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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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TITLE

Complexities and Benefits of Adopting Next-Generation Sequencing-Based Tuberculosis Diagnostics: A Qualitative Study Among Stakeholders in Low and High-Income Countries

RUNNING TITLE

Perceived complexities of *Mycobacterium tuberculosis* next generation sequencing

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Version 1 – 2022.06.17

32

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For submission to BMJ Global Health

Version 1 – 2022.06.17

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 semi-structured interviews with key stakeholders engaged with next-generation sequencing implementation in Madagascar and Canada. Team-based descriptive analysis supported by Nvivo 12.0 was used to identify key themes.

Setting

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

Participants

Eighteen participants were interviewed (9 Madagascar, 9 Canada) and included individuals purposively sampled based on involvement with tuberculosis 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) Evidence key to expand adoption; (4) Ethical arguments and concerns; (5) Operational and system-level considerations.

Conclusion

There persists important lack of familiarity with TB NGS applications among stakeholders in Canada and Madagascar. This translates in skepticism on the evidence underlying its use and its true potential value added within global public health systems. If deployed, TB NGS testing should

For submission to BMJ Global Health
Version 1 – 2022.06.17

be integrated with clinical and surveillance programs. 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.

Key words: Tuberculosis, Diagnostics, Next-generation sequencing, Madagascar, Canada, Qualitative research, Perceptions.

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For submission to BMJ Global Health

Version 1 – 2022.06.17

ARTICLE SUMMARY

What is already known on this topic

Tuberculosis (TB) next-generation sequencing (NGS)-based diagnostics are increasingly used by reference laboratories and supported by technical guidance from the World Health Organization. Knowledge on key stakeholders' perception of their value added, and implementation challenges, is lacking. Previous qualitative studies have focused on trust in new tuberculosis diagnostics results and reported on concerns regarding access to the genomic data they yield.

Strengths

- This study is the first to explore the barriers and facilitators to TB NGS adoption within a diverse panel of stakeholders including experts from the entire continuum of clinical, laboratory and surveillance spectrum and interviewees from low TB burden/high-income and high TB burden/low-income countries.
- This study has generated rich qualitative data providing unique insight on gaps in evidence and experience and ethical and operational questions which strike key stakeholders as important, and need to be filled and answered to assess whether, and how, TB NGS diagnostics can be successfully implemented within national and global public health systems.

Limitations

- Some participants in this study noted their limited familiarity with existing evidence, as well as limited experience with TB NGS diagnostics. This may have limited their assessments of how and why, for whom, adoption would be advantageous or complicated within their country.
- Canada does not have a single centralized approach to its clinical and diagnostic management of TB. Our sampling is limited in terms of capturing the potential variability in experiences and perceptions amongst stakeholders working in distinct provincial health systems.
- This study was conducted with participants in two countries with low TB drug resistance. Findings may differ in regions with high TB drug resistance.

102 INTRODUCTION

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

108
109 Appropriately treating TB patients, including those infected with drug resistant strains, and tracing
110 contacts have become even more important to recover from the recent COVID-19 related set back
111 in the fight against TB. (3) Next-generation sequencing (NGS) technologies and genomics-based
112 diagnostics represent the latest revolution in TB microbiology diagnostics since the advent of
113 Xpert MTB/RIF™ (Cepheid, Sunnyvale CA USA) PCR platform. Bacterial genomes hold
114 extensive information on drug resistance conferring mutations and relative evolutionary distance
115 between isolates allowing to guide the choice of personalized therapeutic regimens and support or
116 refute putative person to person transmission hypotheses. (4-8) Hence, TB DNA sequencing
117 promises to play a significant role in universal access to drug susceptibility testing (DST) and
118 interruption of transmission chains.

119
120 The uptake of novel diagnostics cannot be taken for granted. The experience of Xpert MTB/RIF™
121 global adoption and market penetration exemplifies how clinical performance, WHO endorsement
122 and end-users’ enthusiasm alone do not necessarily translate to rapid and disseminated uptake. (9,
123 10) Despite technical guidelines and laboratory methods standardization efforts, significant
124 barriers to DNA sequencing-based diagnostics adoption remain. (11-13) These include users’
125 (stakeholders and public) anticipated or experience-based ethical challenges inherent to genomics
126 data sharing which have previously been explored. (14, 15)

127
128 Beyond data sharing challenges, this study takes a first step in understanding stakeholders’
129 perceptions of the value added and implementation complexity within specific health systems: one
130 high-income and one low-income setting. Understanding that individuals with different
131 professional backgrounds, roles and responsibilities will use and potentially understand new TB
132 diagnostics in distinct ways, this study captures perceptions from a diversity of clinical, laboratory

For submission to BMJ Global Health

Version 1 – 2022.06.17

133 and surveillance stakeholders in two contexts exemplifying the case scenarios of low TB
134 burden/high-income and high TB burden/low-income countries: Canada and Madagascar. In doing
135 so, this study generates original and needed evidence on human and contextual factors that may
136 impact DNA sequencing-based TB diagnostics adoption.

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Context
Madagascar exemplifying low-income high TB burden settings

Madagascar is a low-income country (LIC) with a gross national income of \$520 USD per capita, the ninth lowest in the world. (16) In health as in other sectors, financial challenges are omnipresent and partially result from an unfavorable 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). (17) In 2020, apart the in kind contributions from the Malagasy government including medical staff salaries and health centers buildings, the TB specific program of Madagascar the program reported a cumulative budget of 6 million USD and was funded by international sources including contributions from the Global Fund to fight AIDS, Tuberculosis and Malaria (GFATM) and operational research funding supporting partnerships with international and domestic academic institutions.

Like other low- and middle-income countries (LMICs), Madagascar faces significant challenges with respect to novel diagnostics implementation including underfunding, paucity of trained laboratory personnel, low geographic coverage of centralized 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. (18, 19) 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. (20) TB whole genome sequencing (WGS) testing was first implemented in the country in 2018 to improve reference DST capacity, contribute to global standardization efforts and better inform local choices of diagnostic platforms and algorithms. (21, 22)

Canada exemplifying high income low TB burden settings

Canada is a high-income country (HIC) with a gross national income of \$44,940 USD 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 active TB cases totaled 1,765, representing an increase from the previous year and 80.2% of the 2,200 cases (5.9/100,000 population) estimated to have occurred by the WHO. (17) 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. (23-25) 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. (26) 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 as demonstrated by recent contributions to global pathogen genomic surveillance efforts. (27) Despite this expertise and capacity, Canada has not implemented systematic prospective TB sequencing programs. Isolated initiatives from provincial and academic laboratories have leveraged this approach to better understand disease transmission in Canadian sub-populations, but these are research rather than care and treatment driven. (28, 29) Canada faces its own challenges when it comes to the implementation of innovative diagnostics for TB control. Prioritizing 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

Qualitative studies are well suited to gaining rich, detailed understanding of social phenomenon, including insight on how new technologies are being understood and used. Data collection involved semi-structured interviews. Data were analyzed via directed thematic analysis attentive to country-specific differences and similarities in perceptions of DNA sequencing-based TB diagnostics.

Sampling and Recruitment

Recruitment for this study was purposive. 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, and all potential participants had to be fluent in either French or English.

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 policy makers. The initial list of participants included 24 individuals – 12 from each country – with a plan to stop data collection once interviews were no longer surfacing unique themes (i.e. thematic saturation).

Data collection

Semi-structured 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 minutes and two hours, and were administered using an interview guide developed collaboratively by the team in advance (See Supplementary Materials 1) based on the team’s interdisciplinary expertise and following piloting of the guide.

Semi-structured 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 organized around the six following axes: (1) current involvement with TB diagnostics; (2) technical understanding of new diagnostics; (3) perceived accuracy, limits, and potential of TB DNA sequencing for drug susceptibility testing; (4) perceived value added and limits of DNA sequencing for molecular epidemiology and surveillance; (5) experienced and anticipated challenges and impacts of integrating and expanding use of new TB diagnostics in national health system; (6) perceived access and equity issues. In accordance with the semi-structured interview

For submission to BMJ Global Health

Version 1 – 2022.06.17

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 12™ (QSR International) for directed and thematic analysis. 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, EN) independently coded four transcripts to propose adjustments to the initial thematic categorization of findings and to identify specific sub-themes. 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 (AC) proceeded to code all transcripts line-by-line. Names of key themes and the number of sub-themes were revised slightly as the analysis proceeded.

The PIs re-read all transcripts against the NVivo organization of the data as an additional verification that the themes reflected and accurately captured all key data. Co-authors 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 synthesized 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 forms 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.

262

263 **ETHICS**

264 Ethics approval for this study was obtained from the Centre de Recherche du Centre Hospitaliser
265 de l’Université de Montréal (CRCHUM) (Ref. 2020-8310), and the Comité d’Éthique à la
266 Recherche Biomédicale à Madagascar (CERBM) (Ref. 056/MSANP/SG). All participants
267 provided written consent prior to the interview.

268

269 **Role of the funding source**

270 The funders had no role in the study design, in the collection, analysis, and interpretation of data,
271 in the writing of the report and in the decision to submit the paper for publication.

272

RESULTS

A total of 18 participants were interviewed, including nine participants from each country. Participants held a range of positions translating into different past or anticipated experiences with TB diagnostic and surveillance: six worked primarily in clinical practice, with face-to-face patient interactions; six worked in surveillance; six were lab-based.

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 quotes¹, 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 drug susceptibility testing.

"As far as [anti-tuberculosis] drug susceptibility, it's still phenotypic testing for susceptibility to anti-tuberculosis drugs per se." (P0/Canada/Clinician)

In Madagascar, only one of the three clinicians interviewed routinely used Xpert MTB/RIF™ but a surveillance expert was clearly appreciative of how Xpert MTB/RIF™ had been a game changer in the diagnosis of TB and prediction of multi-drug 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)

¹ Quotes from French language interviews were translated into English by the fully bilingual co-PIs (first and last author).

For submission to BMJ Global Health
Version 1 – 2022.06.17

When asked about previous experiences, Malagasy participants systematically referred to WHO-endorsed technologies. While most Canadian laboratory participants were unsure how DNASeq technology compared to 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)

Canadian participants were also more familiar with next-generation sequencing as a technology given its use in several medical application other than TB, which was not the case in Madagascar.

“C’est pas nouveau, parce que tu sais que pour le VIH on fait ça. Alors on a développé en 2001 des tests génotypiques pour prédire la résistance phénotypique du VIH aux antirétroviraux, puis ça fonctionne très, très, bien.” (P0/Canada/Clinician)

“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)

Variable understanding of DNA sequencing diagnostics potential

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.

"Personally, I have not yet used sequencing in the daily management of patients." (P3/Madagascar/Clinician)

For submission to BMJ Global Health

Version 1 – 2022.06.17

Alongside limited usage came uncertainty amongst 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. 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 drug susceptibility testing.

"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 although some thought it would be a marginal one.

"I think the rapidity of results compared to phenotyping which can take one week, two weeks, to get the result, I think that is a big advantage." (P0/Canada/Clinician)

"Right now, you already see the resistance right now" (P11/Madagascar/Surveillance)

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

For submission to BMJ Global Health
Version 1 – 2022.06.17

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

372
373 *"We already have, as a standard here, as a first intention the GeneXpert. We can see the*
374 *results in an hour. And if it's [sequencing] specific, and if it's faster than that, and if it's*
375 *cheaper than that, why not?" (P4/Madagascar/Laboratory)*

376
377 In Madagascar, since molecular epidemiological analyses had so far relied on testing at a
378 centralized lab and within a research context, participants were unsure how data generated through
379 DNA sequencing could realistically serve in case finding at the community level. Some
380 participants identified some potential value in differentiating reinfections from relapse in patients
381 experiencing a second episode of TB infection. Others referred to the potential of sequencing to
382 identify bacterial lineages.

383
384 *"Because a patient that's having a relapse: is it a relapse or is it treatment failure of the initial*
385 *strain?" (P5/Madagascar/Surveillance)*

386
387 *"The objective is to know which strain is responsible for someone's disease"*
388 *(P8/Madagascar/Laboratoire)*

389
390 In Canada, mostly surveillance experts explicitly noted the epidemiological value added of past
391 and current DNA-based diagnostics to support TB-focused public health efforts. Perception of
392 added value varied between interviewees based on their respective previous experiences ranging
393 from participants believing it would not significantly impact TB control efforts to others
394 suggesting the implementation of national genomics-based surveillance networks.

For submission to BMJ Global Health
Version 1 – 2022.06.17

395
396 “So, I think the main use-case is that epidemiological intelligence that you get into your
397 provincial or your state situation, identifying clusters that do need active management and
398 public health follow up.” (P15/Canada/Surveillance)

399
400 “Epidemiological investigations did identify outbreaks mostly, and then, the added value of
401 sequencing wasn’t trendy anymore because it did not add something clinically significant
402 really” (P2/Canada/Surveillance)

403
404 “And it would be good eventually that there would even be a Canadian network for this.
405 There would eventually be a possibility to create a TB molecular epidemiology reference
406 center, based on the genome.” (P0/Canada/Clinician)

407 408 **Evidence perceived as key to expanded adoption**

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

413
414 “Demonstrate a benefit over what’s already out there, an added value, define it however you
415 want. That’s going to be the best message that can be pitched or the biggest hurdle if it’s not
416 demonstrated.” (P2/Canada/Surveillance)

417
418 “No doctor, clinician, will refuse if there is evidence” (P7/Madagascar/Clinician)

419
420 A few differences were notable in the ways in which the importance of evidence was framed by
421 Canadian versus Malagasy participants. Canadian participants stressed, for example, the need for
422 proven changes on *clinical impact* beyond the intrinsic capabilities of the technology for DST and
423 phylogenetic. Canadian participants’ analysis was rooted in the context of already available
424 standard of care diagnostics for all.

For submission to BMJ Global Health
Version 1 – 2022.06.17

"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 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 burden 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 skeptical this would have a significant impact on the epidemic given the important burden 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)

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

For submission to BMJ Global Health

Version 1 – 2022.06.17

457 funding. Statements such as the following do indicate the likely need for some cost-effectiveness
458 studies in the country, to justify investment.

459
460 *"But the problem with these new tests is mainly the cost. The cost of the tests is high and that's*
461 *why we can't diagnose all the samples with culture. Because it is expensive."*
462 *(P4/Madagascar/Laboratory)*

463
464 *"So, therefore, it has to be funded by the government, if you will. Through what, I don't know,*
465 *should it be financed through the Global Fund, or through donors... It should be in the budget,*
466 *it should be in the program budget. But from which donor?" (P5/Madagascar/Surveillance)*

467
468 While both Canadian and Malagasy respondents stressed the importance of evidence to national-
469 level investment in sequencing technology, Malagasy respondents more commonly emphasized
470 the key role evidence would play in determining whether current practice in the country would
471 change.

472
473 *"If we want the National Program and the Ministry to recommend the use of sequencing, I*
474 *think that we must first demonstrate in a project or a study the importance of this*
475 *examination." (P3/Madagascar/Clinician)*

476
477 *"We have to do the study first, and then if we have the result, we will show them the result that*
478 *here, we did such and such a study, here are the results. And we must try to convince them to*
479 *integrate the diagnostic tool into the national tuberculosis control program. I think we need*
480 *to start there because so far we have no experience." (P7/Madagascar/Clinician)*

481
482 *"And also to install this as an operational diagnostic method at the level of the Ministry of*
483 *Health, we need to, that the authorities are convinced, with the results with the input. We need*
484 *a lot of evaluations with real patients and also I think we need a big study on the evaluation*
485 *of the sensitivity and specificity of sequencing compared to other standard diagnostics.*
486 *(P4/Madagascar/Laboratory)*

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)

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.

“No doubt that there is an interest almost everywhere: we want to sequence all that moves.” (P2/Canada/Surveillance)

“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)

Ethical arguments and considerations

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

“So, [...] we could reduce our anti-TBs, give less of them, possibly with less toxicity right away, because we would have a rapid resistance test that would allow us to adjust our therapy

For submission to BMJ Global Health

Version 1 – 2022.06.17

519 *more quickly, instead of having our patients on four anti-TB drugs with possible interactions,*
520 *INH, Rifampin, with drug toxicity to the liver, so maybe we could... I think it would be a better*
521 *service in that respect. So it's a benefit, it's that benefit versus the cost."*
522 *(P0/Canada/Clinician)*

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

528 As is evident from the above quotes, the need to consider cost, alongside benefit, came across in
529 several participants' statements. In the case of Malagasy participants, cost of expanding use of the
530 new technology was framed as a barrier with clear, if not explicitly noted, ethical implications in
531 the context of an under-resourced health care system. The cost-related ethics of wider use of DNA
532 sequencing emerged in Canada in conjunction to statements, already noted before (See Evidence
533 perceived as key to expanded adoption), that adoption would not make sense unless this "made a
534 difference".

536 *"Of course, there is some interest everywhere on, we want to sequence everything that moves"*
537 *(P2/Canada/Surveillance)*

539 *"Well, you know, basically a diagnostic test, you have to do it if it's going to change your*
540 *practice."* *(P1/Canada/Clinician)*

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

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

For submission to BMJ Global Health
Version 1 – 2022.06.17

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

552
553 "Maybe we just need to make sure that the availability of medication is there, which is already
554 not the case everywhere. So: can we make sure we're treating the cases we diagnose well
555 before we think about improving diagnostic techniques?" (P2/Canada/Surveillance)

556
557 One Canadian participant raised concerns about the possibility in the Canadian context of the
558 government contracting sequencing procedures out to private companies. Such a scenario raised
559 clear ethical concerns for this participant, with respect to ownership of biological samples in
560 particular.

561
562 "You know, it depends on how it's done. If you say, 'we're going to do it here and then such
563 and such a company is interested in developing X business, we're going to send the specimen
564 back to them' and then after that they still own the specimen and they can do whatever they
565 want with it, you know, that, that's not going to work, ethically." (P1/Canada/Clinician)

566
567 Whether managed privately or not, routine sequencing would need to be paired with a thoughtful
568 plan for the ethical management and sharing of data, to ensure appropriate consent from patients.

569
570 "Because afterwards, if you want to be able to do, if you want to be able to exchange your
571 information with the other provinces, with the United States, with the rest of the Western
572 countries. Then it also requires, at the ethical level, an informed and prolonged consent,
573 where you don't have to go back to your patient every ten years to ask them to reconsent.,"
574 (P2/Canada/Surveillance)

575
576 In Canada, given the small number of tuberculosis cases, the same participant noted that
577 epidemiological results reporting would need to be limited to avoid personal identification.

578
579 "The whole ethical aspect, consent. It's more important that it be denominated, that it be

For submission to BMJ Global Health

Version 1 – 2022.06.17

580 *anonymized practically reported in aggregate to avoid identification. That is, it would be like*
581 *reporting just region zero six, just for region fifteen, just for region eight, that kind of thing.*
582 *It's going to be hard to go smaller than that because it's always possible to identify someone*
583 *with their zip code, because there's not that many TB cases." (P2/Canada/Clinical)*

584
585 At the end of the day, improved health outcomes, especially amongst populations with known
586 higher rates or risks of TB, emerges in the interviews as a core ethical rationale for expanded
587 adoption. Several Canadian participants noted benefits could be greatest to Indigenous populations
588 in the country, whereas in Madagascar, participants highlighted the value of the technology if
589 applied towards reducing high TB rates amongst incarcerated individuals in the country, or to
590 improve TB care for Malagasy living in remote regions. Plans to expand use of sequencing,
591 however, would need to be intentionally designed to ensure benefit to these populations in greatest
592 need. Several Canadian participants noted that sequencing had been used in recent outbreaks in
593 the North. This had built understanding of transmission patterns within high-risk Indigenous
594 communities, but this had not, to the participants' knowledge, led to a reduction in outbreaks.

595
596 In Madagascar, concerns were raised with respect to building up capacity for sequencing
597 exclusively in the country's capital of Antananarivo, as this could reproduce existing inequities
598 between urban and non-urban Malagasy.

599
600 *"Sending the sample to Antananarivo discourages many people from taking the test."*
601 *(P3/Madagascar/Clinician)*

602
603 *"For me, can we... the concern, if you use it just in Tana, won't it make a bit of bias, because*
604 *it's already, in Tana everything is already available. You will still hammer there, it is just in*
605 *Tana. But, how can it be that it is necessary to make, at the beginning, in the big cities for*
606 *example, in the six provinces for example, the six big provincial capitals. And then, if it works,*
607 *we will perhaps scale it up in the regions, little by little, but not directly. But not just in Tana*
608 *too, but in the provinces and then, if it works well, in the regions. I don't know.*
609 *(P11/Madagascar/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 organization in order to appropriately integrate new sequencing analyses within already existing infrastructures, lab workflows and available human resources.

For submission to BMJ Global Health
Version 1 – 2022.06.17

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

643
644 Canadian and Malagasy participants noted the importance of building support amongst diverse
645 end users and intended beneficiaries. For example, in Madagascar, it was suggested engagement
646 with multiple Ministries could pave the way for support, while in Canada, engaging early on with
647 clinicians and professional associations such as the Canadian Public Health Laboratories,
648 alongside provincial and federal government institutions and ministries was noted as key.

649
650 *"You have to get the buy-in of whatever agency oversees the lab directors, the section heads,*
651 *the lab technologist as well. So it's got to be the policy decision that ideally you engaged your*
652 *APHL or CPHL people upfront in crafting that policy so that rather than a complete top down,*
653 *like, "Okay, this is the new way of doing things", the lab director and lab technologies can*
654 *be like: "Oh, our leadership worked with the Ministry of Health, or Health Canada, Public*
655 *Health Canada, to make this decision. Clearly they know what they're doing. I'm going to get*
656 *on board with this." (P15/Canada/Surveillance)*

657
658 *"Once people understand the benefit of using one technique over another, or adding that to*
659 *the standard stuff, on the face of it, it should go down well." (P1/Canada/Clinician)*

660
661 In both country settings, participants recognized multi-level decision-making chains that would
662 need to be activated to receive government endorsement and enable adoption. The importance of
663 user buy-in evident in the above quotes from Canada did not come across in the comments from
664 Madagascar. Instead, Malagasy participants implied those expected to do so would use sequencing,
665 if their government endorsed this as an expected part of TB management in the country through
666 the National TB program.

667
668 *"You have to go through the program and you have to see what they think. Because we*
669 *clinicians here, we can't make a decision like that, we can't say no. For us it's, it's going to*
670 *make our lives easier. So it's not our role to refuse. If they say: "we're going to integrate*

For submission to BMJ Global Health
Version 1 – 2022.06.17

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 above, in Madagascar, decisions on adoption were understood to not depend solely on Malagasy leaders. National TB program 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

TB NGS-based diagnostics remain an emerging technology which have been shown to yield comprehensive and high-resolution information for drug resistance prediction and disease transmission characterization. Despite over a decade of research and clinical translation case studies leading to WHO policy statements, the use of TB NGS as a routine test within health systems remains limited to a few HIC settings.

This study is the first to explore the barriers and facilitators to TB NGS adoption within a diverse panel of stakeholders including (i) experts from the entire continuum of clinical, laboratory and surveillance spectrum and (ii) interviewees from low TB burden/high-income and high TB burden/low-income countries. In accordance with the level of detail enabled by a qualitative approach, this study builds nuanced understanding of why TB NGS adoption holds promise to bring benefit to under-served populations in two distinct settings and health systems. It also elucidates several considerations complicating diversely positioned stakeholders' enthusiasm for 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 TB programs 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 program are not in the hands of the Malagasy alone, but dependent on decisions made by external funders and policy makers.

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. One recent study did find that the potential utility of TB WGS for public health programs was questioned, and our participants echoed such doubts. 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. (14, 15) 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. (15) 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.

TAKEWAY 1 – Our study reveals that, even among TB experts from high income or high TB-burden countries, there persist important lack of familiarity with TB NGS applications. This could be partially due to the limited numbers of laboratories having previously embedded TB NGS within their TB diagnostics 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. (30, 31) This led to additional lack of clarity regarding where this technology would appropriately fit within respective countries’ diagnostic algorithms.

TAKEWAY 2 – This lack of clarity regarding what TB NGS could achieve was accompanied by significant skepticism on the evidence underlying its use and its true value. In Madagascar, this

For submission to BMJ Global Health

Version 1 – 2022.06.17

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.

TAKEWAY 3 – Independent of TB NGS performance and accuracy, Canadian and Malagasy participants all highlighted the importance of ensuring genomic data would be integrated with clinical and surveillance programs. 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 personalized therapeutic regimens in clinical settings should be secured.

TAKEWAY 4 – Despite providing important insights on 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 and why, for whom, adoption would be advantageous or complicated within their specific TB program, it will be

For submission to BMJ Global Health
Version 1 – 2022.06.17

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 centralized in the capital, significant variability likely exists across Canada which likely was not captured by our purposive sampling strategy. 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 regions with high TB drug resistance.

CONCLUSION

The COVID-19 pandemic triggered unprecedented efforts for pathogen genomic data sharing and integration within the global scientific and public health community. Successes achieved during this global health crisis served as a template for other transmissible diseases in this era of rapid and molecular-guided surveillance. (1, 32). For this transition to happen in TB, our study confirms that multiple steps still need to be taken and multiple gaps still need to be filled.

For submission to BMJ Global Health
Version 1 – 2022.06.17

805

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808

809 AUTHOR CONTRIBUTIONS

810 All authors meet the ICMJE criteria for authorship. Conception and design (SGL, EN), data
811 acquisition (C-AB), data analysis and interpretation (SGL, C-AB, M-SR, AC, OM, MJS, NR, EN),
812 initial draft of the manuscript (SGL, EN, C-AB). All authors had access to the primary data, have
813 reviewed the final version of the manuscript and accept the responsibility to submit for publication.

814

815 DECLARATION OF INTERESTS

816 Authors declare having no financial and/or personal relationships with other people or
817 organisations that could inappropriately influence (bias) the reported research work.

818

819 DATA SHARING

820 Deidentified participants' interviews data will be made available with publication upon request to
821 the corresponding author.

822

823 AUTHOR REFLEXIVITY STATEMENT

824 We report on research from and international partnership between a high-income country (Canada)
825 and a low-income country (Madagascar). The authorship includes a diversity of early- and mid-stage
826 researchers from both partner countries. Two co-authors from Madagascar participated in the research
827 but did not assume leadership in study design or manuscript preparation. The authorship order,
828 including co-first and last author reflects the contribution of every co-author as per ICMJE guidelines.

829

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For submission to BMJ Global Health
Version 1 – 2022.06.17

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For submission to BMJ Global Health
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For submission to BMJ Global Health
Version 1 – 2022.06.17

929

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SUPPLEMENTARY MATERIALS

Supplementary Materials 1 – Semi-structured interview guides

Interview Guide (Disease surveillance experts)

Introduction

Thank you for agreeing to take part in this interview. In our discussion today, I am going to ask you some questions about your experience with new Tuberculosis diagnostics.

Part 1: Participant identification

- 1.1 Tell me a little more about your work. What is your job title and what are your responsibilities in this role? Rephrase: What do you do?
- 1.2 How long have you been working in this role?
- 1.3 What is your previous or active role and affiliations regarding TB diagnostics and data management?
- 1.4 You are affiliated with [*institution*]. Do you work closely with any other organizations or institutions at the local, national, or international level?

Part 2: Background knowledge of TB diagnostics

- 1.1 How have TB diagnostic methods evolved since you have been working in the field of TB?
- 1.2 What would you say are the biggest challenges in TB diagnosis?

Follow up: Are all of these common challenges here in [*country*]?

Probe: (*To understand what are contributing factors to these challenges in the country in their view – an opportunity to break the ice by letting them share thoughts and theories about a topic they probably have thought about at length, and may give us some useful context info*)

- 1.3 In your recollection, when was TB DNA sequencing introduced in [*country*] and when do you think it became accessible to more clinics or patients?

1.4 How was the diffusion of access to TB DNA sequencing at various levels of the health system?

1.5 What are the applications of TB DNA sequencing in [*country*]?

Part 3: Perception of DNA sequencing to predict drug susceptibility testing (DST)

1.1 In your experience, when is DNA sequencing used to predict DST? And how accurate has it been in predicting DST?

1.2 What are advantages and disadvantages of using DNA sequencing for TB DST in the [*country*] context?

1.3 How do you feel about DNA sequencing for TB DST potentially being used more widely here, in [*country*]? Do you support such expanded use? Why or why not?

Part 4: Knowledge and understanding of molecular epidemiology and surveillance

1.1 In your experience, is DNA sequencing useful for understanding TB epidemiology?

1.2 What are some advantages and disadvantages of using DNA sequencing for epidemiologic investigations here in [*country*]?

Follow up: Have you experienced or witnessed those advantages / disadvantages? Could you tell me about it?

Part 5: Facilitators, limitations, challenges, and the way forward

1.1 Has TB DNA sequencing and DST changed your work? In what way(s)?

1.2 Has DNA sequencing made your job more difficult or easier in any way(s)? How so?

1.3 What are the facilitators for TB DNA sequencing implementation in your working environment and country?

Rephrase: What policies, attitudes, or other conditions are facilitating the use of TB DNA sequencing here in [*institution and country*]?

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3 1.4 Are there any technical barriers or limitations to TB DNA sequencing implementation in
4 your working environment?

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6 1.4.1 What might be possible solutions to those previously mentioned challenges?

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8 1.4.2 Do you think these solutions will be implemented in the near future?

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11 If yes: When and who is leading that change?

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13 If no or perhaps/maybe: Tell me more, why do you say that?

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16 1.5 Are there any technical barriers or limitations to TB DNA sequencing implementation in
17 your country?

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19 1.1.1 What might be possible solutions to those previously mentioned challenges?

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21 1.1.2 Do you think these solutions will be implemented in the near future?

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23 If yes: When and who is leading that change?

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25 If no or perhaps/maybe: Tell me more, why do you say that?

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27
28 1.2 How are sequencing data management and interpretation currently handled here in [country]?

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30 1.2.1 Did you personally have a good or a bad experience with data management of TB
31 DNA sequencing?

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33 1.2.2 Can you describe any work you have done involving the interpretation of TB DNA
34 sequencing?

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36 1.2.3 Are there any challenges or concerns associated with sequencing data management and
37 interpretation at the moment, or has there been any challenges with this in the past?

38
39 1.2.4 What might be possible solutions to those previously mentioned challenges?

40
41 1.2.5 Do you think these solutions will be implemented in the near future?

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44 If yes: When and who is leading that change?

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46 If no or perhaps/maybe: Tell me more, why not?

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48
49 1.3 In your experience, with whom are TB diagnostic data shared?

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51 1.3.1 Do you see or foresee any issues regarding data privacy?

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53 1.4 How is TB DNA sequencing funded here in [country]?

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55 1.4.1 Do you think more funding should be put into TB DNA sequencing in [country]?
56 Why or why not?

If yes: Who should invest more in TB DNA sequencing in [country]?

1.4.2 Do you think richer countries or international organizations should support less rich countries in TB DNA sequencing implementation? Why or why not?

1.4.3 What is your perception of the cost-effectiveness and sustainability of TB DNA sequencing for [country]?

1.4.4 Which organizations and countries currently support TB DNA sequencing in [country] as far as you know?

1.5 Do you have any other concerns, challenges, doubts or questions related to TB DNA sequencing, management, or interpretation in the country that you would like to share?

Probe: (to understand exactly why this is a concern/challenge for them)

Part 6: In country patient access and diagnostics involving DNA sequencing

1.1 Currently in [country] who do you think has access to TB DST?

1.1.1 Are there specific individuals or communities in [country] less able to access the best quality TB diagnostics at present?

Rephrase: Do some populations in [country] have access to TB DNA sequencing diagnostics that other people in the country cannot currently access?

1.1.2 Do some patients who could potentially benefit from DST in the country not have access?

1.1.3 What factors contribute to that (in)equality in access in [country]?

Follow up if access not equal at present: Do you see everyone having equal access in the next 5 years? Why or why not?

1.1.4 Do you have any thoughts on that?

Probe: (e.g. feelings, any comment that would help explain that current situation and/or recommendations?)

1.2 In your assessment, will only some individuals or communities in [country] benefit from the implementation of new TB DNA sequencing in [country]? Please explain.

1.3 Do you think that TB DNA sequencing has the potential to improve or exacerbate health disparities within the country? Why yes or why not?

Follow-up if could exacerbate: Is this something you worry about? Why or why not?

- 1.4 Do you have any concerns that TB DNA sequencing could exacerbate health disparities between countries? Why or why not?
- 1.5 In your experience, what social supports, if any, are provided to patients following TB diagnosis?
- 1.6 Does it ever happen that patients are offered DST in [country] when the corresponding treatment is not available?

Follow up if yes: Is that often the case or not very often the case as far as you know, in [country]?

- 1.6.1 Do you think it is ethical for patients to be offered drug susceptibility testing (with or without DNA sequencing) when the corresponding treatment is not available? Why or why not?

Part 7: Perceived impact and conclusion

- 1.1 Has TB DNA sequencing already had an impact on TB here in [country]? Why/how or why not?
- 1.2 Do you see TB DNA sequencing having a major or minor impact on TB surveillance in [country] in the future? Why?
- 1.3 What is the greatest potential impact of using TB DNA sequencing in [country]?
- 1.4 Do you consider TB DNA sequencing to be essential to TB elimination in [country]?
- 1.5 Do you consider TB DNA sequencing to be a necessary tool for TB elimination worldwide?

Conclusion

Thank you. I have learnt so much. Is there anything you would like to add? Is there anything we missed?

Interview Guide (Care providers)

Introduction

Thank you agreeing to take part in this interview. In our discussion today, I am going to ask you some questions about your experience with new Tuberculosis diagnostics.

Part 1: Participant identification

- 1.1 Tell me a little more about your work. What is your job title and what are your responsibilities in this role? Rephrase: What do you do?
- 1.2 How long have you been working in this role?
- 1.3 What is your previous or active role and affiliation regarding TB diagnostics and data management in your work institution?
- 1.4 You are affiliated with [*institution*]. Do you work closely with any other organizations or institutions at the local, national, or international level?

Part 2: Background knowledge on TB diagnostics

- 1.1 How have TB diagnostic methods evolved since you have been working in the field of TB?
- 1.2 What would you say are the biggest challenges in TB diagnosis?

Follow up: Are all of these common challenges here in [*country*]?

Probe: (*To understand what are contributing factors to these challenges in the country in their view – an opportunity to break the ice by letting them share thoughts and theories about a topic they probably have thought about at length, and may give us some useful context info*)

- 1.3 In your recollection, when was TB DNA sequencing introduced in [*country*] and when do you think it became accessible to more clinicians and patients?
- 1.4 How was the diffusion of access to TB DNA sequencing at the various levels of the health system?
- 1.5 What are the applications of DNA sequencing in TB in your clinical practice?

Part 3: Perception on effectiveness of DNA sequencing to predict Drug susceptibility testing (DST)

- 1.1 In your experience, what is the role of DNA sequencing in predicting DST? How accurate or effective is DNA sequencing in predicting DST?
- 1.2 What are advantages and disadvantages of using DNA sequencing for TB DST in the [country] context?
- 1.3 How do you feel about DNA sequencing for TB DST potentially being used more widely here, in [country]? Do you support such expanded use? Why or why not?

Part 4: Knowledge and understanding of molecular epidemiology and surveillance

- 1.1 In your experience, is DNA sequencing useful for understanding TB epidemiology?
- 1.2 What are some advantages and disadvantages of using DNA sequencing for epidemiologic investigations here in [country]?

Follow up: Have you experienced or witnessed those advantages / disadvantages? Could you tell me a little about how that played out?

Part 5: Facilitators, limitations, challenges, and the way forward

- 1.1 Has TB DNA sequencing and DST changed your work? In what way(s)?
- 1.2 Has prescription or interpretation of TB DNA sequencing assays made your job more difficult or easier in any way(s)? How so?
- 1.3 What are the facilitators for TB DNA sequencing implementation in your working environment?
Rephrase: What policies, attitudes, or other conditions are facilitating the use of TB DNA sequencing in your working environment?
- 1.4 Are there any technical barriers or limitations to TB DNA sequencing implementation in your working environment?
 - 1.4.1 What might be possible solutions to those previously mentioned challenges?

1.4.2 Do you think these solutions will be implemented in the near future?

If yes: When and who is leading that change?

If no or perhaps/maybe: Tell me more: why do you say that?

1.5 How are sequencing data management and interpretation currently handled here in your work environment and in [country]?

1.5.1 Did you personally have a good or a bad experience with interpretation of TB DNA sequencing results?

1.5.2 Are there any challenges or concerns associated with sequencing data management and interpretation at the moment, or have there been any challenges with this in the past?

1.5.3 What might be possible solutions to those previously mentioned challenges?

1.5.4 Do you think these solutions will be implemented in the near future?

If yes: When and who is leading that change?

If no: Tell me more: why not?

1.6 In your experience, with whom are TB diagnostic data shared?

1.6.1 Do you see or foresee any issues regarding data privacy?

1.7 How is TB diagnostics funded here in [country]?

1.7.1 Do you think more funding should be put into TB DNA sequencing in [country]? Why or why not?

1.7.2 Which organizations currently support TB DNA sequencing in [country] as far as you know?

1.8 Do you have any other concerns, challenges, doubts or questions related to TB DNA sequencing, management, or interpretation in your workplace that you would like to share?

Probe: (to understand exactly why this is a concern/challenge for them)

Part 6: In country patient access and diagnostics involving DNA sequencing

1.1 Which patient populations in [country] currently have access to DST as part of their TB treatment?

1.1.1 Are there specific individuals or communities in [country] less able to access the best quality TB diagnostics at present?

Rephrase: Do some populations in [country] have access to TB DNA sequencing diagnostics that other people in the country cannot currently access?

1.1.2 Do some patients who could potentially benefit from DST in the country not have access?

1.1.3 What factors contribute to that (in)equality in access in [country]?

Follow up if access not equal at present: Do you see everyone having equal access in the next 5 years? Why or why not?

1.1.4 Do you have any thoughts on that?

Probe: (e.g. feelings, any comment that would help explain that current situation and/or recommendations?)

1.2 In your assessment, will only some individuals or communities in [country] benefit from the implementation of TB DNA sequencing in [country]? Please explain.

1.3 Do you think that TB DNA sequencing has the potential to improve or exacerbate health disparities within the country? Why yes or why not?

Follow-up if could exacerbate: Is this something you worry about? Why or why not?

1.4 Do you have any concerns that TB DNA sequencing could exacerbate health disparities between countries? Why or why not?

1.5 In your experience, what social supports, if any, are provided to patients following TB diagnosis?

1.6 Does it ever happen that patients are offered DST in (country) when the corresponding treatment is not available?

Follow up if yes: Is that often the case or not very often the case as far as you know, in [country]?

1.6.1 Do you think it is ethical for patients to be offered drug susceptibility testing (with or without DNA sequencing) when the corresponding treatment is not available? Why or why not?

Part 7: Perceived impact and conclusion

1.1 Has TB DNA sequencing already had an impact on TB here in [country]? Why/how or why not?

1.2 Do you see TB DNA sequencing having a major or minor impact on TB clinical management in [country]? Why?

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3 1.3 What is the greatest potential impact of using TB DNA sequencing in [*country*]?
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5 1.4 Do you consider TB DNA sequencing to be essential to TB elimination in [*country*]?
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7 1.5 Do you consider TB DNA sequencing to be a necessary tool for TB elimination
8 worldwide?
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11 12 **Conclusion** 13

14 Thank you. I have learnt so much. Is there anything you would like to add? Is there anything we
15 missed?
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Interview Guide (Laboratory personnel)

Introduction

Thank you agreeing to take part in this interview. In our discussion today, I am going to ask you some questions about your experience with new Tuberculosis diagnostics.

Part 1: Participant identification and experience

- 1.1 Tell me a little more about your work. What is your job title and what are your responsibilities in this role? Rephrase: What do you do?
- 1.2 How long have you been working in this role?
- 1.3 What is your previous or active role and affiliations regarding TB diagnostics and data management?
- 1.4 You are affiliated with [*institution*]. Do you work closely with any other organizations or institutions at the local, national, or international level?

Part 2: Background knowledge and perceptions on TB diagnostics

- 1.1 How have TB diagnostic methods evolved since you have been working in the field of TB?
- 1.2 What would you say are the biggest challenges in TB diagnosis?

Follow up: Are all of these common challenges here in [*country*]?

Probe: (*To understand what are contributing factors to these challenges in the country in their view – an opportunity to break the ice by letting them share thoughts and theories about a topic they probably have thought about at length, and may give us some useful context info*)
- 1.3 In your recollection, when was TB DNA sequencing introduced in [*country*] and when do you think it became accessible to more clinics or patients?
- 1.4 How was the expansion of the TB DNA sequencing sector in your work environment?

Part 3: Perception on effectiveness of DNA sequencing to predict Drug susceptibility testing (DST)

- 1.1 In your experience, when is DNA sequencing used to predict DST? And how accurate has it been in predicting DST?
- 1.2 What are advantages and disadvantages of using DNA sequencing for TB DST in the [country] context?
- 1.3 How do you feel about DNA sequencing for TB DST potentially being used more widely here, in [country]? Do you support such expanded use? Why or why not?

Part 4: Knowledge and understanding of molecular epidemiology and surveillance

- 1.1 In your experience, is DNA sequencing useful for understanding TB epidemiology?
- 1.2 What are some advantages and disadvantages of using DNA sequencing for epidemiologic investigations here in [country]?

Follow up: Have you experienced or witnessed those advantages / disadvantages? Could you tell me a little about how that played out?

Part 5: Facilitators, limitations, challenges, and the way forward

- 1.1 Has TB DNA sequencing and DST changed your work? In what way(s)?
- 1.2 Has DNA sequencing made your job more difficult or easier in any way(s)? How so?
- 1.3 What are the facilitators for TB DNA sequencing implementation in your working environment?

Rephrase: What policies, attitudes, or other conditions are facilitating the use of TB DNA sequencing here in [institution]?

- 1.4 Are there any technical barriers or limitations to TB DNA sequencing implementation in your working environment?
 - 1.4.1 What might be possible solutions to those previously mentioned challenges?
 - 1.4.2 Do you think these solutions will be implemented in the near future?

If yes: When and who is leading that change?

If no or perhaps/maybe: Tell me more, why do you say that?

1.5 How are sequencing data management and interpretation currently handled?

1.5.1 Did you personally have a good or a bad experience with TB DNA sequencing?

1.5.2 Are there any challenges or concerns associated with sequencing data management and interpretation at the moment, or have there been any challenges with this in the past?

1.5.3 What might be possible solutions to those previously mentioned challenges?

1.5.4 Do you think these solutions will be implemented in the near future?

If yes: When and who is leading that change?

If no or perhaps/maybe: Tell me more, why not?

1.6 In your experience, with whom are TB diagnostic data shared?

1.6.1 Do you see or foresee any issues regarding data privacy?

1.7 How is TB DNA sequencing funded here in [country]?

1.7.1 Do you think more funding should be put into TB DNA sequencing in [country]?
Why or why not?

If yes: Who should invest more in TB DNA sequencing in [country]?

1.7.2 Which organizations and countries currently support TB DNA sequencing in [country] as far as you know?

1.9 Do you have any other concerns, challenges, doubts or questions related to TB DNA sequencing, management, or interpretation in your workplace that you would like to share?

Probe: (to understand exactly why this is a concern/challenge for them)

Part 6: In country patient access and diagnostics involving DNA sequencing

1.1 Currently in [country] who do you think has access to TB DST?

1.1.1 Are there specific individuals or communities in [country] less able to access the best quality TB diagnostics at present?

Rephrase: Do some populations in [country] have access to TB DNA sequencing diagnostics that other people in the country cannot currently access?

1.1.2 Do some patients who could potentially benefit from DST in the country not have access?

1.1.3 What factors contribute to that (in)equality in access in [country]?

Follow up if access not equal at present: Do you see everyone having equal access in the next 5 years? Why or why not?

1.1.4 Do you have any thoughts on that?

Probe: (e.g. feelings, any comment that would help explain that current situation and/or recommendations?)

1.2 In your assessment, will only some individuals or communities in [country] benefit from the implementation of new TB DNA sequencing in [country]? Please explain.

1.3 Do you think that TB DNA sequencing has the potential to improve or exacerbate health disparities within the country? Why yes or why not?

Follow-up if could exacerbate: Is this something you worry about? Why or why not?

1.4 Do you have any concerns that TB DNA sequencing could exacerbate health disparities between countries? Why or why not?

Part 7: Perceived impact and conclusion

1.1 Has TB DNA sequencing already had an impact on TB here in [country]? Why/how or why not?

1.2 Do you see TB DNA sequencing having a major or minor impact on TB clinical management in [country]? Why?

1.3 What is the greatest potential impact of using TB DNA sequencing in [country]?

1.4 Do you consider TB DNA sequencing to be essential to TB elimination in [country]?

1.5 Do you consider TB DNA sequencing to be a necessary tool for TB elimination worldwide?

Conclusion

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Thank you. I have learnt so much. Is there anything you would like to add? Is there anything we missed?

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Standards for Reporting Qualitative Research (SRQR)*

<http://www.equator-network.org/reporting-guidelines/srqr/>

Page/line no(s).

Title and abstract

Title - Concise description of the nature and topic of the study Identifying the study as qualitative or indicating the approach (e.g., ethnography, grounded theory) or data collection methods (e.g., interview, focus group) is recommended	1
Abstract - Summary of key elements of the study using the abstract format of the intended publication; typically includes background, purpose, methods, results, and conclusions	2

Introduction

Problem formulation - Description and significance of the problem/phenomenon studied; review of relevant theory and empirical work; problem statement	6-7
Purpose or research question - Purpose of the study and specific objectives or questions	6

Methods

Qualitative approach and research paradigm - Qualitative approach (e.g., ethnography, grounded theory, case study, phenomenology, narrative research) and guiding theory if appropriate; identifying the research paradigm (e.g., postpositivist, constructivist/ interpretivist) is also recommended; rationale**	8-9
Researcher characteristics and reflexivity - Researchers' characteristics that may influence the research, including personal attributes, qualifications/experience, relationship with participants, assumptions, and/or presuppositions; potential or actual interaction between researchers' characteristics and the research questions, approach, methods, results, and/or transferability	10 & 30
Context - Setting/site and salient contextual factors; rationale**	8-9
Sampling strategy - How and why research participants, documents, or events were selected; criteria for deciding when no further sampling was necessary (e.g., sampling saturation); rationale**	10
Ethical issues pertaining to human subjects - Documentation of approval by an appropriate ethics review board and participant consent, or explanation for lack thereof; other confidentiality and data security issues	10
Data collection methods - Types of data collected; details of data collection procedures including (as appropriate) start and stop dates of data collection and analysis, iterative process, triangulation of sources/methods, and modification of procedures in response to evolving study findings; rationale**	10-11

Data collection instruments and technologies - Description of instruments (e.g., interview guides, questionnaires) and devices (e.g., audio recorders) used for data collection; if/how the instrument(s) changed over the course of the study	10-11 + supplementary materials
Units of study - Number and relevant characteristics of participants, documents, or events included in the study; level of participation (could be reported in results)	13
Data processing - Methods for processing data prior to and during analysis, including transcription, data entry, data management and security, verification of data integrity, data coding, and anonymization/de-identification of excerpts	11
Data analysis - Process by which inferences, themes, etc., were identified and developed, including the researchers involved in data analysis; usually references a specific paradigm or approach; rationale**	11
Techniques to enhance trustworthiness - Techniques to enhance trustworthiness and credibility of data analysis (e.g., member checking, audit trail, triangulation); rationale**	11-12

Results/findings

Synthesis and interpretation - Main findings (e.g., interpretations, inferences, and themes); might include development of a theory or model, or integration with prior research or theory	13-26
Links to empirical data - Evidence (e.g., quotes, field notes, text excerpts, photographs) to substantiate analytic findings	13-26

Discussion

Integration with prior work, implications, transferability, and contribution(s) to the field - Short summary of main findings; explanation of how findings and conclusions connect to, support, elaborate on, or challenge conclusions of earlier scholarship; discussion of scope of application/generalizability; identification of unique contribution(s) to scholarship in a discipline or field	27-30
Limitations - Trustworthiness and limitations of findings	5

Other

Conflicts of interest - Potential sources of influence or perceived influence on study conduct and conclusions; how these were managed	31
Funding - Sources of funding and other support; role of funders in data collection, interpretation, and reporting	31-32

*The authors created the SRQR by searching the literature to identify guidelines, reporting standards, and critical appraisal criteria for qualitative research; reviewing the reference lists of retrieved sources; and contacting experts to gain feedback. The SRQR aims to improve the transparency of all aspects of qualitative research by providing clear standards for reporting qualitative research.

**The rationale should briefly discuss the justification for choosing that theory, approach, method, or technique rather than other options available, the assumptions and limitations implicit in those choices, and how those choices influence study conclusions and transferability. As appropriate, the rationale for several items might be discussed together.

Reference:

O'Brien BC, Harris IB, Beckman TJ, Reed DA, Cook DA. **Standards for reporting qualitative research: a synthesis of recommendations.** *Academic Medicine*, Vol. 89, No. 9 / Sept 2014
DOI: 10.1097/ACM.0000000000000388

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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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Primary Subject Heading:	Diagnostics
Secondary Subject Heading:	Global health, Public health
Keywords:	Tuberculosis < INFECTIOUS DISEASES, QUALITATIVE RESEARCH, Diagnostic microbiology < INFECTIOUS DISEASES

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For submission to BMJ Global Health
Review Version 1 – 2023.02.12 - CLEAN

TITLE

**Complexities and Benefits of Adopting Next-Generation Sequencing-Based Tuberculosis
Diagnostics: A Qualitative Study Among Stakeholders in Low and High-Income Countries**

RUNNING TITLE

Perceived complexities of *Mycobacterium tuberculosis* next generation sequencing

AUTHORS

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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 semi-structured interviews with key stakeholders engaged with next-generation sequencing implementation in Madagascar and Canada. Team-based descriptive analysis supported by Nvivo 12.0 was used to identify key themes.

Setting

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

Participants

Eighteen participants were interviewed (9 Madagascar, 9 Canada) and included individuals purposively sampled based on involvement with tuberculosis 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) Evidence key to expand adoption; (4) Ethical arguments and concerns; (5) Operational and system-level considerations.

Conclusion

There persists important lack of familiarity with TB NGS applications among stakeholders in Canada and Madagascar. This translates in skepticism on the evidence underlying its use and its true potential value added within global public health systems. If deployed, TB NGS testing should

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63 be integrated with clinical and surveillance programs. Although this is perceived as a priority,
64 leadership, and funding responsibilities for this integration to happen remains unclear to clinical,
65 laboratory and public health stakeholders.

66
67 **Key words: Tuberculosis, Diagnostics, Next-generation sequencing, Madagascar, Canada,**
68 **Qualitative research, Perceptions.**

For peer review only

ARTICLE SUMMARY

Strengths

- This study provides unique insight on gaps in evidence and experience, ethical and operational questions that need to be filled and answered prior to NGS diagnostics successful implementation within national and global public health systems.

Limitations

- Some participants in this study noted their limited familiarity with existing evidence, as well as limited experience with 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 World Health Organization (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 supra-national 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 has long hampered surveillance efforts. (2)

Appropriately treating TB patients, 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 CA USA) 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 to other isolates. NGS technology and TB WGS can thus guide the choice of personalized 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 to conventional culture-based drug susceptibility testing. (9, 10) Hence, TB DNA sequencing promises to play a significant role in universal access to drug susceptibility testing (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 standardization 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)

For submission to BMJ Global Health
Review Version 1 – 2023.02.12 - CLEAN

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: 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.

*For submission to BMJ Global Health
Review Version 1 – 2023.02.12 - CLEAN*

Context

Madagascar exemplifying low-income high TB incidence settings

Madagascar is a low-income country (LIC) with a gross national income of \$520 USD per capita, the ninth lowest in the world. (18) In health as in other sectors, financial challenges are omnipresent and partially result from an unfavorable 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 centers buildings, the TB specific program of Madagascar the program 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 (GFATM) and operational research funding supporting partnerships with international and domestic academic institutions.

Like other low- and middle-income countries (LMICs), Madagascar faces significant challenges with respect to novel diagnostics implementation including underfunding, paucity of trained laboratory personnel, low geographic coverage of centralized 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 whole genome sequencing (WGS) testing was first implemented in the country in 2018 to improve reference DST capacity, contribute to global standardization 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 \$44,940 USD 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 totaled 1,765, representing an increase from the previous year and 80.2% of the 2,200 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 programs to date. The potential benefits of such programs 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 sub-populations, 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. Prioritizing 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 on how new technologies are being understood and used. Data

For submission to BMJ Global Health
Review Version 1 – 2023.02.12 - CLEAN

collection involved semi-structured interviews. Data were analyzed 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 policy makers. 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 pre-specified 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

Semi-structured 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 minutes and two hours, and were administered using an interview guide developed collaboratively by the team in advance (See Supplementary Materials 1) based on the team’s interdisciplinary expertise and following piloting of the guide.

Semi-structured 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 organized around the six following axes: (1) current involvement with TB diagnostics; (2) technical understanding of new diagnostics; (3) perceived accuracy, limits, and potential of TB DNA sequencing for drug susceptibility testing; (4) perceived value added and limits of DNA sequencing for molecular epidemiology and surveillance; (5) experienced and anticipated challenges and impacts of integrating and expanding use of new TB diagnostics in national health system; (6) perceived access and equity issues. In accordance with the semi-structured 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 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”

For submission to BMJ Global Health
Review Version 1 – 2023.02.12 - CLEAN

and “Equity considerations”. From this point of departure, two members of the team (C-AB, EN) independently coded four transcripts to propose adjustments to the initial thematic categorization of findings and to identify specific sub-themes. 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 (AC) proceeded to code all transcripts line-by-line. Names of key themes and the number of sub-themes were revised slightly as the analysis proceeded.

The PIs re-read all transcripts against the NVivo organization of the data as an additional verification that the themes reflected and accurately captured all key data. Co-authors 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 synthesized 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 forms 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.

270 **RESULTS**

271 Key themes identified are described below. These include: (1) Heterogeneity in experience with
272 established TB diagnostics; (2) Variable understanding of new DNA diagnostics potential; (3)
273 Evidence key to expand adoption; (4) Ethical arguments and concerns; (5) Operational and system-
274 level considerations. In what follows, we elaborate on each of these with illustrative quotes¹,
275 highlighting similarities and differences between perceptions from Canada and Madagascar, and
276 across participant categories (clinical, lab-based, surveillance-based).

278 **Heterogeneity in experience with established TB diagnostics**

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

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

287 Canadian participants expressed some familiarity with next-generation sequencing as a technology
288 given its use in several medical application other than TB:

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

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

¹ Quotes from French language interviews were translated into English by the fully bilingual co-PIs (first and last author).

For submission to BMJ Global Health
Review Version 1 – 2023.02.12 - CLEAN

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

303
304 In Madagascar, only one of the three clinicians interviewed routinely used Xpert MTB/RIF™ and
305 none expressed familiarity based on prior use in non-TB contexts. One Malagasy individual
306 involved in surveillance seemed to have more experience with the technology, and ascertained its
307 value added in accelerating diagnosis of TB and prediction of multi-drug resistant (MDR)-TB
308 resistance profiles:

309
310 “For me, the GeneXpert is really a plus, because in two hours you can know if it's really
311 tuberculosis, and if it's resistant or not. So, it has improved a lot. Before, we used to wait for
312 the culture for three months.” (P11/Madagascar/Surveillance)

314 Variable understanding of DNA sequencing diagnostics potential

315
316 Alongside limited usage came uncertainty amongst clinicians and some surveillance experts in
317 Canada and Madagascar about how this technology would complement already existing techniques
318 and transform the diagnostic and patient care landscape. As participants noted, they had heard of
319 the diagnostic advantage of DNA sequencing at conferences, but they did not feel able to comment
320 specifically on how it would represent an advantage over already available methods. Many
321 participants were unclear as to whether DNA sequencing could be used as a first line assay and
322 whether it would improve screening, diagnosis, and/or drug susceptibility testing.

323
324 “Will it help with screening? Especially for MDR-TB?”. (P11/Madagascar/Surveillance)

325
326 “But you know, you have to see, you know, if on average, I get a result that's PCR-positive,
327 smear-positive, I get the culture about a week later, a liquid culture confirmation a week later.
328 Is the sequencing going to be faster than that? Well if it's faster by two days, is that really
329 going to make a difference?” (P2/Canada/Surveillance)

330
331 *"It's done from, again, the isolates, and it seems to me, I don't think I've seen any publications*
332 *yet that allow for direct sequencing from biological samples." (P5/Madagascar/Surveillance)*

333
334 Despite heterogeneity in familiarity and understanding of the technology, the potential role of
335 DNA sequencing to accelerate access to DST results emerged as a hope among almost all
336 participants in both settings. Despite low rates of resistance in the country, Canadian participants
337 highlighted this as an advantage, though the perceived importance of this advantage was variable.

338
339 *"I think the rapidity of results compared to phenotyping which can take one week, two weeks,*
340 *to get the result, I think that is a big advantage." (P0/Canada/Clinician)*

341
342 *"Uncertainty about how much faster would be to get sensitivity results. If a couple of days*
343 *sooner, is that worth it?" (P2/Canada/Surveillance)*

344
345 Lack of familiarity with the practical potential of new TB DNA sequencing technology contrasted
346 with more extensive understanding of this technology's potential at the laboratory level in both
347 countries. Comprehension of that potential did vary across participants. Value of TB DNA
348 sequencing for epidemiological investigations and outbreak identification emerged as particularly
349 obscure to Malagasy participants who could not identify specific situations where it had been or
350 could be used for such application in their specific setting. Some indicated support for expanded
351 use of sequencing, but to accelerate diagnosis, reflecting a lack of familiarity with the additional
352 epidemiological information generated by the new technology.

353
354 *"We already have, as a standard here, as a first intention the GeneXpert. We can see the*
355 *results in an hour. And if it's [sequencing] specific, and if it's faster than that, and if it's*
356 *cheaper than that, why not?" (P4/Madagascar/Laboratory)*

357
358 In Madagascar, since molecular epidemiological analyses had so far relied on testing at a
359 centralized lab and within a research context, participants were unsure how data generated through
360 DNA sequencing could realistically serve in case finding at the community level. Some

For submission to BMJ Global Health
Review Version 1 – 2023.02.12 - CLEAN

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

For submission to BMJ Global Health
Review Version 1 – 2023.02.12 - CLEAN

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 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 skeptical 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.

For submission to BMJ Global Health
Review Version 1 – 2023.02.12 - CLEAN

"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 emphasized 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

For submission to BMJ Global Health
Review Version 1 – 2023.02.12 - CLEAN

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 favor of, as well as ethical concerns related to, sequencing adoption within TB national programs. 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 hospitalization 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 amongst 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 tuberculosis 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.

For submission to BMJ Global Health
Review Version 1 – 2023.02.12 - CLEAN

"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 re-consent.,"
(P2/Canada/Surveillance)

Several participants in both country settings mentioned 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 amongst 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 recognized 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

For submission to BMJ Global Health
Review Version 1 – 2023.02.12 - CLEAN

546 too, but in the provinces and then, if it works well, in the regions. I don't know.
547 (P11/Madagascar/Surveillance)

548
549 Finally, wider use of sequencing would not be ethical, according to participants in both countries,
550 in the absence of clinical access to treatments identified as most appropriate by this new
551 technology.

552
553 "The disadvantages if it's we predict resistance and we don't have anything, and we don't have
554 anything to offer, and we don't, and we don't have a treatment alternative."
555 (P5/Madagascar/Surveillance)

556
557 "So I imagine a patient with a sequencing and they find out that they have isoniazid mono-
558 resistance and the patients end up on therapy and then on monotherapy, for the remaining
559 four months. Wouldn't anyone have planned what to do." (P10/Madagascar/Clinician)

560
561 "Maybe we just need to make sure that the availability of medication is there, which is already
562 not the case everywhere. So: can we make sure we're treating the cases we diagnose well
563 before we think about improving diagnostic techniques?" (P2/Canada/Surveillance)

564 565 **Operational and system-level considerations**

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

569
570 "I think the best thing is when there's a clear protocol that says: here's the new method, here's
571 how we're going to use it, and here's what patients we're going to use it with, and then it's,
572 like, standardized a little bit, and then people have more or less the choice, if you will. That
573 way everyone does the same thing and it's less creative and artistic in the way it's used and
574 implemented. (P1/Canada/Clinician)

For submission to BMJ Global Health
Review Version 1 – 2023.02.12 - CLEAN

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

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

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

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

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

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

604 *“You have to get the buy-in of whatever agency oversees the lab directors, the section heads,*
605 *the lab technologist as well. So it's got to be the policy decision that ideally you engaged your*
606 *APHL or CPHL people upfront in crafting that policy so that rather than a complete top down,*

For submission to BMJ Global Health
Review Version 1 – 2023.02.12 - CLEAN

607 like, “Okay, this is the new way of doing things”, the lab director and lab technologies can
608 be like: “Oh, our leadership worked with the Ministry of Health, or Health Canada, Public
609 Health Canada, to make this decision. Clearly they know what they're doing. I'm going to get
610 on board with this.” (P15/Canada/Surveillance)

611
612 ~~“Once people understand the benefit of using one technique over another, or adding that to~~
613 ~~the standard stuff, on the face of it, it should go down well.” (P1/Canada/Clinician)~~
614

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

621
622 “You have to go through the program and you have to see what they think. Because we
623 clinicians here, we can't make a decision like that, we can't say no. For us it's, it's going to
624 make our lives easier. So it's not our role to refuse. If they say: “we're going to integrate
625 sequencing in the diagnosis of tuberculosis, we can't refuse, so we have to talk to the higher
626 authorities. (P7/Madagascar/Clinician)

627
628 “Of course, it is the program that will introduce this method into the program in the national
629 strategic plan and then when the, this method is among the diagnostic methods in the NSP,
630 the donors can finance the methods.” (P8/Madagascar/Laboratory)

631
632 As is evident from the last quote, in Madagascar, decisions on adoption were understood to not
633 depend solely on Malagasy leaders. National TB program methods hinge on external funders’
634 decisions. In both countries, governmental endorsement was seen to be most likely following
635 WHO recommendations.

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

639
640 "For the moment, and in Madagascar the National Tuberculosis Control Program and the
641 Ministry do not often agree to put in the national TB policy an examination or treatment that
642 the WHO does not recommend." (P3/Madagascar/Clinician)

643
644 Madagascar’s limited agency to lead adoption decisions was recurrent in the comments from that
645 country’s participants. Madagascar could develop evidence and grow convinced that adoption
646 made sense, but ultimately any change to existing practice was seen as being the call of the WHO,
647 not Madagascar.

648
649 "After the results so we will implement, we will suggest WHO after I don't know to put in
650 among the diagnostics used in routine." (P9/Madagascar/Laboratory)

DISCUSSION

Principal findings

This study elucidates several considerations complicating diversely positioned stakeholders' enthusiasm for 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 TB programs 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 program are not in the hands of the Malagasy alone, but dependent on decisions made by external funders and policy makers.

TAKEWAY 1 – 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 numbers of laboratories having previously embedded TB NGS within their TB diagnostics 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.

TAKEWAY 2 – This lack of clarity regarding what TB NGS could achieve was accompanied by significant skepticism 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.

TAKEWAY 3 – Independent of TB NGS performance and accuracy, Canadian and Malagasy participants all highlighted the importance of ensuring genomic data would be integrated with clinical and surveillance programs. 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 personalized therapeutic regimens in clinical settings should be secured.

TAKEWAY 4 – Despite providing important insights on 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 and why, for whom, adoption would be advantageous or complicated within their specific TB program, 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 centralized in the capital, further variability might exist across Canada where this expertise is decentralized 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 amongst a diverse panel of stakeholders including (i) experts from the entire continuum of clinical, laboratory and surveillance spectrum and (ii) interviewees from low TB incidence/high-income and high TB incidence/low-income countries. 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 synthesize 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 programs 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 programs 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

744 previous qualitative explorations of this technology. (16, 17) For example, Jackson et al.'s study
745 focused on trust in the new diagnostics and reported on concerns regarding who has access to, and
746 can benefit from, the technology and data as well as the necessary epidemiological and clinical
747 metadata which needs to be linked to TB genomic data. (14) This concern was also raised by
748 Davies et al. in their report on a public debate on TB WGS for outbreak investigation. (17) In this
749 public consultation, participants generally agreed that medical professionals and the research
750 community should have access to TB WGS data without specifically addressing through which
751 mechanisms. Although participants within our study were specifically asked about potential ethical
752 issues and concerns related to adoption, trust and the ethics of surveillance and data ownership did
753 not emerge as primary concerns in our data. One study participant expressed data worries about
754 eventual partnerships with third party (potentially including commercial) partners, and the
755 potential for such partnerships in the absence of a clear plan to ensure sensitive patient information
756 remained protected. Calls for evidence-based adoption and assurance that care protocols would
757 match improved diagnostics were much more prominent concerns for both Canadian and Malagasy
758 participants.

759
760 **CONCLUSION**

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

765

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768

769 AUTHOR CONTRIBUTIONS

770 All authors meet the ICMJE criteria for authorship. Conception and design (SGL, EN), data
771 acquisition (C-AB), data analysis and interpretation (SGL, EN, C-AB, M-SR, OM, MJS, NR),
772 initial draft of the manuscript (SGL, EN, C-AB). All authors had access to the primary data, have
773 reviewed the final version of the manuscript and accept the responsibility to submit for publication.

774

775 DECLARATION OF INTERESTS

776 Authors declare having no financial and/or personal relationships with other people or
777 organisations that could inappropriately influence (bias) the reported research work.

778

779 ROLE OF THE FUNDING SOURCE

780 The funders had no role in the study design, in the collection, analysis, and interpretation of data,
781 in the writing of the report and in the decision to submit the paper for publication.

782

783 DATA SHARING

784 Deidentified participants' interviews data will be made available with publication upon request to
785 the corresponding author.

786

787 AUTHOR REFLEXIVITY STATEMENT

788 We report on research from and international partnership between a high-income country (Canada)
789 and a low-income country (Madagascar). The authorship includes a diversity of early- and mid-stage
790 researchers from both partner countries. Two co-authors from Madagascar participated in the research
791 but did not assume leadership in study design or manuscript preparation. The authorship order,
792 including co-first and last author reflects the contribution of every co-author as per ICMJE guidelines.

793

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ETHICS

Ethics approval for this study was obtained from the Centre de Recherche du Centre Hospitaliser de l’Université de Montréal (CRCHUM) (Ref. 2020-8310), and the Comité d’Éthique à la Recherche Biomédicale à Madagascar (CERBM) (Ref. 056/MSANP/SG). All participants provided written consent prior to the interview.

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SUPPLEMENTARY MATERIALS

Supplementary Materials 1 – Semi-structured interview guides

Interview Guide (Disease surveillance experts)

Introduction

Thank you for agreeing to take part in this interview. In our discussion today, I am going to ask you some questions about your experience with new Tuberculosis diagnostics.

Part 1: Participant identification

- 1.1 Tell me a little more about your work. What is your job title and what are your responsibilities in this role? Rephrase: What do you do?
- 1.2 How long have you been working in this role?
- 1.3 What is your previous or active role and affiliations regarding TB diagnostics and data management?
- 1.4 You are affiliated with [*institution*]. Do you work closely with any other organizations or institutions at the local, national, or international level?

Part 2: Background knowledge of TB diagnostics

- 1.1 How have TB diagnostic methods evolved since you have been working in the field of TB?
- 1.2 What would you say are the biggest challenges in TB diagnosis?

Follow up: Are all of these common challenges here in [*country*]?

Probe: (*To understand what are contributing factors to these challenges in the country in their view – an opportunity to break the ice by letting them share thoughts and theories about a topic they probably have thought about at length, and may give us some useful context info*)

- 1.3 In your recollection, when was TB DNA sequencing introduced in [*country*] and when do you think it became accessible to more clinics or patients?

1.4 How was the diffusion of access to TB DNA sequencing at various levels of the health system?

1.5 What are the applications of TB DNA sequencing in [*country*]?

Part 3: Perception of DNA sequencing to predict drug susceptibility testing (DST)

1.1 In your experience, when is DNA sequencing used to predict DST? And how accurate has it been in predicting DST?

1.2 What are advantages and disadvantages of using DNA sequencing for TB DST in the [*country*] context?

1.3 How do you feel about DNA sequencing for TB DST potentially being used more widely here, in [*country*]? Do you support such expanded use? Why or why not?

Part 4: Knowledge and understanding of molecular epidemiology and surveillance

1.1 In your experience, is DNA sequencing useful for understanding TB epidemiology?

1.2 What are some advantages and disadvantages of using DNA sequencing for epidemiologic investigations here in [*country*]?

Follow up: Have you experienced or witnessed those advantages / disadvantages? Could you tell me about it?

Part 5: Facilitators, limitations, challenges, and the way forward

1.1 Has TB DNA sequencing and DST changed your work? In what way(s)?

1.2 Has DNA sequencing made your job more difficult or easier in any way(s)? How so?

1.3 What are the facilitators for TB DNA sequencing implementation in your working environment and country?

Rephrase: What policies, attitudes, or other conditions are facilitating the use of TB DNA sequencing here in [*institution and country*]?

1
2
3 1.4 Are there any technical barriers or limitations to TB DNA sequencing implementation in
4 your working environment?

5
6 1.4.1 What might be possible solutions to those previously mentioned challenges?

7
8 1.4.2 Do you think these solutions will be implemented in the near future?

9
10
11 If yes: When and who is leading that change?

12
13 If no or perhaps/maybe: Tell me more, why do you say that?

14
15
16 1.5 Are there any technical barriers or limitations to TB DNA sequencing implementation in
17 your country?

18
19 1.1.1 What might be possible solutions to those previously mentioned challenges?

20
21 1.1.2 Do you think these solutions will be implemented in the near future?

22
23 If yes: When and who is leading that change?

24
25 If no or perhaps/maybe: Tell me more, why do you say that?

26
27
28 1.2 How are sequencing data management and interpretation currently handled here in [country]?

29
30 1.2.1 Did you personally have a good or a bad experience with data management of TB
31 DNA sequencing?

32
33 1.2.2 Can you describe any work you have done involving the interpretation of TB DNA
34 sequencing?

35
36 1.2.3 Are there any challenges or concerns associated with sequencing data management and
37 interpretation at the moment, or has there been any challenges with this in the past?

38
39 1.2.4 What might be possible solutions to those previously mentioned challenges?

40
41 1.2.5 Do you think these solutions will be implemented in the near future?

42
43
44 If yes: When and who is leading that change?

45
46 If no or perhaps/maybe: Tell me more, why not?

47
48
49 1.3 In your experience, with whom are TB diagnostic data shared?

50
51 1.3.1 Do you see or foresee any issues regarding data privacy?

52
53 1.4 How is TB DNA sequencing funded here in [country]?

54
55 1.4.1 Do you think more funding should be put into TB DNA sequencing in [country]?
56 Why or why not?

If yes: Who should invest more in TB DNA sequencing in [country]?

1.4.2 Do you think richer countries or international organizations should support less rich countries in TB DNA sequencing implementation? Why or why not?

1.4.3 What is your perception of the cost-effectiveness and sustainability of TB DNA sequencing for [country]?

1.4.4 Which organizations and countries currently support TB DNA sequencing in [country] as far as you know?

1.5 Do you have any other concerns, challenges, doubts or questions related to TB DNA sequencing, management, or interpretation in the country that you would like to share?

Probe: (to understand exactly why this is a concern/challenge for them)

Part 6: In country patient access and diagnostics involving DNA sequencing

1.1 Currently in [country] who do you think has access to TB DST?

1.1.1 Are there specific individuals or communities in [country] less able to access the best quality TB diagnostics at present?

Rephrase: Do some populations in [country] have access to TB DNA sequencing diagnostics that other people in the country cannot currently access?

1.1.2 Do some patients who could potentially benefit from DST in the country not have access?

1.1.3 What factors contribute to that (in)equality in access in [country]?

Follow up if access not equal at present: Do you see everyone having equal access in the next 5 years? Why or why not?

1.1.4 Do you have any thoughts on that?

Probe: (e.g. feelings, any comment that would help explain that current situation and/or recommendations?)

1.2 In your assessment, will only some individuals or communities in [country] benefit from the implementation of new TB DNA sequencing in [country]? Please explain.

1.3 Do you think that TB DNA sequencing has the potential to improve or exacerbate health disparities within the country? Why yes or why not?

- Follow-up if could exacerbate: Is this something you worry about? Why or why not?
- 1.4 Do you have any concerns that TB DNA sequencing could exacerbate health disparities between countries? Why or why not?
- 1.5 In your experience, what social supports, if any, are provided to patients following TB diagnosis?
- 1.6 Does it ever happen that patients are offered DST in [country] when the corresponding treatment is not available?
- Follow up if yes: Is that often the case or not very often the case as far as you know, in [country]?
- 1.6.1 Do you think it is ethical for patients to be offered drug susceptibility testing (with or without DNA sequencing) when the corresponding treatment is not available? Why or why not?

Part 7: Perceived impact and conclusion

- 1.1 Has TB DNA sequencing already had an impact on TB here in [country]? Why/how or why not?
- 1.2 Do you see TB DNA sequencing having a major or minor impact on TB surveillance in [country] in the future? Why?
- 1.3 What is the greatest potential impact of using TB DNA sequencing in [country]?
- 1.4 Do you consider TB DNA sequencing to be essential to TB elimination in [country]?
- 1.5 Do you consider TB DNA sequencing to be a necessary tool for TB elimination worldwide?

Conclusion

Thank you. I have learnt so much. Is there anything you would like to add? Is there anything we missed?

Interview Guide (Care providers)

Introduction

Thank you agreeing to take part in this interview. In our discussion today, I am going to ask you some questions about your experience with new Tuberculosis diagnostics.

Part 1: Participant identification

- 1.1 Tell me a little more about your work. What is your job title and what are your responsibilities in this role? Rephrase: What do you do?
- 1.2 How long have you been working in this role?
- 1.3 What is your previous or active role and affiliation regarding TB diagnostics and data management in your work institution?
- 1.4 You are affiliated with [*institution*]. Do you work closely with any other organizations or institutions at the local, national, or international level?

Part 2: Background knowledge on TB diagnostics

- 1.1 How have TB diagnostic methods evolved since you have been working in the field of TB?
- 1.2 What would you say are the biggest challenges in TB diagnosis?

Follow up: Are all of these common challenges here in [*country*]?

Probe: (*To understand what are contributing factors to these challenges in the country in their view – an opportunity to break the ice by letting them share thoughts and theories about a topic they probably have thought about at length, and may give us some useful context info*)

- 1.3 In your recollection, when was TB DNA sequencing introduced in [*country*] and when do you think it became accessible to more clinicians and patients?
- 1.4 How was the diffusion of access to TB DNA sequencing at the various levels of the health system?
- 1.5 What are the applications of DNA sequencing in TB in your clinical practice?

Part 3: Perception on effectiveness of DNA sequencing to predict Drug susceptibility testing (DST)

- 1.1 In your experience, what is the role of DNA sequencing in predicting DST? How accurate or effective is DNA sequencing in predicting DST?
- 1.2 What are advantages and disadvantages of using DNA sequencing for TB DST in the [country] context?
- 1.3 How do you feel about DNA sequencing for TB DST potentially being used more widely here, in [country]? Do you support such expanded use? Why or why not?

Part 4: Knowledge and understanding of molecular epidemiology and surveillance

- 1.1 In your experience, is DNA sequencing useful for understanding TB epidemiology?
 - 1.2 What are some advantages and disadvantages of using DNA sequencing for epidemiologic investigations here in [country]?
- Follow up: Have you experienced or witnessed those advantages / disadvantages? Could you tell me a little about how that played out?

Part 5: Facilitators, limitations, challenges, and the way forward

- 1.1 Has TB DNA sequencing and DST changed your work? In what way(s)?
 - 1.2 Has prescription or interpretation of TB DNA sequencing assays made your job more difficult or easier in any way(s)? How so?
 - 1.3 What are the facilitators for TB DNA sequencing implementation in your working environment?
- Rephrase: What policies, attitudes, or other conditions are facilitating the use of TB DNA sequencing in your working environment?
- 1.4 Are there any technical barriers or limitations to TB DNA sequencing implementation in your working environment?
 - 1.4.1 What might be possible solutions to those previously mentioned challenges?

1.4.2 Do you think these solutions will be implemented in the near future?

If yes: When and who is leading that change?

If no or perhaps/maybe: Tell me more: why do you say that?

1.5 How are sequencing data management and interpretation currently handled here in your work environment and in [country]?

1.5.1 Did you personally have a good or a bad experience with interpretation of TB DNA sequencing results?

1.5.2 Are there any challenges or concerns associated with sequencing data management and interpretation at the moment, or have there been any challenges with this in the past?

1.5.3 What might be possible solutions to those previously mentioned challenges?

1.5.4 Do you think these solutions will be implemented in the near future?

If yes: When and who is leading that change?

If no: Tell me more: why not?

1.6 In your experience, with whom are TB diagnostic data shared?

1.6.1 Do you see or foresee any issues regarding data privacy?

1.7 How is TB diagnostics funded here in [country]?

1.7.1 Do you think more funding should be put into TB DNA sequencing in [country]? Why or why not?

1.7.2 Which organizations currently support TB DNA sequencing in [country] as far as you know?

1.8 Do you have any other concerns, challenges, doubts or questions related to TB DNA sequencing, management, or interpretation in your workplace that you would like to share?

Probe: (to understand exactly why this is a concern/challenge for them)

Part 6: In country patient access and diagnostics involving DNA sequencing

1.1 Which patient populations in [country] currently have access to DST as part of their TB treatment?

1.1.1 Are there specific individuals or communities in [country] less able to access the best quality TB diagnostics at present?

Rephrase: Do some populations in [country] have access to TB DNA sequencing diagnostics that other people in the country cannot currently access?

1.1.2 Do some patients who could potentially benefit from DST in the country not have access?

1.1.3 What factors contribute to that (in)equality in access in [country]?

Follow up if access not equal at present: Do you see everyone having equal access in the next 5 years? Why or why not?

1.1.4 Do you have any thoughts on that?

Probe: (e.g. feelings, any comment that would help explain that current situation and/or recommendations?)

1.2 In your assessment, will only some individuals or communities in [country] benefit from the implementation of TB DNA sequencing in [country]? Please explain.

1.3 Do you think that TB DNA sequencing has the potential to improve or exacerbate health disparities within the country? Why yes or why not?

Follow-up if could exacerbate: Is this something you worry about? Why or why not?

1.4 Do you have any concerns that TB DNA sequencing could exacerbate health disparities between countries? Why or why not?

1.5 In your experience, what social supports, if any, are provided to patients following TB diagnosis?

1.6 Does it ever happen that patients are offered DST in (country) when the corresponding treatment is not available?

Follow up if yes: Is that often the case or not very often the case as far as you know, in [country]?

1.6.1 Do you think it is ethical for patients to be offered drug susceptibility testing (with or without DNA sequencing) when the corresponding treatment is not available? Why or why not?

Part 7: Perceived impact and conclusion

1.1 Has TB DNA sequencing already had an impact on TB here in [country]? Why/how or why not?

1.2 Do you see TB DNA sequencing having a major or minor impact on TB clinical management in [country]? Why?

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3 1.3 What is the greatest potential impact of using TB DNA sequencing in [*country*]?
4

5 1.4 Do you consider TB DNA sequencing to be essential to TB elimination in [*country*]?
6

7 1.5 Do you consider TB DNA sequencing to be a necessary tool for TB elimination
8 worldwide?
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11 12 **Conclusion** 13

14 Thank you. I have learnt so much. Is there anything you would like to add? Is there anything we
15 missed?
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Interview Guide (Laboratory personnel)

Introduction

Thank you agreeing to take part in this interview. In our discussion today, I am going to ask you some questions about your experience with new Tuberculosis diagnostics.

Part 1: Participant identification and experience

- 1.1 Tell me a little more about your work. What is your job title and what are your responsibilities in this role? Rephrase: What do you do?
- 1.2 How long have you been working in this role?
- 1.3 What is your previous or active role and affiliations regarding TB diagnostics and data management?
- 1.4 You are affiliated with [*institution*]. Do you work closely with any other organizations or institutions at the local, national, or international level?

Part 2: Background knowledge and perceptions on TB diagnostics

- 1.1 How have TB diagnostic methods evolved since you have been working in the field of TB?
- 1.2 What would you say are the biggest challenges in TB diagnosis?
Follow up: Are all of these common challenges here in [*country*]?
Probe: (*To understand what are contributing factors to these challenges in the country in their view – an opportunity to break the ice by letting them share thoughts and theories about a topic they probably have thought about at length, and may give us some useful context info*)
- 1.3 In your recollection, when was TB DNA sequencing introduced in [*country*] and when do you think it became accessible to more clinics or patients?
- 1.4 How was the expansion of the TB DNA sequencing sector in your work environment?

Part 3: Perception on effectiveness of DNA sequencing to predict Drug susceptibility testing (DST)

- 1.1 In your experience, when is DNA sequencing used to predict DST? And how accurate has it been in predicting DST?
- 1.2 What are advantages and disadvantages of using DNA sequencing for TB DST in the [country] context?
- 1.3 How do you feel about DNA sequencing for TB DST potentially being used more widely here, in [country]? Do you support such expanded use? Why or why not?

Part 4: Knowledge and understanding of molecular epidemiology and surveillance

- 1.1 In your experience, is DNA sequencing useful for understanding TB epidemiology?
- 1.2 What are some advantages and disadvantages of using DNA sequencing for epidemiologic investigations here in [country]?

Follow up: Have you experienced or witnessed those advantages / disadvantages? Could you tell me a little about how that played out?

Part 5: Facilitators, limitations, challenges, and the way forward

- 1.1 Has TB DNA sequencing and DST changed your work? In what way(s)?
- 1.2 Has DNA sequencing made your job more difficult or easier in any way(s)? How so?
- 1.3 What are the facilitators for TB DNA sequencing implementation in your working environment?

Rephrase: What policies, attitudes, or other conditions are facilitating the use of TB DNA sequencing here in [institution]?

- 1.4 Are there any technical barriers or limitations to TB DNA sequencing implementation in your working environment?
 - 1.4.1 What might be possible solutions to those previously mentioned challenges?
 - 1.4.2 Do you think these solutions will be implemented in the near future?

If yes: When and who is leading that change?

If no or perhaps/maybe: Tell me more, why do you say that?

1.5 How are sequencing data management and interpretation currently handled?

1.5.1 Did you personally have a good or a bad experience with TB DNA sequencing?

1.5.2 Are there any challenges or concerns associated with sequencing data management and interpretation at the moment, or have there been any challenges with this in the past?

1.5.3 What might be possible solutions to those previously mentioned challenges?

1.5.4 Do you think these solutions will be implemented in the near future?

If yes: When and who is leading that change?

If no or perhaps/maybe: Tell me more, why not?

1.6 In your experience, with whom are TB diagnostic data shared?

1.6.1 Do you see or foresee any issues regarding data privacy?

1.7 How is TB DNA sequencing funded here in [country]?

1.7.1 Do you think more funding should be put into TB DNA sequencing in [country]?
Why or why not?

If yes: Who should invest more in TB DNA sequencing in [country]?

1.7.2 Which organizations and countries currently support TB DNA sequencing in [country] as far as you know?

1.9 Do you have any other concerns, challenges, doubts or questions related to TB DNA sequencing, management, or interpretation in your workplace that you would like to share?

Probe: (to understand exactly why this is a concern/challenge for them)

Part 6: In country patient access and diagnostics involving DNA sequencing

1.1 Currently in [country] who do you think has access to TB DST?

1.1.1 Are there specific individuals or communities in [country] less able to access the best quality TB diagnostics at present?

Rephrase: Do some populations in [country] have access to TB DNA sequencing diagnostics that other people in the country cannot currently access?

1.1.2 Do some patients who could potentially benefit from DST in the country not have access?

1.1.3 What factors contribute to that (in)equality in access in [country]?

Follow up if access not equal at present: Do you see everyone having equal access in the next 5 years? Why or why not?

1.1.4 Do you have any thoughts on that?

Probe: (e.g. feelings, any comment that would help explain that current situation and/or recommendations?)

1.2 In your assessment, will only some individuals or communities in [country] benefit from the implementation of new TB DNA sequencing in [country]? Please explain.

1.3 Do you think that TB DNA sequencing has the potential to improve or exacerbate health disparities within the country? Why yes or why not?

Follow-up if could exacerbate: Is this something you worry about? Why or why not?

1.4 Do you have any concerns that TB DNA sequencing could exacerbate health disparities between countries? Why or why not?

Part 7: Perceived impact and conclusion

1.1 Has TB DNA sequencing already had an impact on TB here in [country]? Why/how or why not?

1.2 Do you see TB DNA sequencing having a major or minor impact on TB clinical management in [country]? Why?

1.3 What is the greatest potential impact of using TB DNA sequencing in [country]?

1.4 Do you consider TB DNA sequencing to be essential to TB elimination in [country]?

1.5 Do you consider TB DNA sequencing to be a necessary tool for TB elimination worldwide?

Conclusion

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Thank you. I have learnt so much. Is there anything you would like to add? Is there anything we missed?

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<http://www.equator-network.org/reporting-guidelines/srqr/>

Page/line no(s).

Title and abstract

Title - Concise description of the nature and topic of the study Identifying the study as qualitative or indicating the approach (e.g., ethnography, grounded theory) or data collection methods (e.g., interview, focus group) is recommended	1
Abstract - Summary of key elements of the study using the abstract format of the intended publication; typically includes background, purpose, methods, results, and conclusions	2

Introduction

Problem formulation - Description and significance of the problem/phenomenon studied; review of relevant theory and empirical work; problem statement	6-7
Purpose or research question - Purpose of the study and specific objectives or questions	6

Methods

Qualitative approach and research paradigm - Qualitative approach (e.g., ethnography, grounded theory, case study, phenomenology, narrative research) and guiding theory if appropriate; identifying the research paradigm (e.g., postpositivist, constructivist/ interpretivist) is also recommended; rationale**	8-9
Researcher characteristics and reflexivity - Researchers' characteristics that may influence the research, including personal attributes, qualifications/experience, relationship with participants, assumptions, and/or presuppositions; potential or actual interaction between researchers' characteristics and the research questions, approach, methods, results, and/or transferability	10 & 30
Context - Setting/site and salient contextual factors; rationale**	8-9
Sampling strategy - How and why research participants, documents, or events were selected; criteria for deciding when no further sampling was necessary (e.g., sampling saturation); rationale**	10
Ethical issues pertaining to human subjects - Documentation of approval by an appropriate ethics review board and participant consent, or explanation for lack thereof; other confidentiality and data security issues	10
Data collection methods - Types of data collected; details of data collection procedures including (as appropriate) start and stop dates of data collection and analysis, iterative process, triangulation of sources/methods, and modification of procedures in response to evolving study findings; rationale**	10-11

Data collection instruments and technologies - Description of instruments (e.g., interview guides, questionnaires) and devices (e.g., audio recorders) used for data collection; if/how the instrument(s) changed over the course of the study	10-11 + supplementary materials
Units of study - Number and relevant characteristics of participants, documents, or events included in the study; level of participation (could be reported in results)	13
Data processing - Methods for processing data prior to and during analysis, including transcription, data entry, data management and security, verification of data integrity, data coding, and anonymization/de-identification of excerpts	11
Data analysis - Process by which inferences, themes, etc., were identified and developed, including the researchers involved in data analysis; usually references a specific paradigm or approach; rationale**	11
Techniques to enhance trustworthiness - Techniques to enhance trustworthiness and credibility of data analysis (e.g., member checking, audit trail, triangulation); rationale**	11-12

Results/findings

Synthesis and interpretation - Main findings (e.g., interpretations, inferences, and themes); might include development of a theory or model, or integration with prior research or theory	13-26
Links to empirical data - Evidence (e.g., quotes, field notes, text excerpts, photographs) to substantiate analytic findings	13-26

Discussion

Integration with prior work, implications, transferability, and contribution(s) to the field - Short summary of main findings; explanation of how findings and conclusions connect to, support, elaborate on, or challenge conclusions of earlier scholarship; discussion of scope of application/generalizability; identification of unique contribution(s) to scholarship in a discipline or field	27-30
Limitations - Trustworthiness and limitations of findings	5

Other

Conflicts of interest - Potential sources of influence or perceived influence on study conduct and conclusions; how these were managed	31
Funding - Sources of funding and other support; role of funders in data collection, interpretation, and reporting	31-32

*The authors created the SRQR by searching the literature to identify guidelines, reporting standards, and critical appraisal criteria for qualitative research; reviewing the reference lists of retrieved sources; and contacting experts to gain feedback. The SRQR aims to improve the transparency of all aspects of qualitative research by providing clear standards for reporting qualitative research.

**The rationale should briefly discuss the justification for choosing that theory, approach, method, or technique rather than other options available, the assumptions and limitations implicit in those choices, and how those choices influence study conclusions and transferability. As appropriate, the rationale for several items might be discussed together.

Reference:

O'Brien BC, Harris IB, Beckman TJ, Reed DA, Cook DA. **Standards for reporting qualitative research: a synthesis of recommendations.** *Academic Medicine*, Vol. 89, No. 9 / Sept 2014
DOI: 10.1097/ACM.0000000000000388

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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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TITLE

Complexities and Benefits of Adopting Next-Generation Sequencing-Based Tuberculosis Diagnostics: A Qualitative Study Among Stakeholders in Low and High-Income Countries

RUNNING TITLE

Perceived complexities of *Mycobacterium tuberculosis* next generation sequencing

AUTHORS

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32 **ABSTRACT**

33 **Objectives**

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

39 **Design**

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

44 **Setting**

45 The study was conducted with participants involved at the clinical, diagnostic, and surveillance
46 levels of TB management from Madagascar and Canada.

48 **Participants**

49 Eighteen participants were interviewed (9 Madagascar, 9 Canada) and included individuals
50 purposively sampled based on involvement with tuberculosis surveillance, laboratory diagnosis
51 and clinical management.

53 **Results**

54 The following five themes emerged in the analysis of Malagasy and Canadian interviews: (1)
55 Heterogeneity in experience with established TB diagnostics; (2) Variable understanding of new
56 sequencing-based diagnostics potential; (3) Further evidence as being key to expand adoption; (4)
57 Ethical arguments and concerns; (5) Operational and system-level considerations.

59 **Conclusion**

60 There persists important lack of familiarity with TB NGS applications among stakeholders in
61 Canada and Madagascar. This translates into skepticism on the evidence underlying its use and its
62 true potential value added within global public health systems. If deployed, TB NGS testing should

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be integrated with clinical and surveillance programs. 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.

Key words: Tuberculosis, Diagnostics, Next-generation sequencing, Madagascar, Canada, Qualitative research, Perceptions.

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ARTICLE SUMMARY

Strengths

- This study provides unique insight into gaps in evidence and experience, ethical and operational questions that need to be filled and answered prior to NGS diagnostics’ successful implementation within national and global public health systems.

Limitations

- Some participants in this study noted their limited familiarity with existing evidence, as well as limited experience with 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 World Health Organization (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 supra-national 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 has long hampered surveillance efforts. (2)

Appropriately treating TB patients, 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 CA USA) 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 to other isolates. NGS technology and TB WGS can thus guide the choice of personalized 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 to conventional culture-based drug susceptibility testing. (9, 10) Hence, TB DNA sequencing promises to play a significant role in universal access to drug susceptibility testing (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 standardization 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)

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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: 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 low-income country (LIC) with a gross national income of \$520 USD per capita, the ninth lowest in the world. (18) In health as in other sectors, financial challenges are omnipresent and partially result from an unfavorable 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 centers buildings, the TB specific program of Madagascar the program 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 (GFATM) and operational research funding supporting partnerships with international and domestic academic institutions.

Like other low- and middle-income countries (LMICs), Madagascar faces significant challenges with respect to novel diagnostics implementation including underfunding, paucity of trained laboratory personnel, low geographic coverage of centralized 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 whole genome sequencing (WGS) testing was first implemented in the country in 2018 to improve reference DST capacity, contribute to global standardization 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 \$44,940 USD 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 totaled 1,765, representing an increase from the previous year and 80.2% of the 2,200 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 programs to date. The potential benefits of such programs 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 sub-populations, 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. Prioritizing 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 on how new technologies are being understood and used. Data

collection involved semi-structured interviews. Data were analyzed 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 policy makers. 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 pre-specified 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

Semi-structured 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 minutes and two hours, and were administered using an interview guide developed collaboratively by the team in advance (See Supplementary Materials 1) based on the team’s interdisciplinary expertise and following piloting of the guide.

Semi-structured 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 organized around the six following axes: (1) current involvement with TB diagnostics; (2) technical understanding of new diagnostics; (3) perceived accuracy, limits, and potential of TB DNA sequencing for drug susceptibility testing; (4) perceived value added and limits of DNA sequencing for molecular epidemiology and surveillance; (5) experienced and anticipated challenges and impacts of integrating and expanding use of new TB diagnostics in national health system; (6) perceived access and equity issues. In accordance with the semi-structured 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 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, EN) independently coded four transcripts to propose adjustments to the initial thematic categorization of findings and to identify specific sub-themes. 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 (AC) proceeded to code all transcripts line-by-line. Names of key themes and the number of sub-themes were revised slightly as the analysis proceeded.

The PIs re-read all transcripts against the NVivo organization of the data as an additional verification that the themes reflected and accurately captured all key data. Co-authors 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 synthesized 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 forms 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 quotes¹, 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 drug susceptibility testing.

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 next-generation sequencing 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 to 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.

¹ Quotes from French language interviews were translated into English by the fully bilingual co-PIs (first and last author).

“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 multi-drug 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 amongst 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 mischaracterized 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 drug susceptibility testing.

“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.

For submission to BMJ Global Health
Review Version 2 – 2023.03.14– Main Document

326 *Is the sequencing going to be faster than that? Well if it's faster by two days, is that really*
327 *going to make a difference?" (P2/Canada/Surveillance)*

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

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

337 *"I think the rapidity of results compared to phenotyping which can take one week, two weeks,*
338 *to get the result, I think that is a big advantage." (P0/Canada/Clinician)*

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

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

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

For submission to BMJ Global Health
Review Version 2 – 2023.03.14– Main Document

In Madagascar, since molecular epidemiological analyses had so far relied on testing at a centralized 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 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 skeptical 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 emphasized 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 favor of, as well as ethical concerns related to, sequencing adoption within TB national programs. 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 hospitalization 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 amongst 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 tuberculosis 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.

511
512 *"Because afterwards, if you want to be able to do, if you want to be able to exchange your*
513 *information with the other provinces, with the United States, with the rest of the Western*
514 *countries. Then it also requires, at the ethical level, an informed and prolonged consent,*
515 *where you don't have to go back to your patient every ten years to ask them to re-consent."*
516 *(P2/Canada/Surveillance)*

517
518 Several participants in both country settings mentioned DNASeq technology might improve health
519 outcomes for particular populations with known higher rates or risks of TB. Within the Canadian
520 context, several participants stated benefits of adoption could be most significant for Indigenous
521 populations. In Madagascar, participants highlighted the value of the technology if applied towards
522 reducing high TB rates amongst incarcerated individuals in the country, or to improve TB care for
523 Malagasy living in remote regions. Plans to expand use of sequencing, however, would need to be
524 intentionally designed to ensure benefit to these populations in greatest need. As one Canadian
525 participant recalled, sequencing had been used in recent outbreaks in the North. This had built
526 understanding of transmission patterns within high-risk Indigenous communities, but this had not,
527 to the participants' knowledge, led to a reduction in outbreaks.

528
529 While participants in both countries recognized the potential for DNASeq technology to reduce
530 health inequities, Malagasy participants also cautioned that inequities might be deepened in the
531 process of adoption. Specifically, concerns were raised with respect to building up capacity for
532 sequencing exclusively in the country's capital of Antananarivo, as this could reproduce existing
533 inequities between urban and non-urban Malagasy.

534
535 *"Sending the sample to Antananarivo discourages many people from taking the test."*
536 *(P3/Madagascar/Clinician)*

537
538 *"For me, can we... the concern, if you use it just in Tana, won't it make a bit of bias, because*
539 *it's already, in Tana everything is already available. You will still hammer there, it is just in*
540 *Tana. But, how can it be that it is necessary to make, at the beginning, in the big cities for*
541 *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 monotherapy, 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 *géno-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 organization 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 amongst diverse end users and intended beneficiaries. For example, in Madagascar, it was suggested engagement with multiple Ministries could pave the way for support, while in Canada, engaging early on 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,

For submission to BMJ Global Health
Review Version 2 – 2023.03.14– Main Document

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 recognized 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 program.

“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 program 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 submission to BMJ Global Health
Review Version 2 – 2023.03.14– Main Document

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

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

642
643 "After the results so we will implement, we will suggest WHO after I don't know to put in
644 among the diagnostics used in routine." (P9/Madagascar/Laboratory)

DISCUSSION

Principal findings

This study elucidates several considerations complicating diversely positioned stakeholders' enthusiasm for 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 TB programs 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 program are not in the hands of the Malagasy alone, but dependent on decisions made by external funders and policy makers.

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 numbers of laboratories having previously embedded TB NGS within their TB diagnostics 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 skepticism 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 genomic data would be integrated with clinical and surveillance programs. 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 personalized therapeutic regimens in clinical settings should be secured.

Despite providing important insights on 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 program. 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 centralized in the capital, further variability might exist across Canada where this expertise is decentralized 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 amongst a diverse panel of stakeholders including (i) experts from the entire continuum of clinical, laboratory and surveillance spectrum and (ii) interviewees from low TB incidence/high-income and high TB incidence/low-income countries. 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 synthesize 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 programs 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 programs 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 emphasized a need for broader programmatic and operational research to ensure decisions for and against wider implementation are evidence-based. Such research might include questions related to cost-effectiveness, impact on results turn-around 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 program is committed to reducing higher disease prevalence in particular populations, assessing the impact of TB WGS integration within specific sub-national 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 programs prior to future larger scale implementation.

CONCLUSION

For submission to BMJ Global Health
Review Version 2 – 2023.03.14– Main Document

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

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771
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774

775 **AUTHOR CONTRIBUTIONS**

776 All authors meet the ICMJE criteria for authorship. Conception and design (SGL, EN), data
777 acquisition (C-AB), data analysis and interpretation (SGL, EN, C-AB, M-SR, OM, MJS, NR),
778 initial draft of the manuscript (SGL, EN, C-AB). All authors had access to the primary data, have
779 reviewed the final version of the manuscript and accept the responsibility to submit for publication.
780

781 **DECLARATION OF INTERESTS**

782 Authors declare having no financial and/or personal relationships with other people or
783 organisations that could inappropriately influence (bias) the reported research work.
784

785 **ROLE OF THE FUNDING SOURCE**

786 The funders had no role in the study design, in the collection, analysis, and interpretation of data,
787 in the writing of the report and in the decision to submit the paper for publication.
788

789 **DATA SHARING**

790 Deidentified participants’ interviews data will be made available with publication upon request to
791 the corresponding author.
792

793 **AUTHOR REFLEXIVITY STATEMENT**

794 We report on research from and international partnership between a high-income country (Canada)
795 and a low-income country (Madagascar). The authorship includes a diversity of early- and mid-stage
796 researchers from both partner countries. Two co-authors from Madagascar participated in the research
797 but did not assume leadership in study design or manuscript preparation. The authorship order,
798 including co-first and last author reflects the contribution of every co-author as per ICMJE guidelines.
799

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ETHICS

Ethics approval for this study was obtained from the Centre de Recherche du Centre Hospitaliser de l’Université de Montréal (CRCHUM) (Ref. 2020-8310), and the Comité d’Éthique à la Recherche Biomédicale à Madagascar (CERBM) (Ref. 056/MSANP/SG). All participants provided written consent prior to the interview.

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820 [platform-for-timely-analysis-and-use-of-tb-data](https://www.who.int/news/item/22-03-2019-a-new-digital-platform-for-timely-analysis-and-use-of-tb-data)].
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SUPPLEMENTARY MATERIALS

Supplementary Materials 1 – Semi-structured interview guides

Interview Guide (Disease surveillance experts)

Introduction

Thank you for agreeing to take part in this interview. In our discussion today, I am going to ask you some questions about your experience with new Tuberculosis diagnostics.

Part 1: Participant identification

- 1.1 Tell me a little more about your work. What is your job title and what are your responsibilities in this role? Rephrase: What do you do?
- 1.2 How long have you been working in this role?
- 1.3 What is your previous or active role and affiliations regarding TB diagnostics and data management?
- 1.4 You are affiliated with [*institution*]. Do you work closely with any other organizations or institutions at the local, national, or international level?

Part 2: Background knowledge of TB diagnostics

- 1.1 How have TB diagnostic methods evolved since you have been working in the field of TB?
- 1.2 What would you say are the biggest challenges in TB diagnosis?

Follow up: Are all of these common challenges here in [*country*]?

Probe: (*To understand what are contributing factors to these challenges in the country in their view – an opportunity to break the ice by letting them share thoughts and theories about a topic they probably have thought about at length, and may give us some useful context info*)

- 1.3 In your recollection, when was TB DNA sequencing introduced in [*country*] and when do you think it became accessible to more clinics or patients?

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- 1.4
- How was the diffusion of access to TB DNA sequencing at various levels of the health system?
- 1.5
- What are the applications of TB DNA sequencing in [*country*]?

Part 3: Perception of DNA sequencing to predict drug susceptibility testing (DST)

- 1.1
- In your experience, when is DNA sequencing used to predict DST? And how accurate has it been in predicting DST?
- 1.2
- What are advantages and disadvantages of using DNA sequencing for TB DST in the [*country*] context?
- 1.3
- How do you feel about DNA sequencing for TB DST potentially being used more widely here, in [*country*]? Do you support such expanded use? Why or why not?

Part 4: Knowledge and understanding of molecular epidemiology and surveillance

- 1.1
- In your experience, is DNA sequencing useful for understanding TB epidemiology?
- 1.2
- What are some advantages and disadvantages of using DNA sequencing for epidemiologic investigations here in [*country*]?

Follow up: Have you experienced or witnessed those advantages / disadvantages? Could you tell me about it?

Part 5: Facilitators, limitations, challenges, and the way forward

- 1.1
- Has TB DNA sequencing and DST changed your work? In what way(s)?
- 1.2
- Has DNA sequencing made your job more difficult or easier in any way(s)? How so?
- 1.3
- What are the facilitators for TB DNA sequencing implementation in your working environment and country?

Rephrase: What policies, attitudes, or other conditions are facilitating the use of TB DNA sequencing here in [*institution and country*]?

1.4 Are there any technical barriers or limitations to TB DNA sequencing implementation in your working environment?

1.4.1 What might be possible solutions to those previously mentioned challenges?

1.4.2 Do you think these solutions will be implemented in the near future?

If yes: When and who is leading that change?

If no or perhaps/maybe: Tell me more, why do you say that?

1.5 Are there any technical barriers or limitations to TB DNA sequencing implementation in your country?

1.1.1 What might be possible solutions to those previously mentioned challenges?

1.1.2 Do you think these solutions will be implemented in the near future?

If yes: When and who is leading that change?

If no or perhaps/maybe: Tell me more, why do you say that?

1.2 How are sequencing data management and interpretation currently handled here in [country]?

1.2.1 Did you personally have a good or a bad experience with data management of TB DNA sequencing?

1.2.2 Can you describe any work you have done involving the interpretation of TB DNA sequencing?

1.2.3 Are there any challenges or concerns associated with sequencing data management and interpretation at the moment, or has there been any challenges with this in the past?

1.2.4 What might be possible solutions to those previously mentioned challenges?

1.2.5 Do you think these solutions will be implemented in the near future?

If yes: When and who is leading that change?

If no or perhaps/maybe: Tell me more, why not?

1.3 In your experience, with whom are TB diagnostic data shared?

1.3.1 Do you see or foresee any issues regarding data privacy?

1.4 How is TB DNA sequencing funded here in [country]?

1.4.1 Do you think more funding should be put into TB DNA sequencing in [country]?

Why or why not?

If yes: Who should invest more in TB DNA sequencing in [country]?

1.4.2 Do you think richer countries or international organizations should support less rich countries in TB DNA sequencing implementation? Why or why not?

1.4.3 What is your perception of the cost-effectiveness and sustainability of TB DNA sequencing for [country]?

1.4.4 Which organizations and countries currently support TB DNA sequencing in [country] as far as you know?

1.5 Do you have any other concerns, challenges, doubts or questions related to TB DNA sequencing, management, or interpretation in the country that you would like to share?

Probe: (to understand exactly why this is a concern/challenge for them)

Part 6: In country patient access and diagnostics involving DNA sequencing

1.1 Currently in [country] who do you think has access to TB DST?

1.1.1 Are there specific individuals or communities in [country] less able to access the best quality TB diagnostics at present?

Rephrase: Do some populations in [country] have access to TB DNA sequencing diagnostics that other people in the country cannot currently access?

1.1.2 Do some patients who could potentially benefit from DST in the country not have access?

1.1.3 What factors contribute to that (in)equality in access in [country]?

Follow up if access not equal at present: Do you see everyone having equal access in the next 5 years? Why or why not?

1.1.4 Do you have any thoughts on that?

Probe: (e.g. feelings, any comment that would help explain that current situation and/or recommendations?)

1.2 In your assessment, will only some individuals or communities in [country] benefit from the implementation of new TB DNA sequencing in [country]? Please explain.

1.3 Do you think that TB DNA sequencing has the potential to improve or exacerbate health disparities within the country? Why yes or why not?

Follow-up if could exacerbate: Is this something you worry about? Why or why not?

1.4 Do you have any concerns that TB DNA sequencing could exacerbate health disparities between countries? Why or why not?

1.5 In your experience, what social supports, if any, are provided to patients following TB diagnosis?

1.6 Does it ever happen that patients are offered DST in [country] when the corresponding treatment is not available?

Follow up if yes: Is that often the case or not very often the case as far as you know, in [country]?

1.6.1 Do you think it is ethical for patients to be offered drug susceptibility testing (with or without DNA sequencing) when the corresponding treatment is not available? Why or why not?

Part 7: Perceived impact and conclusion

1.1 Has TB DNA sequencing already had an impact on TB here in [country]? Why/how or why not?

1.2 Do you see TB DNA sequencing having a major or minor impact on TB surveillance in [country] in the future? Why?

1.3 What is the greatest potential impact of using TB DNA sequencing in [country]?

1.4 Do you consider TB DNA sequencing to be essential to TB elimination in [country]?

1.5 Do you consider TB DNA sequencing to be a necessary tool for TB elimination worldwide?

Conclusion

Thank you. I have learnt so much. Is there anything you would like to add? Is there anything we missed?

Interview Guide (Care providers)

Introduction

Thank you agreeing to take part in this interview. In our discussion today, I am going to ask you some questions about your experience with new Tuberculosis diagnostics.

Part 1: Participant identification

- 1.1 Tell me a little more about your work. What is your job title and what are your responsibilities in this role? Rephrase: What do you do?
- 1.2 How long have you been working in this role?
- 1.3 What is your previous or active role and affiliation regarding TB diagnostics and data management in your work institution?
- 1.4 You are affiliated with [institution]. Do you work closely with any other organizations or institutions at the local, national, or international level?

Part 2: Background knowledge on TB diagnostics

- 1.1 How have TB diagnostic methods evolved since you have been working in the field of TB?
- 1.2 What would you say are the biggest challenges in TB diagnosis?

Follow up: Are all of these common challenges here in [country]?

Probe: (To understand what are contributing factors to these challenges in the country in their view – an opportunity to break the ice by letting them share thoughts and theories about a topic they probably have thought about at length, and may give us some useful context info)

- 1.3 In your recollection, when was TB DNA sequencing introduced in [country] and when do you think it became accessible to more clinicians and patients?
- 1.4 How was the diffusion of access to TB DNA sequencing at the various levels of the health system?
- 1.5 What are the applications of DNA sequencing in TB in your clinical practice?

Part 3: Perception on effectiveness of DNA sequencing to predict Drug susceptibility testing (DST)

- 1.1 In your experience, what is the role of DNA sequencing in predicting DST? How accurate or effective is DNA sequencing in predicting DST?
- 1.2 What are advantages and disadvantages of using DNA sequencing for TB DST in the [country] context?
- 1.3 How do you feel about DNA sequencing for TB DST potentially being used more widely here, in [country]? Do you support such expanded use? Why or why not?

Part 4: Knowledge and understanding of molecular epidemiology and surveillance

- 1.1 In your experience, is DNA sequencing useful for understanding TB epidemiology?
- 1.2 What are some advantages and disadvantages of using DNA sequencing for epidemiologic investigations here in [country]?

Follow up: Have you experienced or witnessed those advantages / disadvantages? Could you tell me a little about how that played out?

Part 5: Facilitators, limitations, challenges, and the way forward

- 1.1 Has TB DNA sequencing and DST changed your work? In what way(s)?
- 1.2 Has prescription or interpretation of TB DNA sequencing assays made your job more difficult or easier in any way(s)? How so?
- 1.3 What are the facilitators for TB DNA sequencing implementation in your working environment?

Rephrase: What policies, attitudes, or other conditions are facilitating the use of TB DNA sequencing in your working environment?
- 1.4 Are there any technical barriers or limitations to TB DNA sequencing implementation in your working environment?
 - 1.4.1 What might be possible solutions to those previously mentioned challenges?

1.4.2 Do you think these solutions will be implemented in the near future?

If yes: When and who is leading that change?

If no or perhaps/maybe: Tell me more: why do you say that?

1.5 How are sequencing data management and interpretation currently handled here in your work environment and in [country]?

1.5.1 Did you personally have a good or a bad experience with interpretation of TB DNA sequencing results?

1.5.2 Are there any challenges or concerns associated with sequencing data management and interpretation at the moment, or have there been any challenges with this in the past?

1.5.3 What might be possible solutions to those previously mentioned challenges?

1.5.4 Do you think these solutions will be implemented in the near future?

If yes: When and who is leading that change?

If no: Tell me more: why not?

1.6 In your experience, with whom are TB diagnostic data shared?

1.6.1 Do you see or foresee any issues regarding data privacy?

1.7 How is TB diagnostics funded here in [country]?

1.7.1 Do you think more funding should be put into TB DNA sequencing in [country]? Why or why not?

1.7.2 Which organizations currently support TB DNA sequencing in [country] as far as you know?

1.8 Do you have any other concerns, challenges, doubts or questions related to TB DNA sequencing, management, or interpretation in your workplace that you would like to share?

Probe: (to understand exactly why this is a concern/challenge for them)

Part 6: In country patient access and diagnostics involving DNA sequencing

1.1 Which patient populations in [country] currently have access to DST as part of their TB treatment?

- 1.1.1 Are there specific individuals or communities in [country] less able to access the best quality TB diagnostics at present?

Rephrase: Do some populations in [country] have access to TB DNA sequencing diagnostics that other people in the country cannot currently access?

- 1.1.2 Do some patients who could potentially benefit from DST in the country not have access?

- 1.1.3 What factors contribute to that (in)equality in access in [country]?

Follow up if access not equal at present: Do you see everyone having equal access in the next 5 years? Why or why not?

- 1.1.4 Do you have any thoughts on that?

Probe: (e.g. feelings, any comment that would help explain that current situation and/or recommendations?)

- 1.2 In your assessment, will only some individuals or communities in [country] benefit from the implementation of TB DNA sequencing in [country]? Please explain.

- 1.3 Do you think that TB DNA sequencing has the potential to improve or exacerbate health disparities within the country? Why yes or why not?

Follow-up if could exacerbate: Is this something you worry about? Why or why not?

- 1.4 Do you have any concerns that TB DNA sequencing could exacerbate health disparities between countries? Why or why not?

- 1.5 In your experience, what social supports, if any, are provided to patients following TB diagnosis?

- 1.6 Does it ever happen that patients are offered DST in (country) when the corresponding treatment is not available?

Follow up if yes: Is that often the case or not very often the case as far as you know, in [country]?

- 1.6.1 Do you think it is ethical for patients to be offered drug susceptibility testing (with or without DNA sequencing) when the corresponding treatment is not available? Why or why not?

Part 7: Perceived impact and conclusion

- 1.1 Has TB DNA sequencing already had an impact on TB here in [country]? Why/how or why not?

- 1.2 Do you see TB DNA sequencing having a major or minor impact on TB clinical management in [country]? Why?

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- 1.3 What is the greatest potential impact of using TB DNA sequencing in [country]?
- 1.4 Do you consider TB DNA sequencing to be essential to TB elimination in [country]?
- 1.5 Do you consider TB DNA sequencing to be a necessary tool for TB elimination worldwide?

Conclusion

Thank you. I have learnt so much. Is there anything you would like to add? Is there anything we missed?

For peer review only

Interview Guide (Laboratory personnel)

Introduction

Thank you agreeing to take part in this interview. In our discussion today, I am going to ask you some questions about your experience with new Tuberculosis diagnostics.

Part 1: Participant identification and experience

- 1.1 Tell me a little more about your work. What is your job title and what are your responsibilities in this role? Rephrase: What do you do?
- 1.2 How long have you been working in this role?
- 1.3 What is your previous or active role and affiliations regarding TB diagnostics and data management?
- 1.4 You are affiliated with [*institution*]. Do you work closely with any other organizations or institutions at the local, national, or international level?

Part 2: Background knowledge and perceptions on TB diagnostics

- 1.1 How have TB diagnostic methods evolved since you have been working in the field of TB?
- 1.2 What would you say are the biggest challenges in TB diagnosis?

Follow up: Are all of these common challenges here in [*country*]?

Probe: (*To understand what are contributing factors to these challenges in the country in their view – an opportunity to break the ice by letting them share thoughts and theories about a topic they probably have thought about at length, and may give us some useful context info*)

- 1.3 In your recollection, when was TB DNA sequencing introduced in [*country*] and when do you think it became accessible to more clinics or patients?
- 1.4 How was the expansion of the TB DNA sequencing sector in your work environment?

Part 3: Perception on effectiveness of DNA sequencing to predict Drug susceptibility testing (DST)

- 1.1 In your experience, when is DNA sequencing used to predict DST? And how accurate has it been in predicting DST?
- 1.2 What are advantages and disadvantages of using DNA sequencing for TB DST in the [country] context?
- 1.3 How do you feel about DNA sequencing for TB DST potentially being used more widely here, in [country]? Do you support such expanded use? Why or why not?

Part 4: Knowledge and understanding of molecular epidemiology and surveillance

- 1.1 In your experience, is DNA sequencing useful for understanding TB epidemiology?
- 1.2 What are some advantages and disadvantages of using DNA sequencing for epidemiologic investigations here in [country]?
Follow up: Have you experienced or witnessed those advantages / disadvantages? Could you tell me a little about how that played out?

Part 5: Facilitators, limitations, challenges, and the way forward

- 1.1 Has TB DNA sequencing and DST changed your work? In what way(s)?
- 1.2 Has DNA sequencing made your job more difficult or easier in any way(s)? How so?
- 1.3 What are the facilitators for TB DNA sequencing implementation in your working environment?
Rephrase: What policies, attitudes, or other conditions are facilitating the use of TB DNA sequencing here in [institution]?
- 1.4 Are there any technical barriers or limitations to TB DNA sequencing implementation in your working environment?
 - 1.4.1 What might be possible solutions to those previously mentioned challenges?
 - 1.4.2 Do you think these solutions will be implemented in the near future?If yes: When and who is leading that change?

If no or perhaps/maybe: Tell me more, why do you say that?

1.5 How are sequencing data management and interpretation currently handled?

1.5.1 Did you personally have a good or a bad experience with TB DNA sequencing?

1.5.2 Are there any challenges or concerns associated with sequencing data management and interpretation at the moment, or have there been any challenges with this in the past?

1.5.3 What might be possible solutions to those previously mentioned challenges?

1.5.4 Do you think these solutions will be implemented in the near future?

If yes: When and who is leading that change?

If no or perhaps/maybe: Tell me more, why not?

1.6 In your experience, with whom are TB diagnostic data shared?

1.6.1 Do you see or foresee any issues regarding data privacy?

1.7 How is TB DNA sequencing funded here in [country]?

1.7.1 Do you think more funding should be put into TB DNA sequencing in [country]?
Why or why not?

If yes: Who should invest more in TB DNA sequencing in [country]?

1.7.2 Which organizations and countries currently support TB DNA sequencing in [country] as far as you know?

1.9 Do you have any other concerns, challenges, doubts or questions related to TB DNA sequencing, management, or interpretation in your workplace that you would like to share?

Probe: (to understand exactly why this is a concern/challenge for them)

Part 6: In country patient access and diagnostics involving DNA sequencing

1.1 Currently in [country] who do you think has access to TB DST?

1.1.1 Are there specific individuals or communities in [country] less able to access the best quality TB diagnostics at present?

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Rephrase: Do some populations in [country] have access to TB DNA sequencing diagnostics that other people in the country cannot currently access?

1.1.2 Do some patients who could potentially benefit from DST in the country not have access?

1.1.3 What factors contribute to that (in)equality in access in [country]?

Follow up if access not equal at present: Do you see everyone having equal access in the next 5 years? Why or why not?

1.1.4 Do you have any thoughts on that?

Probe: (e.g. feelings, any comment that would help explain that current situation and/or recommendations?)

1.2 In your assessment, will only some individuals or communities in [country] benefit from the implementation of new TB DNA sequencing in [country]? Please explain.

1.3 Do you think that TB DNA sequencing has the potential to improve or exacerbate health disparities within the country? Why yes or why not?

Follow-up if could exacerbate: Is this something you worry about? Why or why not?

1.4 Do you have any concerns that TB DNA sequencing could exacerbate health disparities between countries? Why or why not?

Part 7: Perceived impact and conclusion

1.1 Has TB DNA sequencing already had an impact on TB here in [country]? Why/how or why not?

1.2 Do you see TB DNA sequencing having a major or minor impact on TB clinical management in [country]? Why?

1.3 What is the greatest potential impact of using TB DNA sequencing in [country]?

1.4 Do you consider TB DNA sequencing to be essential to TB elimination in [country]?

1.5 Do you consider TB DNA sequencing to be a necessary tool for TB elimination worldwide?

Conclusion

Thank you. I have learnt so much. Is there anything you would like to add? Is there anything we missed?

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Standards for Reporting Qualitative Research (SRQR)*

<http://www.equator-network.org/reporting-guidelines/srqr/>

Page/line no(s).

Title and abstract

Title - Concise description of the nature and topic of the study Identifying the study as qualitative or indicating the approach (e.g., ethnography, grounded theory) or data collection methods (e.g., interview, focus group) is recommended	1
Abstract - Summary of key elements of the study using the abstract format of the intended publication; typically includes background, purpose, methods, results, and conclusions	2

Introduction

Problem formulation - Description and significance of the problem/phenomenon studied; review of relevant theory and empirical work; problem statement	6-7
Purpose or research question - Purpose of the study and specific objectives or questions	6

Methods

Qualitative approach and research paradigm - Qualitative approach (e.g., ethnography, grounded theory, case study, phenomenology, narrative research) and guiding theory if appropriate; identifying the research paradigm (e.g., postpositivist, constructivist/ interpretivist) is also recommended; rationale**	8-9
Researcher characteristics and reflexivity - Researchers' characteristics that may influence the research, including personal attributes, qualifications/experience, relationship with participants, assumptions, and/or presuppositions; potential or actual interaction between researchers' characteristics and the research questions, approach, methods, results, and/or transferability	10 & 30
Context - Setting/site and salient contextual factors; rationale**	8-9
Sampling strategy - How and why research participants, documents, or events were selected; criteria for deciding when no further sampling was necessary (e.g., sampling saturation); rationale**	10
Ethical issues pertaining to human subjects - Documentation of approval by an appropriate ethics review board and participant consent, or explanation for lack thereof; other confidentiality and data security issues	10
Data collection methods - Types of data collected; details of data collection procedures including (as appropriate) start and stop dates of data collection and analysis, iterative process, triangulation of sources/methods, and modification of procedures in response to evolving study findings; rationale**	10-11

Data collection instruments and technologies - Description of instruments (e.g., interview guides, questionnaires) and devices (e.g., audio recorders) used for data collection; if/how the instrument(s) changed over the course of the study	10-11 + supplementary materials
Units of study - Number and relevant characteristics of participants, documents, or events included in the study; level of participation (could be reported in results)	13
Data processing - Methods for processing data prior to and during analysis, including transcription, data entry, data management and security, verification of data integrity, data coding, and anonymization/de-identification of excerpts	11
Data analysis - Process by which inferences, themes, etc., were identified and developed, including the researchers involved in data analysis; usually references a specific paradigm or approach; rationale**	11
Techniques to enhance trustworthiness - Techniques to enhance trustworthiness and credibility of data analysis (e.g., member checking, audit trail, triangulation); rationale**	11-12

Results/findings

Synthesis and interpretation - Main findings (e.g., interpretations, inferences, and themes); might include development of a theory or model, or integration with prior research or theory	13-26
Links to empirical data - Evidence (e.g., quotes, field notes, text excerpts, photographs) to substantiate analytic findings	13-26

Discussion

Integration with prior work, implications, transferability, and contribution(s) to the field - Short summary of main findings; explanation of how findings and conclusions connect to, support, elaborate on, or challenge conclusions of earlier scholarship; discussion of scope of application/generalizability; identification of unique contribution(s) to scholarship in a discipline or field	27-30
Limitations - Trustworthiness and limitations of findings	5

Other

Conflicts of interest - Potential sources of influence or perceived influence on study conduct and conclusions; how these were managed	31
Funding - Sources of funding and other support; role of funders in data collection, interpretation, and reporting	31-32

*The authors created the SRQR by searching the literature to identify guidelines, reporting standards, and critical appraisal criteria for qualitative research; reviewing the reference lists of retrieved sources; and contacting experts to gain feedback. The SRQR aims to improve the transparency of all aspects of qualitative research by providing clear standards for reporting qualitative research.

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****The rationale should briefly discuss the justification for choosing that theory, approach, method, or technique rather than other options available, the assumptions and limitations implicit in those choices, and how those choices influence study conclusions and transferability. As appropriate, the rationale for several items might be discussed together.**

Reference:
O'Brien BC, Harris IB, Beckman TJ, Reed DA, Cook DA. **Standards for reporting qualitative research: a synthesis of recommendations.** *Academic Medicine*, Vol. 89, No. 9 / Sept 2014
DOI: 10.1097/ACM.0000000000000388

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