




BMJ Open Complexities and benefits of adopting next-generation sequencing-based tuberculosis diagnostics: a qualitative study among stakeholders in low and high-income countries

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ABSTRACT

Objectives To clarify perceived benefits, barriers and facilitators of *Mycobacterium tuberculosis* next-generation sequencing implementation in Madagascar and Canada, towards informing implementation of this diagnostic technology in public health agencies and clinical settings in and beyond these settings.

Design This qualitative study involved conducting semistructured interviews with key stakeholders engaged with next-generation sequencing implementation in Madagascar and Canada. Team-based descriptive analysis supported by Nvivo V.12.0 was used to identify key themes.

Setting The study was conducted with participants involved at the clinical, diagnostic and surveillance levels of tuberculosis (TB) management from Madagascar and Canada.

Participants Eighteen participants were interviewed (nine Madagascar and nine Canada) and included individuals purposively sampled based on involvement with TB surveillance, laboratory diagnosis and clinical management.

Results The following five themes emerged in the analysis of Malagasy and Canadian interviews: (1) heterogeneity in experience with established TB diagnostics; (2) variable understanding of new sequencing-based diagnostics potential; (3) further evidence as being key to expand adoption; (4) ethical arguments and concerns; (5) operational and system-level considerations.

Conclusion There persists important lack of familiarity with TB next-generation sequencing (TB NGS) applications among stakeholders in Canada and Madagascar. This translates into skepticism on the evidence underlying its use and its true potential value added within global public health systems. If deployed, TB NGS testing should be integrated with clinical and surveillance programmes. Although this is perceived as a priority, leadership and funding responsibilities for this integration to happen remains unclear to clinical, laboratory and public health stakeholders.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This study provides unique insight into gaps in evidence and experience, ethical and operational questions that need to be filled and answered prior to next-generation sequencing (NGS) diagnostics' successful implementation within national and global public health systems.
- ⇒ Some participants in this study noted their limited familiarity with existing evidence as well as limited experience with tuberculosis (TB) NGS diagnostics.
- ⇒ This is an exploratory study with a small sample size. More diversity in experiences and perceptions may exist in each country.
- ⇒ This study was conducted with participants in two countries with low TB drug resistance and findings may differ in regions with a different epidemiology.

INTRODUCTION

In April 2022, the WHO released its first ever strategy for global genomic surveillance of pathogens with pandemic and epidemic potential.¹ There is hope that recent successes in rapid sequencing, data sharing and supranational information integration can be translated from COVID-19 to other diseases, including tuberculosis (TB), where delays in access to global drug resistance and transmission data have long hampered surveillance efforts.²

Appropriately treating patients with TB, including those infected with drug resistant strains, and tracing contacts have become even more important to recover from the recent COVID-19-related set back in the fight against TB.³ Next-generation sequencing (NGS) technologies and genomics-based diagnostics represent the latest revolution in TB microbiology diagnostics since the advent of Xpert MTB/RIF (Cepheid, Sunnyvale,

California) PCR platform. NGS refers to new laboratory platforms, which allow high throughput DNA sequencing and can, hence, be used to sequence a bacterial whole-genome sequence (WGS) for downstream analyses. The *M. tuberculosis* genome hold extensive information on drug resistance and its relative evolutionary distance compared with other isolates. NGS technology and TB WGS can, thus, guide the choice of personalised therapeutic regimens and support or refute putative person to person transmission hypotheses.⁴⁻⁸ With recent progresses on both the laboratory and the bioinformatics components of genomic-based diagnostics workflows, it is suggested that this approach could be more rapid and cost-effective compared with conventional culture-based drug susceptibility testing (DST).^{9 10} Hence, TB DNA sequencing promises to play a significant role in universal access to DST and interruption of transmission chains.

The uptake of novel diagnostics cannot be taken for granted. The experience of Xpert MTB/RIF global adoption and market penetration exemplifies how clinical performance, WHO endorsement and end-users' enthusiasm alone do not necessarily translate to rapid and disseminated uptake.^{11 12} Despite technical guidelines and laboratory methods standardisation efforts, significant barriers to DNA sequencing-based diagnostics adoption remain.¹³⁻¹⁵ These include users' (stakeholders and public) anticipated or experience-based ethical challenges inherent to genomics data sharing, which have previously been explored.^{16 17}

Beyond data sharing challenges, this study takes a first step in understanding stakeholders' perceptions of the value added and implementation complexity within specific health systems: one high-income and one low-income setting. Understanding that individuals with different professional backgrounds, roles and responsibilities will use and potentially understand new TB diagnostics in distinct ways, this study captures perceptions from a diversity of clinical, laboratory and surveillance stakeholders in two contexts exemplifying the case scenarios of low TB incidence/high-income and high TB incidence/low-income countries (LICs): Canada and Madagascar. In doing so, this study generates original and needed evidence on human and contextual factors that may impact DNA sequencing-based TB diagnostics adoption.

Context

Madagascar exemplifying low-income high TB incidence settings

Madagascar is a LIC with a gross national income of US\$520 per capita, the ninth lowest in the world.¹⁸ In health as in other sectors, financial challenges are omnipresent and partially result from an unfavourable investment environment, severe infrastructure deficit and political instability with two recent crises in 2002 and 2009.

In Madagascar, TB control remains a public health challenge with only 36 122 of the WHO estimated 66 000 (238/100 000 population) patients infected with TB being appropriately diagnosed and notified to the

National Tuberculosis Program (NTP).¹⁹ In 2020, apart the in-kind contributions from the Malagasy government including medical staff salaries and health centres buildings, the TB-specific programme of Madagascar the programme reported a cumulative annual budget of 6 million USD and was funded by international sources including contributions from the Global Fund to fight AIDS, Tuberculosis and Malaria and operational research funding supporting partnerships with international and domestic academic institutions.

Like other low and middle-income countries, Madagascar faces significant challenges with respect to novel diagnostics implementation, including underfunding, paucity of trained laboratory personnel, low geographic coverage of centralised diagnostic facilities, remoteness and sparse distribution of rural communities and complex sample transportation systems. Research collaboration has fostered local evaluation of targeted molecular assays for DST, including Xpert MTB/RIF, which is currently being further scaled up throughout the country.^{20 21} Conventional TB molecular epidemiology methods were also previously used to track disease transmission among vulnerable populations and identify disease 'hot spots' in Antananarivo, the capital city.²² TB WGS testing was first implemented in the country in 2018 to improve reference DST capacity, contribute to global standardisation efforts and better inform local choices of diagnostic platforms and algorithms.^{23 24}

Canada exemplifying high-income low TB incidence settings

Canada is a high-income country (HIC) with a gross national income of US\$44 940 per capita. TB services are integrated within one of the world's most developed and accessible health system.

Canada has not achieved TB elimination. In 2020, the number of reported active TB cases totalled 1765, representing an increase from the previous year and 80.2% of the 2200 cases estimated to have occurred.¹⁹ Despite low rates of drug resistance, TB remains a public health concern due to disease reactivation following immigration, episodic domestic person-to-person transmission and ongoing outbreaks within remote communities.²⁵⁻²⁷ Case distribution is disproportionate, with most cases presenting in foreign-born individuals (71.8%) and Canadian-born Indigenous populations (17.4%), where rates reached 360/100 000 population between 2012 and 2015, a higher rate than most sub-Saharan African countries.²⁸ As is the case in most HICs, TB services in Canada are entirely funded by the country's public health system.

Canada's clinical, reference and research laboratory networks have significant capacity and experience with NGS technologies and those were further improved in the recent COVID-19 pandemic as demonstrated by the country's contributions to global pathogen genomic surveillance efforts.²⁹ Despite this expertise and capacity, Canada has not implemented systematic prospective TB sequencing programmes to date. The potential benefits of such programmes are expected to be distinct from

those observed during the COVID pandemic given the intrinsic differences between both pathogens' modes of transmission and therapeutic challenges. Isolated initiatives from provincial and academic laboratories have leveraged this approach to better understand disease transmission in Canadian subpopulations, but these are research rather than care and treatment driven.^{30 31} Canada faces its own challenges when it comes to the implementation of innovative diagnostics for TB control. Prioritising interventions within a finite domestic budget to ensure relevance and equity in access to services is one of them. When improved diagnostics are deemed part of the solution, reaching the highly dispersed population in Canada also represents a logistical challenge.

METHODS

This is an exploratory qualitative study,³² aiming to surface new insights on, rather than conclusively define, engagements with DNA sequencing-based TB diagnostics in Canada and Madagascar. Qualitative studies are well suited to gaining rich, detailed understanding of social phenomenon, including insight into how new technologies are being understood and used. Data collection involved semistructured interviews. Data were analysed via directed thematic analysis attentive to country-specific differences and similarities in perceptions of DNA sequencing-based TB diagnostics.

Sampling and recruitment

Sampling and recruitment for this study were purposive and reflected the study's exploratory goals. We aimed for maximal diversity in participants' experiences with TB diagnostics in each country. This was in line with norms of sampling in exploratory qualitative research, wherein the goal is to access a range of perspectives to advance understanding of a phenomenon.^{32 33} Each interview would provide a unique perspective on TB WGS adoption within a shared setting (a national health system), rather than being approached as representative of a participant category in a country.³²

The first author and co-PI (SGL) is a clinician scientist working with new TB diagnostics in Canada and Madagascar. His familiarity with TB diagnostic implementation processes and key actors in both settings served to develop a list of potential participants: care providers, diagnostics personnel, disease surveillance experts and policymakers. Some were part of the extended clinical and research networks of the investigators, whereas others had the relevant skill sets and positions within healthcare systems without having had prior contact with the investigators. Cautious not to over-represent experts in TB genomics research, we aimed for the majority of participants to be involved in routine TB work within the Malagasy and Canadian health systems. We also aimed for a balance of Malagasy and Canadian participants, and for participants with diverse levels of familiarity with new TB diagnostics based on their roles and responsibilities vis a vis the actual

or anticipated use of new TB diagnostics. All potential participants had to be fluent in either French or English.

The initial list of potential participants included 24 individuals—12 from each country. Participants matching the prespecified and diverse expertise profiles in both countries were directly approached by the investigators. A total of 18 participants ultimately agreed to being interviewed, including nine participants from each country: six worked primarily in clinical practice, with face-to-face patient interactions; six worked in surveillance; six were lab based. Participants with distinct expertise were equally represented in both countries.

Data collection

Semistructured in-depth interviews occurred between June and September 2019 and occurred in person or by phone depending on the participant's preference. Interviews were digitally recorded with participants' permission, lasted between 30 min and 2 hours and were administered using an interview guide developed collaboratively by the team in advance (see online supplemental materials 1) based on the team's interdisciplinary expertise and following piloting of the guide.

Semistructured interviews are well suited to exploratory studies aiming to build understanding not only of how, why and by whom new technologies are being used within a given context but also on what bases these engagements are occurring: based on what prior knowledge, experiences and contextual factors or considerations? With an eye to eliciting such detail, the interview guide was organised around the six following axes¹: current involvement with TB diagnostics²; technical understanding of new diagnostics³; perceived accuracy, limits and potential of TB DNA sequencing for DST⁴; perceived value added and limits of DNA sequencing for molecular epidemiology and surveillance⁵; experienced and anticipated challenges and impacts of integrating and expanding use of new TB diagnostics in national health system⁶; perceived access and equity issues. In accordance with the semistructured interview approach, the order of questions did shift slightly across interviews, as the interviewer left space for the participant to answer questions in ways that sometimes merged responses to questions in the guide. Follow-up questions posed to participants likewise were contingent on statements made by a participant, and interview-specific need for clarification.

Analysis

Interviews were transcribed verbatim by two trainees and verified against the original audio for accuracy by a bilingual member of the team. All transcripts were uploaded to NVivo V.12 (QSR International), a widely used computer-assisted qualitative analysis software, to facilitate directed and thematic analysis.³⁴ The directed approach involved establishing an initial tree of themes based on study goals reflected in interview question axes, such as 'Knowledge of the Technology' and 'Equity considerations'. From this point of departure, two members of the team (C-AB and

EN) independently coded four transcripts to propose adjustments to the initial thematic categorisation of findings and to identify specific subthemes. They compared and reached consensus on a revised coding structure then used by other team members who had also read transcripts and noted dominant themes in the data. With all in agreement on this revised coding structure, one member of the team proceeded to code all transcripts line-by-line. Names of key themes and the number of subthemes were revised slightly as the analysis proceeded.

The Principal Investigators (SGL and EN) reread all transcripts against the NVivo organisation of the data as an additional verification that the themes reflected and accurately captured all key data. Coauthors then met for a team analysis session. Agreement was reached on key findings reflected in the NVivo codebook, and each author worked to draft proposed wording for a synthesised description of a key finding, including overarching patterns, differences and similarities between Canadian and Malagasy content. Team members collectively reviewed and agreed on revisions as necessary to the description of findings and the choice of supporting quotes. This team-based discussion and writing form the basis for the findings presented below.

Patient and public involvement

Neither patients nor the public were involved in the design, or conduct, or reporting or dissemination plans of our research.

RESULTS

Key themes identified are described below. These include: (1) heterogeneity in experience with established TB diagnostics, (2) variable understanding of new DNA diagnostics potential, (3) evidence key to expand adoption, (4) ethical arguments and concerns, (5) operational and system-level considerations. In what follows, we elaborate on each of these with illustrative quotes (Quotes from French language interviews were translated into English by the fully bilingual co-PIs (first and last author)), highlighting similarities and differences between perceptions from Canada and Madagascar and across participant categories (clinical, lab based, surveillance based).

Heterogeneity in experience with established TB diagnostics

In both countries, all clinicians were aware of the expanding use of TB DNAseq-based diagnostics but expressed being more comfortable with, and relying on, clinically available PCR diagnostics including Xpert MTB/RIF and culture-based TB isolation and DST.

In both Canada and Madagascar, clinician participants had limited experience with translation of TB DNAseq technologies to clinical care and patient management. Canadian clinicians all confirmed routinely using PCR diagnostics, but none reported requesting or being provided sequencing reports on a routine basis.

Canadian participants expressed some familiarity with NGS as a technology given its use in several medical application other than TB:

It's not new, because you know for HIV we did this. So we developed in 2001 some genotypic tests to predict HIV phenotypic resistance to antiretrovirals, and it works really really well (P0/Canada/Clinician).

While most Canadian laboratory participants were unsure how DNAseq technology compared with other new emerging technologies such as proteomics and how this new approach would be deployed in a whole genome versus targeted sequencing approach, some were aware of specific routine implementation in distinct settings.

You've got a few groups: Public Health England, for example, the state lab in New York, to a certain extent, CDC in Atlanta, that did decide to make the switch completely [to TB DNA sequencing]. But for a lot of the smaller state labs [...] they're really just using exactly the same techniques (P15/Canada/Surveillance).

In Madagascar, only one of the three clinicians interviewed routinely used Xpert MTB/RIF and none expressed familiarity based on prior use in non-TB contexts. One Malagasy individual involved in surveillance seemed to have more experience with the technology, and ascertained its value added in accelerating diagnosis of TB and prediction of multidrug resistant (MDR)-TB resistance profiles:

For me, the GeneXpert is really a plus, because in two hours you can know if it's really tuberculosis, and if it's resistant or not. So, it has improved a lot. Before, we used to wait for the culture for three months (P11/Madagascar/Surveillance).

Variable understanding of DNA sequencing diagnostics potential

Alongside limited usage came uncertainty among clinicians and some surveillance experts in Canada and Madagascar about how this technology would complement already existing techniques and transform the diagnostic and patient care landscape. Some of the participants mischaracterised DNA sequencing's role or technical capabilities with other already available diagnostic platforms. As participants noted, they had heard of the diagnostic advantage of DNA sequencing at conferences, but they did not feel able to comment specifically on how it would represent an advantage over already available methods. Many participants were unclear as to whether DNA sequencing could be used as a first-line assay and whether it would improve screening, diagnosis and/or DST.

Will it help with screening? Especially for MDR-TB? (P11/Madagascar/surveillance).

But you know, you have to see, you know, if on average, I get a result that's PCR-positive, smear-positive, I get the culture about a week later, a liquid culture confirmation a week later. Is the sequencing going to be faster than that? Well if it's faster by two days, is that really going to make a difference? (P2/Canada/Surveillance).

It's done from, again, the isolates, and it seems to me, I don't think I've seen any publications yet that allow for direct sequencing from biological samples (P5/Madagascar/Surveillance).

Despite heterogeneity in familiarity and understanding of the technology, the potential role of DNA sequencing to accelerate access to DST results emerged as a hope among almost all participants in both settings. Despite low rates of resistance in the country, Canadian participants highlighted this as an advantage, though the perceived importance of this advantage was variable.

I think the rapidity of results compared to phenotyping which can take oneweek, twoweeks, to get the result, I think that is a big advantage (P0/Canada/Clinician).

Uncertainty about how much faster would be to get sensitivity results. If a couple of days sooner, is that worth it? (P2/Canada/Surveillance).

Lack of familiarity with the practical potential of new TB DNA sequencing technology contrasted with more extensive understanding of this technology's potential at the laboratory level in both countries. Comprehension of that potential did vary across participants. Value of TB DNA sequencing for epidemiological investigations and outbreak identification emerged as particularly obscure to Malagasy participants who could not identify specific situations where it had been or could be used for such application in their specific setting. Some indicated support for expanded use of sequencing, but to accelerate diagnosis, reflecting a lack of familiarity with the additional epidemiological information generated by the new technology.

We already have, as a standard here, as a first intention the GeneXpert. We can see the results in an hour. And if it's [sequencing] specific, and if it's faster than that, and if it's cheaper than that, why not? (P4/Madagascar/Laboratory).

In Madagascar, since molecular epidemiological analyses had so far relied on testing at a centralised lab and within a research context, participants were unsure how data generated through DNA sequencing could realistically serve in case finding at the community level. Some participants identified some potential value in differentiating reinfections from relapse in patients experiencing a second episode of TB infection. Others referred to the potential of sequencing to identify bacterial lineages.

Because a patient that's having a relapse: is it a relapse or is it treatment failure of the initial strain? (P5/Madagascar/Surveillance).

The objective is to know which strain is responsible for someone's disease (P8/Madagascar/Laboratoire).

In Canada, mostly surveillance experts explicitly noted the epidemiological value added of past and current DNA-based diagnostics to support TB-focused public health efforts. Perception of added value varied between interviewees based on their respective previous experiences, ranging from participants believing it would not significantly impact TB control efforts to others suggesting the implementation of national genomics-based surveillance networks.

So, I think the main use-case is that epidemiological intelligence that you get into your provincial or your state situation, identifying clusters that do need active management and public health follow up (P15/Canada/Surveillance).

Epidemiological investigations did identify outbreaks mostly, and then, the added value of sequencing wasn't trendy anymore because it did not add something clinically significant really (P2/Canada/Surveillance).

And it would be good eventually that there would even be a Canadian network for this. There would eventually be a possibility to create a TB molecular epidemiology reference center, based on the genome. (P0/Canada/Clinician).

Evidence perceived as key to expanded adoption

As is clear from above, not all participants had a strong grasp of the current state of DNA sequencing technology and its potential. Participants in both settings who did seem less familiar with the technology asserted that expanded adoption would hinge on solid evidence of the technology's value added over previous approaches. As one participant noted,

Demonstrate a benefit over what's already out there, an added value, define it however you want. That's going to be the best message that can be pitched or the biggest hurdle if it's not demonstrated (P2/Canada/Surveillance).

No doctor, clinician, will refuse if there is evidence (P7/Madagascar/Clinician).

A few differences were notable in the ways in which the importance of evidence was framed by Canadian versus Malagasy participants. Canadian participants stressed, for example, the need for proven changes on *clinical impact* beyond the intrinsic capabilities of the technology for DST and phylogenetic. Canadian participants' analysis was rooted in the context of already available standard of care diagnostics for all.

It would be interesting to know that if we identify that much, what would it change? Because sometimes it's fun but sometimes it's not relevant. It's like us, it's just diagnosis, treatment. Sometimes if you want to know what exactly it is, but if it doesn't change the treatment, you have to ask yourself why you're investing time and money in it, if it doesn't change anything for the patient. If it makes a major difference, well, that's what sells, and people will buy it (P12/Canada/Laboratory).

Malagasy participants not only noted the importance of proving impact on clinical outcomes but also raised concerns regarding available evidence supporting the use of sequencing to identify MDR strains in general, and specifically in the high incidence context of Madagascar. Furthermore, they stressed the importance of locally generated evidence to support larger implementation. Regarding the value added of molecular epidemiology, participants were sceptical that having the ability to cluster TB isolates together and perhaps infer person to person transmission would have a significant impact on the epidemic given the important incidence of disease and disseminated transmission.

I think that the sensitivity and specificity of this, of sequencing for the detection of resistance, of mutations responsible for resistance, should still be evaluated. I think that a comparison should be made with conventional methods (P5/Madagascar/Surveillance).

The clinical impact is something else because in Madagascar, tuberculosis is so, at the moment I have the impression that it has spread so much in the community that if we manage to put a chain of transmission that we would discover sequencing and all that, and does it really have an impact clinically? (P10/Madagascar/Clinician).

Malagasy respondents more commonly emphasised the key role evidence would play in determining whether current practice in the country would change.

If we want the National Program and the Ministry to recommend the use of sequencing, I think that we must first demonstrate in a project or a study the importance of this examination (P3/Madagascar/Clinician).

And also to install this as an operational diagnostic method at the level of the Ministry of Health, we need to, that the authorities are convinced, with the results with the input. We need a lot of evaluations with real patients and also I think we need a big study on the evaluation of the sensitivity and specificity of sequencing compared to other standard diagnostics (P4/Madagascar/Laboratory).

Several Canadian participants noted the importance of proving cost-effectiveness within the country's public health system and its finite resources, to justify adoption.

We need to see what the cost-benefit is of wanting to implement this, compared to what already exists, that's the first question to ask (P2/Canada/Surveillance).

Malagasy participants were not as explicit about the need for cost-effectiveness evidence. Many did, however, note cost as a barrier to adoption, and the contingency of adoption on external funding. Statements such as the following do indicate the likely need for some cost-effectiveness studies in the country, to justify investment.

But the problem with these new tests is mainly the cost. The cost of the tests is high and that's why we can't diagnose all the samples with culture. Because it is expensive (P4/Madagascar/Laboratory).

So, therefore, it has to be funded by the government, if you will. Through what, I don't know, should it be financed through the Global Fund, or through donors... It should be in the budget, it should be in the program budget. But from which donor? (P5/Madagascar/Surveillance).

Canadian participants generally expressed more caution towards implementing new technologies for the sake of implementing new technologies. In Madagascar, some participants suggested that despite available evidence and immediate clinical benefits, deploying DNA sequencing technology was also a means to ensure participation in research efforts and enrich the country's understanding about its own TB challenges.

I think we need to move forward on research. To know a little bit about what is happening in Madagascar, because there have never been any studies done in this sense (P7/Madagascar/Clinician).

With the technology being new, it was unsurprising to hear participants underline the need for further development and validation studies. One participant did make an interesting comment, though, that suggests it may be important to question the degree of evidence expected to justify adoption, given no TB diagnostic interventions have been perfect.

But I also think when we are rolling out whole-genome sequencing as a diagnostic tool, people get them a little bit too focused on perfection and don't realize that every other test that we've used in the past is nowhere near perfect, either (P15/Canada/Surveillance).

Ethical arguments and considerations

Pending evidence of proven impact on TB control, Canadian and Malagasy participants raised ethical arguments in favour of, as well as ethical concerns related to, sequencing adoption within TB national programmes. Both countries' participants stressed the technology's inherent value if and where it enabled getting the most appropriate treatment to patients faster, and,

thus, improved health outcomes. Canadian participants also noted adoption might constitute the 'right' way to proceed, if this could reduce costly hospitalisation and, thus, enable more cost-effective stewardship of public healthcare resources:

Well, for sure, if there was a way to get it done faster, then reduce delays, it could be interesting for patients, and then ultimately it can save hospital days, which is probably what costs the most in the system, well, it's win/win, I think (P1/Canada/Clinician).

While cost-effectiveness was a clear ethical consideration among Canadian participants, moving responsibility for investment in adoption beyond the public health system raised its own set of ethical concerns. One participant from Canada flagged the possibility that sequencing procedures might be contracted out by the Canadian government to private companies. Such a scenario raised clear ethical concerns for this participant, with respect to ownership of biological samples, in particular.

You know, it depends on how it's done. If you say, 'we're going to do it here and then such and such a company is interested in developing X business, we're going to send the specimen back to them' and then after that they still own the specimen and they can do whatever they want with it, you know, that, that's not going to work, ethically. (P1/Canada/Clinician)

In Canada, given the small number of TB cases, the same participant noted that epidemiological results reporting would need to be limited to avoid personal identification.

Whether managed privately or not, routine sequencing would need to be paired with a thoughtful plan for the ethical management and sharing of data, to ensure appropriate consent from patients.

Because afterwards, if you want to be able to do, if you want to be able to exchange your information with the other provinces, with the United States, with the rest of the Western countries. Then it also requires, at the ethical level, an informed and prolonged consent, where you don't have to go back to your patient every ten years to ask them to consent (P2/Canada/Surveillance).

Several participants in both country settings mentioned that DNaseq technology might improve health outcomes for particular populations with known higher rates or risks of TB. Within the Canadian context, several participants stated benefits of adoption could be most significant for Indigenous populations. In Madagascar, participants highlighted the value of the technology if applied towards reducing high TB rates among incarcerated individuals in the country, or to improve TB care for Malagasy living in remote regions. Plans to expand use of sequencing, however, would need to be intentionally designed to ensure benefit to these populations in greatest need. As one Canadian participant recalled, sequencing had been

used in recent outbreaks in the North. This had built understanding of transmission patterns within high-risk Indigenous communities, but this had not, to the participants' knowledge, led to a reduction in outbreaks.

While participants in both countries recognised the potential for DNaseq technology to reduce health inequities, Malagasy participants also cautioned that inequities might be deepened in the process of adoption. Specifically, concerns were raised with respect to building up capacity for sequencing exclusively in the country's capital of Antananarivo, as this could reproduce existing inequities between urban and non-urban Malagasy.

Sending the sample to Antananarivo discourages many people from taking the test (P3/Madagascar/Clinician).

For me, can we... the concern, if you use it just in Tana, won't it make a bit of bias, because it's already, in Tana everything is already available. You will still hammer there, it is just in Tana. But, how can it be that it is necessary to make, at the beginning, in the big cities for example, in the six provinces for example, the six big provincial capitals. And then, if it works, we will perhaps scale it up in the regions, little by little, but not directly. But not just in Tana too, but in the provinces and then, if it works well, in the regions. I don't know (P11/Madagascar/Surveillance).

Finally, wider use of sequencing would not be ethical, according to participants in both countries, in the absence of clinical access to treatments identified as most appropriate by this new technology.

The disadvantages if it's we predict resistance and we don't have anything, and we don't have anything to offer, and we don't, and we don't have a treatment alternative (P5/Madagascar/Surveillance).

So I imagine a patient with a sequencing and they find out that they have isoniazid mono-resistance and the patients end up on therapy and then on mono-therapy, for the remaining four months. Wouldn't anyone have planned what to do (P10/Madagascar/Clinician).

Maybe we just need to make sure that the availability of medication is there, which is already not the case everywhere. So: can we make sure we're treating the cases we diagnose well before we think about improving diagnostic techniques? (P2/Canada/Surveillance).

Operational and system-level considerations

Participants flagged several operational gaps that could hinder effective adoption as well as system-level norms that would shape any eventual adoption process. In terms of gaps, available expertise for result analysis was a key concern in both settings.

I think the best thing is when there's a clear protocol that says: here's the new method, here's how we're

going to use it, and here's what patients we're going to use it with, and then it's, like, standardized a little bit, and then people have more or less the choice, if you will. That way everyone does the same thing and it's less creative and artistic in the way it's used and implemented (P1/Canada/Clinician).

It's actually very complicated to instore a good test interpretation among clinicians, because at a certain point GeneXpert appeared as a miraculous thing in diagnostics what is not necessarily the case (P10/Madagascar/Clinician).

Proposed strategies to ensure consistent results interpretation included the suggestion of having clear protocols for integration in diagnostic algorithms, hiring bio-informatics experts to support test analysis (in Madagascar), and, for epidemiological purposes in particular, having information technology infrastructure and efficient reporting systems in place to enable identification of *geno-pheno* correlations. In Madagascar, one participant also noted that the sample-testing-results pathway established should be rapid.

As a result, it will be a development of networks perhaps, networks for the delivery of samples and information especially, because that is: we send a sample and then the information must be able to return very quickly (P5/Madagascar/Surveillance).

Another Canadian participant emphasized also needing to think through lab-level organisation in order to appropriately integrate new sequencing analyses within already existing infrastructures, lab workflows and available human resources.

In terms of the organization of the services, in terms of the laboratories, it can have a lot of impact as well (P2/Canada/Surveillance).

Canadian and Malagasy participants noted the importance of building support among diverse end users and intended beneficiaries. For example, in Madagascar, it was suggested that engagement with multiple Ministries could pave the way for support, while in Canada, engaging early with clinicians and professional associations such as the Canadian Public Health Laboratories, alongside provincial and federal government institutions and ministries, was noted as key.

You have to get the buy-in of whatever agency oversees the lab directors, the section heads, the lab technologist as well. So it's got to be the policy decision that ideally you engaged your APHL or CPHL people upfront in crafting that policy so that rather than a complete top down, like, "Okay, this is the new way of doing things", the lab director and lab technologies can be like: "Oh, our leadership worked with the Ministry of Health, or Health Canada, Public Health Canada, to make this decision. Clearly they know

what they're doing. I'm going to get on board with this (P15/Canada/Surveillance).

In both country settings, participants recognised multi-level decision-making chains that would need to be activated to receive government endorsement and enable adoption. The importance of user buy-in evident in the above quotes from Canada did not come across in the comments from Madagascar. Instead, Malagasy participants implied those expected to do so would use sequencing, if their government endorsed this as an expected part of TB management in the country through the National TB programme.

You have to go through the program and you have to see what they think. Because we clinicians here, we can't make a decision like that, we can't say no. For us it's, it's going to make our lives easier. So it's not our role to refuse. If they say: "we're going to integrate sequencing in the diagnosis of tuberculosis, we can't refuse, so we have to talk to the higher authorities (P7/Madagascar/Clinician).

Of course, it is the program that will introduce this method into the program in the national strategic plan and then when the, this method is among the diagnostic methods in the NSP, the donors can finance the methods (P8/Madagascar/Laboratory)

As is evident from the last quote, in Madagascar, decisions on adoption were understood to not depend solely on Malagasy leaders. National TB programme methods hinge on external funders' decisions. In both countries, governmental endorsement was seen to be most likely following WHO recommendations.

I think really the most effective lever is a policy recommendation, whether it's at the national level or whether it's WHO saying you need to do this (P15/Canada/Surveillance).

For the moment, and in Madagascar the National Tuberculosis Control Program and the Ministry do not often agree to put in the national TB policy an examination or treatment that the WHO does not recommend (P3/Madagascar/Clinician).

Madagascar's limited agency to lead adoption decisions was recurrent in the comments from that country's participants. Madagascar could develop evidence and grow convinced that adoption made sense, but, ultimately, any change to existing practice was seen as being the call of the WHO, not Madagascar.

After the results so we will implement, we will suggest WHO after I don't know to put in among the diagnostics used in routine (P9/Madagascar/Laboratory).

DISCUSSION

Principal findings

This study elucidates several considerations complicating diversely positioned stakeholders' enthusiasm for TB

next-generation sequencing (TB NGS) adoption. These include: uncertainty, in the absence of clear evidence, about the cost-benefit value of adoption; recognition that with quicker access to expanded DST results enabled by TB NGS adoption comes an ethical imperative to ensure that TB programmes are ready and able to act on this information; and Malagasy participants' assertions that regardless of what evidence may show is best practice for their needs and country, changes to their national TB programme are not in the hands of the Malagasy alone but dependent on decisions made by external funders and policymakers.

Our study reveals that, even among TB experts from high-income or high TB-incidence countries, there persist important lack of familiarity with TB NGS applications. This could be partially due to the limited number of laboratories having previously embedded TB NGS within their TB diagnostic workflows. Some of the most important questions and concerns include the ability, or not, of TB NGS to be performed directly from clinical samples and, hence, accelerate access to DST and epidemiological information in clinical settings. Potentially due to a diversity of emerging sequencing protocols and commercial assays, participants were uncertain as to whether, and how, comprehensive genotypic DST profiles and WGS data could be obtained from sputum samples.^{9 35} This led to additional lack of clarity regarding where this technology would appropriately fit within respective countries' diagnostic algorithms.

This lack of clarity regarding what TB NGS could achieve was accompanied by significant scepticism on the evidence underlying its use and its true value. In Madagascar, this was most frequently expressed as uncertainty regarding the analytical and clinical performance of sequencing to predict drug resistance, which repeatedly led to participants suggesting that local evaluation of the technology should be required. In Canada, the focus was rather on the outbreak investigation applications of sequencing. Some participants had previous experience with molecular typing assays, but there was no consensus as to whether or not this would have added value in TB control.

Independent of TB NGS performance and accuracy, Canadian and Malagasy participants all highlighted the importance of ensuring that genomic data would be integrated with clinical and surveillance programmes. This was perceived as an ethical imperative. It was made clear that this need for integration goes beyond the simple transfer of laboratory results. On one hand, data confidentiality, patients' consent and long-term data ownership would need to be addressed to facilitate efficient surveillance efforts. On the other hand, clinical guidelines should be adapted to this increased level of resolution in DST and availability of personalised therapeutic regimens in clinical settings should be secured.

Despite providing important insights into paths to adoption, interviews revealed highly diverse perceptions and a lack of clarity among participants regarding leadership

and funding responsibilities in this potential transition towards TB NGS. Although participants from both countries agreed that recommendations from regulatory institutions were crucial, Canadian interviewees referred to a more diverse selection of potential institutions, including ministries of health, national public health agencies and WHO. Malagasy interviewees almost uniformly proposed that initial leadership had to come from WHO in the form of a formal recommendation to use TB NGS within NTP laboratories which would then have to be endorsed by the Ministry of Health.

TB NGS remains an emerging technology, which has not widely penetrated public health and clinical laboratories. Participants in our sample reflected on TB WGS approaches sometimes with limited experience with the technology or the evidence supporting the use of innovative technologies in this field. Potentially limiting their assessments of how, why and for whom, adoption would be advantageous or complicated within their specific TB programme. It will be valuable in future to reproduce this study once knowledge and experience have expanded. As opposed to Madagascar where public health and laboratory expertise is highly centralised in the capital, further variability might exist across Canada where this expertise is decentralised and based within unique provincial and territorial health jurisdictions. A specific study exploring and comparing perceptions of TB WGS adoption across Canada could clarify whether this is the case. Incidence of TB drug resistance in both Canada and Madagascar remains low. Perceived value and complexities of adoption in this study may be less relevant to other regions of the world with high TB drug resistance.

Strengths and weaknesses in relation to other studies

This study is the first to explore the barriers and facilitators to TB NGS adoption among a diverse panel of stakeholders including (1) experts from the entire continuum of clinical, laboratory and surveillance spectrum and (2) interviewees from low TB incidence/high-income and high TB incidence/LICs. In accordance with the level of detail enabled by a qualitative approach, this study builds nuanced understanding of how TB NGS and its adoption are perceived in two distinct settings and health systems. Our sample size was relatively small, with only nine participants per country. While this may be seen as a limitation, we regard this sample as sufficient to delivering on our intention to document and synthesise a diversity of perspectives on new TB diagnostic technology. Findings should not be confused with conclusive evidence of prevalent attitudes or practice in Canada and Madagascar. Instead, and in accordance with our exploratory goals, findings are intended to serve as a window into the diversity of considerations that may drive whether or not, to what extent, and with what level of enthusiasm or speed new TB diagnostics may become integrated into TB programmes in these and other settings.³²

The issues raised by participants in our study build on the currently limited evidence-derived discussion on why

TB NGS may or may not be embraced within specific health systems. A recent review focusing on the potential utility of TB WGS for public health programmes did find that the contribution of WGS to detection, prevention and control of TB transmission remained difficult to establish, and our participants echoed this uncertainty.³⁶ Another similar finding was that jurisdictional capacity to implement the technology remains a challenge and independently of the country, health system structure and funding, there is no consensus as to who has the authority and should assume leadership in the implementation of TB NGS.

With expanded sequencing power comes ethical issues, and the need to ascertain public and health system readiness to expand use of technologies that, alongside greater epidemiological and diagnostic power, extend access to patients' genomic information. Perceived risks and ethical considerations for data sharing and management with TB NGS have been at the centre of the two previous qualitative explorations of this technology.^{16 17} For example, Jackson *et al*'s study focused on trust in the new diagnostics and reported on concerns regarding who has access to, and can benefit from, the technology and data as well as the necessary epidemiological and clinical metadata which needs to be linked to TB genomic data.¹⁴ This concern was also raised by Davies *et al* in their report on a public debate on TB WGS for outbreak investigation.¹⁷ In this public consultation, participants generally agreed that medical professionals and the research community should have access to TB WGS data without specifically addressing through which mechanisms. Although participants within our study were specifically asked about potential ethical issues and concerns related to adoption, trust and the ethics of surveillance, and data ownership did not emerge as primary concerns in our data. One study participant expressed data worries about eventual partnerships with third-party (potentially including commercial) partners, and the potential for such partnerships in the absence of a clear plan to ensure sensitive patient information remained protected. Calls for evidence-based adoption and assurance that care protocols would match improved diagnostics were much more prominent concerns for both Canadian and Malagasy participants.

Unanswered questions and future research

TB WGS adoption remains in its early days internationally. Many participants emphasised a need for broader programmatic and operational research to ensure that decisions for and against wider implementation are evidence based. Such research might include questions related to cost-effectiveness, impact on results turnaround time and the efficiency of linkage to public health and clinical care resources, where the objective is to inform specific health system adoption strategies, thorough investigation of such questions is at least partially contingent on broader implementation. Where a national TB programme is committed to reducing higher

disease prevalence in particular populations, assessing the impact of TB WGS integration within specific subnational settings or for use with specific populations may be a priority. The lack of familiarity with the currently available evidence supporting the use of TB NGS for DST and molecular epidemiology also calls for better knowledge translation and training programmes prior to future larger scale implementation.

CONCLUSION

TB surveillance, diagnostics and clinical care stakeholders generally remain uncertain of the value added of NGS diagnostics in TB control. Whether it is via better knowledge translation of already existing evidence or additional research, anticipated end users still need to be convinced that this technology should be taken to routine practice.

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REFERENCES

- 1 WHO. *Global genomic surveillance strategy for pathogens with pandemic and epidemic potential*. World Health Organization, 2022.
- 2 WHO. A new digital platform for timely analysis and use of TB data. 2019. Available: <https://www.who.int/news/item/22-03-2019-a-new-digital-platform-for-timely-analysis-and-use-of-tb-data>
- 3 Pai M, Kasaeva T, Swaminathan S. COVID-19's devastating effect on tuberculosis care—a path to recovery. *N Engl J Med* 2022;386:1490–3.
- 4 CRyPTIC Consortium and the 100,000 Genomes Project, Allix-Béguec C, Arandjelovic I, et al. Prediction of susceptibility to first-line tuberculosis drugs by DNA sequencing. *N Engl J Med* 2018;379:1403–15.
- 5 Whitney AA, Gould KA, Arnold A, et al. Clinical application of whole-genome sequencing to inform treatment for multidrug-resistant tuberculosis cases. *J Clin Microbiol* 2015;53:1473–83.
- 6 Gardy JL, Johnston JC, Ho Sui SJ, et al. Whole-genome sequencing and social-network analysis of a tuberculosis outbreak. *N Engl J Med* 2011;364:730–9.
- 7 Walker TM, Merker M, Knoblauch AM, et al. A cluster of multidrug-resistant mycobacterium tuberculosis among patients arriving in Europe from the horn of Africa: a molecular epidemiological study. *Lancet Infect Dis* 2018;18:431–40.
- 8 Meehan CJ, Goig GA, Kohl TA, et al. Whole genome sequencing of Mycobacterium tuberculosis: current standards and open issues. *Nat Rev Microbiol* 2019;17:533–45.
- 9 Votintseva AA, Bradley P, Pankhurst L, et al. Same-Day diagnostic and surveillance data for tuberculosis via whole-genome sequencing of direct respiratory samples. *J Clin Microbiol* 2017;55:1285–98.
- 10 Mugwagwa T, Abubakar I, White PJ. Using molecular testing and whole-genome sequencing for tuberculosis diagnosis in a low-burden setting: a cost-effectiveness analysis using transmission-dynamic modelling. *Thorax* 2021;76:281–91.
- 11 McDowell A, Raizada N, Khaparde SD, et al. “Before xpert I only had my expertise”: a qualitative study on the utilization and effects of xpert technology among pediatricians in 4 Indian cities. *PLoS One* 2018;13:e0193656.
- 12 Cazaban D, Pande T, Kik S, et al. Market penetration of xpert MTB/RIF in high tuberculosis burden countries: a trend analysis from 2014–2016. *Gates Open Res* 2018;2:35.
- 13 WHO. *The use of next-generation sequencing technologies for the detection of mutations associated with drug-resistance in mycobacterium tuberculosis complex: technical guide*. World Health Organization – Foundation for Innovative and New Diagnostics, 2018.
- 14 Crisan A, McKee G, Munzner T, et al. Evidence-Based design and evaluation of a whole genome sequencing clinical report for the reference microbiology laboratory. *PeerJ* 2018;6:e4218.
- 15 Jajou R, Kohl TA, Walker T, et al. Towards standardisation: comparison of five whole genome sequencing (WGS) analysis pipelines for detection of epidemiologically linked tuberculosis cases. *Euro Surveill* 2019;24:1900130.
- 16 Jackson C, Gardy JL, Shadiloo HC, et al. Trust and the ethical challenges in the use of whole genome sequencing for tuberculosis surveillance: a qualitative study of stakeholder perspectives. *BMC Med Ethics* 2019;20:43.
- 17 Davies A, Scott S, Badger S, et al. Public perceptions of bacterial whole-genome sequencing for tuberculosis. *Trends Genet* 2015;31:58–60.
- 18 World Bank. Madagascar – World Bank data. 2021. Available: <https://data.worldbank.org/country/madagascar>
- 19 World Health Organization. *Global tuberculosis report*. 2021.
- 20 Rakotosamimanana N, Lapierre SG, Raharimanga V, et al. Performance and impact of GeneXpert MTB/RIF® and loopamp MTBC detection kit® assays on tuberculosis case detection in Madagascar. *BMC Infect Dis* 2019;19:542.
- 21 Knoblauch AM, Grandjean Lapierre S, Randriamanana D, et al. Multidrug-resistant tuberculosis surveillance and cascade of care in Madagascar: a five-year (2012–2017) retrospective study. *BMC Med* 2020;18:173.
- 22 Ratovonirina NH, Rakotosamimanana N, Razafimahatratra SL, et al. Assessment of tuberculosis spatial hotspot areas in Antananarivo, Madagascar, by combining spatial analysis and genotyping. *BMC Infect Dis* 2017;17:562.
- 23 Walker TM, Miotto P, Köser CU, et al. The 2021 who Catalogue of Mycobacterium tuberculosis complex mutations associated with drug resistance: a genotypic analysis. *Lancet Microbe* 2022;3:e265–73.
- 24 Hall MB, Rabodoarivelo MS, Koch A, et al. Nanopore sequencing for mycobacterium tuberculosis drug susceptibility testing and outbreak investigation. *Infectious Diseases (except HIV/AIDS)* [Preprint] 2022.
- 25 LaFreniere M, Dam D, Strudwick L, et al. Tuberculosis drug resistance in Canada: 2018. *Can Commun Dis Rep* 2020;46:9–15.
- 26 Chakravarti A, Soualhine H, Sharma M, et al. Indigenous transmission of Mycobacterium Africanum in Canada: a case series and cluster analysis. *Open Forum Infect Dis* 2019;6:ofz088.
- 27 Patterson M, Flinn S, Barker K. Addressing tuberculosis among Inuit in Canada. *Can Commun Dis Rep* 2018;44:82–5.
- 28 WHO. *Global tuberculosis report* World Health Organization. 2021.
- 29 Genome Canada Canadian COVID-19 Genomics Network (CanCOGeN) and the Canadian Public Health Laboratory Network CanCOGeN Working Group. Canadian national COVID-19 genomics surveillance priorities for existing and emerging variants of concern. *Can Commun Dis Rep* 2021;47:139–41.
- 30 Guthrie JL, Kong C, Roth D, et al. Universal genotyping for tuberculosis prevention programs: a 5-year comparison with on-request genotyping. *J Clin Microbiol* 2018;56:e01778–17.
- 31 Lee RS, Radomski N, Proulx J-F, et al. Population genomics of Mycobacterium tuberculosis in the Inuit. *Proc Natl Acad Sci U S A* 2015;112:13609–14.
- 32 Crouch M, McKenzie H. The logic of small samples in interview-based qualitative research. *Social Science Information* 2006;45:483–99.
- 33 O'Reilly M, Parker N. Unsatisfactory saturation: a critical exploration of the notion of saturated sample sizes in qualitative research. *Qualitative Research* 2013;13:190–7.
- 34 Welsh E. Dealing with data: using nvivo in the qualitative data analysis process. *Forum Qual Soc Res* 2002;3.
- 35 Feuerriegel S, Kohl TA, Utpatel C, et al. Rapid genomic first- and second-line drug resistance prediction from clinical Mycobacterium tuberculosis specimens using deeplex-mycTb. *Eur Respir J* 2021;57:2001796.
- 36 Nikolayevskyy V, Niemann S, Anthony R, et al. Role and value of whole genome sequencing in studying tuberculosis transmission. *Clin Microbiol Infect* 2019;25:1377–82.