negotiate fair IP agreements with international partners, which could potentially result in missed opportunities for local biotechnology development. Furthermore, current IP frameworks often overlook traditional knowledge associated with TB management in low-resource settings, leading to ethical and legal dilemmas.

4. Strategies for equitable and sustainable implementation of WGS in TB surveillance in low-resource settings

Sustainable integration of WGS into TB control programs in LMICs requires careful coordination with national public health strategies. The WHO Global Genomic Surveillance Strategy for Pathogens with Pandemic and Epidemic Potential 2022–2032 provides a critical framework, encouraging member states to incorporate genomic surveillance into their existing disease control systems (66). For TB-endemic countries, this means explicitly integrating WGS in their national strategic plans, for example by setting targets for genomic characterisation of a defined proportion like at least 20%) of MDR-TB cases and incorporating sequencing data into routine surveillance reporting (67). Kenya's National TB Strategic Plan 2023–2027 provides a pertinent example, outlining concrete measures to strengthen genomic capacity through partnerships with academic and research institutions such as Kenya Medical Research Institute (KEMRI) and by embedding WGS indicators within its laboratory system strengthening framework (51). Academic institutions play a critical role in these partnerships by providing technical expertise and providing hands-on training in genomic TB surveillance and diagnostics to students. Complementarily, research institutions contribute by laboratory infrastructure for WGS laboratories and facilitating essential practical training to students. Together, such partnerships can harness combined academic and industry to support the establishment of decentralized rapid pathogen WGS units within these institutions. Furthermore, strategic collaborations between hospitals, research, academic institutions and commercial Next Generation Sequencing (NGS) providers such as bioMérieux, Macrogen, Oxford Nanopore MinION/GridION, and Illumina can facilitate effective WGS implementation, through cost-benefit sharing models (30,40).

Beyond cost-sharing, these partnerships have the potential to address some of the perceived TB WGS implementation barriers including financial, skills-related, and infrastructural constraints. Ultimately, such policy-level commitments are essential to ensure that genomic tools move beyond mere research initiatives and become integral componentsof public health decision-making. However, policy alignment alone is insufficient without parallel investments in implementation infrastructure. A multifaceted approach is therefore required, one that integrates WGS into existing diagnostic networks while strengthening local laboratory capacity and establishing regional reference sequencing hubs is essential. These reference hubs could be collaboratively established and co-supported by the neighboring countries through an integrated TB laboratory surveillance networks. A tiered service delivery approach has been proposed whereby local reference laboratories perform targeted sequencing for high-priority cases such as drug-resistance screening, while broader surveillance samples are processed at regional hubs (63). This public health strategy optimises resource allocation by concentrating advanced sequencing capacity where it is most needed, thereby reducing delays in diagnosis of complex cases. In parallel, there is growing advocacy for public-private partnerships and shared funding models to mitigate cost barriers, with evidence indicating that collaborative financing mechanisms can improve

sustainability of TB genomic surveillance in low-resource settings (61, 67). The effectiveness of this approach has been demonstrated among mine workers along the Botswana–South Africa border (19,20), and it holds particular promise for resource-constrained settings where regionalized hubs can help offset national capacity limitations These approaches are further supported by findings from pilot programs in high-burden countries, where tiered service models systems improved turnaround times for drug resistance profiling, and public-private collaborations expanded access to sequencing without overburdening public health budgets. Collectively, such frameworks address infrastructural and financial constraints while promoting a more equitable adoption of WGS across endemic regions (67).

Others argue that public-private partnerships and shared funding models could help distribute costs more equitably. A qualitative study in Botswana found that TB program stakeholders broadly support introducing WGS-based surveillance provided that implementation is accompanied by adequate planning, sustainable funding, and meaningful community engagement (19). Without dedicated funding and sustained political goodwill, the high costs of sequencing technologies, laboratory upgrades, and cold chain logistics will continue hindering equitable access (67). Innovative financing strategies including public-private partnerships and global health funding initiatives such as the Global Fund and TB Alliance, offer viable pathways for sustainable WGS integration. Concurrently, strategic investments in decentralised diagnostic networks and laboratory infrastructure are needed to address operational bottlenecks. Economic evaluations further support the feasibility of this transition as cost-effectiveness modelling suggest that centralised targeted next-generation sequencing (tNGS) for TB drug resistance is likely to be cost-saving in high-burden settings, while decentralised tNGS may also be cost-effective when optimised for efficiency (42). Studies from India and South Africa indicate that tNGS are more cost-effective than the conventional culture-based phenotypic methods, largely due to faster drug resistance detection, earlier diagnosis and improved operational efficiency (4). Additionally, WGS has enhanced TB case detection by enabling identification of TB transmission clusters, mixed infections, and cryptic cases missed by conventional surveillance approaches (6). These data-driven insights should guide investment priorities, ensuring that limited resources are directed toward high-impact genomic surveillance strategies. Without such advances, persistent infrastructural gaps risk perpetuating global disparities in TB control and leave endemic regions disproportionately burdened drug-resistant TB.

New portable sequencing technologies like Oxford Nanopore's MinION are showing great potential for decentralised WGS in areas where TB is endemic, though questions remain about their accuracy and scalability for routine surveillance (22,68). Nanopore sequencing rapidly (<48 hours) generates clinically actionable data on *Mycobacterium tuberculosis* (MTB) drug resistance and strain typing, even in resource-limited environments. However, its accuracy depends on the quality of DNA extracted and bioinformatic processes used, with error rates of approximately 5-10%, higher than those seen with Illumina sequencing, but still achieving >90% concordance for detecting resistance variants (68). Other hurdles to overcome include the need for standardised procedures and trained staff, though capacity building initiatives such as the Nanopore Community in South Africa are helping to address these gaps. While nanopore sequencers are not yet a replacement for high-throughput surveillance systems, they are increasingly becoming more practical for targeted applications including outbreak investigations and use in remote settings where conventional sequencing is not feasible. Continued improvements in library preparation and real-time analysis tools, are likely to enhance their utility for TB control.

Beyond portable platforms, emerging cost-reduction strategies may further expand access to TB genomic surveillance in low-resource settings. Low-coverage whole-genome sequencing (lcWGS), for example, involves sequencing at shallow depth, often below 5× coverage, drastically reducing costs and turnaround times. While individual datasets are sparse, computational approaches such as genotype imputation or reference-based inference can accurately reconstruct essential genetic information. Proven in other fields like human and animal genomics (69), lcWGS could enable rapid, large-scale TB screening for key variants, including drug-resistance mutations and lineage markers, at a fraction of the usual cost. Modeling studies suggest that even decentralized targeted sequencing can be cost-effective in high-burden settings when optimized.

Furthermore, reduced-representation sequencing methods, such as RADseq, offer a complementary strategy by sequencing only selected subsets of the genome using restriction enzymes to target reproducible loci. This approach enables higher coverage per locus and allows multiplexing of many samples in a single sequencing run. In the context of TB surveillance, RADseq-like strategies could be tailored to include drug-resistance genes, lineage-defining single nucleotide polymorphisms (SNPs), and hypervariable regions, enabling efficient variant detection without the need for full-genome coverage. Unlike targeted amplicon panels, RADseq can also capture novel variants, providing flexibility while substantially reducing sequencing costs and data volumes.

Strengthening TB genomic surveillance in resource-limited settings will therefore require a combination of innovations, including culture-free and portable sequencing technologies, lcWGS and RADseq, and the use of both local and cloud-based analytical tools. Combing these approaches with supportive policies and sustainable capacity-building efforts can bridge the implementation gap, and ensure that genomic advances benefit all populations affected by TB, not only those in well-resourced laboratories. Once sequencing data are generated, robust bioinformatics analysis is essential to translate raw reads into actionable outputs such as strain identification, drug resistance prediction and transmission clusters. However, this is often computationally demanding, and many low-resource settings face significant limitations in internet connectivity, computing infrastructure, and bioinformatics expertise. Two broad approaches have emerged for TB WGS analysis: Cloud-Based Platforms and locally deployed tools. Cloud based user-friendly pipelines such as TB-Profiler, GenoMycAnalyzer, PhyResSE, SAM-TB, and integrated platforms like MAGMA-MICK (70) allow laboratories to upload sequencing data to remote servers and receive automated reports on lineage assignment and drug-resistance predictions (70–73). These platforms lower technical barriers by outsourcing computation, enabling near real-time clinical decision support, and facilitating tailored treatment, including resistance prediction for newer drugs such as bedaquiline (7). By reducing diagnostic delays and improving treatment precision, such tools offer both clinical and public health benefits, including more efficient use of limited resources. Notably, many newer platforms are intentionally designed as intuitive web applications requiring minimal local setup, further enhancing accessibility (74,75).

Despite these advantages, reliance on cloud-based analysis presents challenges, particularly in high-burden regions with unreliable internet access. Large sequencing files can be difficult to upload over slow networks, and connectivity disruptions may delay results. Concerns around data sovereignty, privacy, and long-term subscription costs also require careful consideration, even where platforms offer encryption and secure servers. As an alternative, locally run (offline) bioinformatics tools such as Mykrobe and command-line versions of TB-Profiler allow analysis to be performed without internet connectivity, offering greater data control and potentially lower long-term costs (76,77). However, local analysis requires adequate computing hardware and trained personnel, both of which remain scarce in many TB-endemic settings. To address this gap, portable sequencing and analysis setups and targeted bioinformatics training programmes are increasingly being deployed, enabling on-site analysis even in remote locations. In practice, the optimal solution is often a hybrid model that leverages on cloud-based tools for rapid deployment while progressively building local

analytical capacity to ensure long-term sustainability and data autonomy.

That WGS has detected drug resistance to anti-TB drugs more accurately than conventional methods (29) fosters the potential benefits for resource-constrained countries in mitigating TB infection effects on the meagre resources available. However, as sequencing technologies continue to advance rapidly, there's a pressing need for continuous workforce training, which is difficult to sustain in low-resource settings. Strategic local capacity-building initiatives through partnerships with academic institutions and international organisations are crucial for long-term sustainability. For instance, the Pan-African Network for Genomic Surveillance is enhancing TB sequencing capabilities across 12 African countries by training scientists and standardising protocols. Similarly, a World Bank-supported initiative led by South Africa's Centre for Epidemic Response and Innovation has set up genomics laboratories and trained over 200 fellows in multi-pathogen surveillance, including TB. These initiatives complement existing frameworks like the H3Africa Bioinformatics Network, which has created sustainable training models for genomic data analysis (57). Such collaborative efforts demonstrate how institutional partnerships can build long-lasting genomic capacity in low-resource settings while avoiding brain drain.

5. Conclusion

To unlock the full potential of WGS for sustainable TB surveillance in low-resource settings ultimately relies on three key interdependent pillars: (1) robust physical and digital infrastructure to support reliable sequencing and data analysis; (2) investment in local expertise to ensure sustainable long-term operational capacity; and (3) stable, predictable funding mechanisms that align with national health priorities. However, technological adaptation is insufficient. Realising the public health value of WGS also requires policy frameworks that bridges the gap between genomic innovation and frontline healthcare service delivery. This entails high-level strategic commitments, such as embedding WGS in national TB surveillance plans, alongside careful operational planning across the entire system, from standardised sample referral protocols to data-sharing agreements that fit local health systems. Only through such comprehensive, context-sensitive integration can WGS transition from a predominantly research tool into an equitable, transformative component of global TB control.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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