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Whole-genome sequencing for TB source investigations: principles of ethical precision public health

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SUMMARY

BACKGROUND: Whole-genome sequencing (WGS) of *Mycobacterium tuberculosis* allows rapid, accurate inferences about the sources, location and timing of transmission. However, in an era of heightened concern for personal privacy and science distrust, such inferences could result in unintended harm and undermine the public's trust.

METHODS: We held interdisciplinary stakeholder discussions and performed ethical analyses of real-world illustrative cases to identify principles that optimise benefit and mitigate harm of *M. tuberculosis* WGS-driven TB source investigations.

RESULTS: The speed and precision with which real-time WGS can be used to associate *M. tuberculosis* strains with sensitive information has raised important concerns. While detailed understanding of transmission events could mitigate harm to vulnerable patients and communities when otherwise unfairly blamed for TB outbreaks, the precision of WGS can also identify transmission events resulting in social blame, fear, discrimination, individual or location stigma, and the use of defaming language by the public, politicians and scientists. Public health programmes should balance the need to safeguard privacy with public health goals, transparency and individual rights, including the right to know who infects whom or where.

CONCLUSIONS: Ethical challenges raised by real-time WGS-driven TB source investigation requires public health authorities to move beyond their current legal mandate and embrace transparency, privacy and community engagement.

KEY WORDS: epidemiology; tuberculosis; source investigation; whole-genome sequencing; ethics

Improvements in genomic sequencing of pathogens have enabled precision medicine in infectious diseases. Whole-genome sequencing (WGS) of *Mycobacterium tuberculosis* enables individualised treatment of drug-resistant TB by identifying the genomic resistance profile.[1] As WGS *M. tuberculosis* typing can be used to reveal the spread of drug-resistant *M. tuberculosis*[2] and explain TB outbreaks,[3–5] WGS paves the way for precision public health, where WGS data are used to develop the right intervention for the right population at the right time.[6,7]

Despite these benefits, WGS is currently mainly used to retrospectively study drug resistance or untangle the origins and size of outbreaks,[8–10] and examples of the prospective use of WGS of *M. tuberculosis* for surveillance or clinical care are still rare.[11] This is mainly due to laboratory delays associated with culture-based WGS, which limits its utility for precision medicine and precision public health. In future, direct WGS of sputum samples could increase the impact of WGS on TB control by enabling clinical and public health action in real time.

From a precision public health perspective, the high accuracy and actionable nature of real-time WGS data raise ethical challenges.[12] TB remains a stigmatising disease, as it affects marginalised groups such as homeless individuals, immigrants and people living with HIV.[13–15] The association of meta-data with a specific *M. tuberculosis* strain may reveal information on the location where infection occurred or on 'who infected whom', which could be harmful if specific people with TB or their communities are blamed for the spread of *M. tuberculosis*.[12] This raises several important ethical questions, including the need for

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accountability and transparency in communicating WGS data, the right or obligation to collect, report and act on WGS data by public health officials, the right to receive results by people with TB and their communities, and the need to build trust between the public and public health agencies.[12,16]

METHODS

We held consultations with a range of stakeholders as part of the development of a TB source investigation programme in Belgium that aims to use WGS data in real time by performing WGS directly on sputum samples (further referred to as real-time WGS). We included experts in *M. tuberculosis* molecular epidemiology research, members of the TB national reference laboratory, an expert in forensic infectious diseases, experts in public health practice of TB contact investigations in Belgium, and an expert in ethical issues in human genetics and biotechnology. In addition, we sought the input of two Belgian ex-TB patients. Consultations took the form of small group meetings and individual interviews during which stakeholders' experiences, insights and opinions on ethical and policy issues regarding the use of real-time *M. tuberculosis* WGS were explored. The aim of the discussion was 1) to identify challenges that could either be amplified or alleviated by real-time WGS-driven TB source investigation; 2) to explore ethical issues that should be considered when implementing such programmes; and 3) to assess how technical challenges of real-time WGS may modulate the moral weight of the ethical considerations raised.

Following the series of consultations, analyses of real-world illustrative cases were performed to further discern the ethical challenges real-time *M. tuberculosis* WGS may pose to TB source investigation programmes. Finally, drawing from the discussions and case analyses, guiding principles for ethically sound public health surveillance in the era of real-time *M. tuberculosis* phyloepidemiology were developed.

Ethical approval was not required for this study as the study did not involve human subjects.

RESULTS

Ethical analysis of illustrative cases

Each of the cases was purposefully chosen to represent different contexts, deal with populations and social settings relevant to TB in low-burden countries, and highlight both unique and overlapping ethical considerations. Because real-time WGS directly on sputum instead of culture is still in its infancy, real-word illustrative cases are rare. We therefore reflected on the potential ethical issues of real-time WGS starting from published cases of investigations using culture-based WGS or other molecular methods.

TB in marginalised populations

In Spain, the diagnosis of two drug-resistant TB cases in commercial sex workers who had recently migrated from Russia raised public health alarm, as they were believed to be the index cases of a drug-resistant TB outbreak.[17] MIRU-VNTR (mycobacterial interspersed repetitive unit-variable number of tandem repeat) on respiratory specimens showed two different strains commonly found in Russia, and prospective strain-specific analysis did not find any onwards transmission from the two sex workers.

In a Canadian community, an outbreak of 41 cases with identical MIRU-VNTR genotype occurred over a 2-year period.[18] While contact tracing failed to identify a common source, social network analyses identified two hotels, a meal centre, two community centres and a series of "crack houses" as likely locations of transmission. Epidemiological investigation revealed that most cases had a history of crack cocaine use. Retrospective WGS identified two co-circulating strains and one super-spreader.

These two examples highlight the potential ethical risk of inducing stigma through real-time identification of transmission events, along with the potential significant benefit of informing more tailored interventions and tracing. In the Spanish example, real-time WGS could have cleared the Russian sex workers from the social blame for causing a drug-resistant TB outbreak in Spain. In the Canadian example, real-time WGS could have informed interventions to contain the outbreak, but the association in real-time of the outbreak with illegal drug use could have placed unfair suspicion of cocaine use in people with TB and may have jeopardised the disclosure of contacts to public health authorities. These examples also highlight the fact that the need for caution in communicating real-time WGS results to avoid the association of TB with certain behaviours such as drug use could result in a moralistic interpretation, where the public perceives the outbreak as driven by blameworthy choices of individuals rather than intersecting risks and complex social inequalities.[19]

The real-time identification of a super-spreader may allow interruption of transmission and alert public health workers of possible failures in the health system. At the same time, the identification of a super-spreader can result in disclosure of the person's identity and reinforce the stigmatising rhetoric of culpability. It is important to note that assigning moral responsibility for spreading *M. tuberculosis* is complex, as transmission can occur before the person is aware of his/her diagnosis and methods to prevent *M. tuberculosis* transmission are not 100% effecacious.[12]

TB in asylum seekers and migrants

The diagnosis of four drug-resistant TB cases by the National Reference Laboratories of Switzerland and Germany triggered an investigation that led to the identification of 29 cases in seven European countries.[2] All were asylum seekers from Somalia and Eritrea, smuggled into Europe by human traffickers. Retrospective WGS analyses suggested that all individuals were infected at the overcrowded Bani Walid (Libya) internment facility.

Use of real-time WGS could have facilitated earlier diagnosis of TB in asylum seekers who arrived in Europe after detention in Bani Walid, and would ideally have resulted in targeted interventions such as screening, isolation and treatment at the Bani Walid facility in order to mitigate the spread in migrant populations. On the other hand, the ability to accurately associate the outbreak to an internment camp in real time could have created location stigma around the Bani Walid facility, which could have carried over to asylum seekers from other camps, whether or not they had TB.

In is important to note that clusters of foreign-born cases can either result from transmission en-route to the country of destination, from importation with transmission after arrival accelerated by the circumstances in which many migrants live, or from independent importation events of genetically related strains that are prevalent in the country of origin.[20] The differentiation between these three scenarios is important as the association of TB with immigration can compound the social challenges already experienced by asylum seekers and recent immigrants. Real-time WGS can prevent false accusation of *M. tuberculosis* importation. On the other hand, accurate associations in real-time could exacerbate anti-immigrant sentiments and lead to the public or politicians blaming asylum seekers. For example, when a girl was diagnosed with TB in a Belgian school in 2019, Filip De Winter, a leading member of a right-wing Flemish political party, tweeted that "Foreigners 8x more #TB infections than in Belgians. Asylum seekers/illegals biggest group with heightened #TB-risk. #TB=import disease!".[21]

TB in congregate settings

In Serbia, a retrospective analysis of WGS and epidemiological data demonstrated a two-decade long outbreak of drug-resistant TB at a centre for psychiatric patients with concomitant respiratory illnesses.[22] Drug stock-outs, non-completion of treatment due to schizophrenia, long-term hospitalisation under adverse living conditions, and absence of infection control were the likely drivers of the nosocomial outbreak. Later, *M. tuberculosis* transmission throughout the country to non-psychiatric patients were also documented.

Real-time identification of this outbreak could have allowed timely implementation of active case finding and infection control and could have de-associated the specific *M. tuberculosis* strain from psychiatric patients when transmission also continued in the community. On the other hand, demonstrating permeability between the psychiatric hospital and communities in real-time could result in blaming people with psychiatric disorders for transmission of drug-resistant TB, exacerbating the intersectional vulnerability of psychiatric patients and generate location stigma at the psychiatric hospital.

Extension of a drug-resistant outbreak from a congregate setting to surrounding communities was also documented in overcrowded Peruvian prisons.[23] In this case, researchers rather than politicians used potentially prejudicial and defaming language by using the word "spillover" in the title of the publication and painting the prison as a "reservoir" of drug-resistant TB.[24–27] In the context of nosocomial transmission, real-time WGS could result in legal action where WGS phylogenetic information is used to prove transmission.[12] While recent developments in molecular phylogeny methods make it possible to estimate how likely a particular isolate is part of a given transmission chain or outbreak, it is important to note that WGS data can never be used on its own and should always be complemented with clinical and epidemiological information to make accurate inferences.

TB in schools

In 2016, two 3-year old Spanish girls were diagnosed with TB at a nursery school, alarming parents and prompting extensive contact tracing efforts. Four months later, a 17-year old Spanish boy attending the same school was diagnosed with TB, inciting public panic of a widespread school outbreak. WGS showed that the toddlers' *M. tuberculosis* strains were identical but differed from the adolescent's strain. The toddlers' strain was genetically linked to TB cases in Romanian immigrants, one of whom had previously worked at the school.[28]

In the Spanish school outbreak, real-time WGS could have allowed public health officials to intercept increasing parental concern and limit the need for school-wide screening for *M. tuberculosis* infection, but would also raise important questions about how to safeguard confidentiality and the privacy of the affected children and the Romanian index case. In low-burden countries, school outbreaks are exceptional and scare students, parents and the community. For example, when a 16-year old Vietnamese girl was the index case of an outbreak of drug-resistant TB that led to 12 cases and 222 *M. tuberculosis* infections in a Californian high school, the community's fear resulted in discrimination ("my best friend's dad won't even stand next to me") and location stigma ("we're the TB school").[29]

Table Seven key recommendations for ethical practice of real-time WGS of *Mycobacterium tuberculosis* for public health surveillance and TB source investigation

Public health mandate for actionable real-time *M. tuberculosis* WGS	Given the promise of high efficacy through improved speed and precision of TB source investigation, real-time WGS can be implemented within the current legally mandated TB surveillance programmes WGS can guide and complement—but does not replace—traditional epidemiological TB source investigation
Individual consent for *M. tuberculosis* WGS	Because TB outbreaks constitute a public health threat, routine *M. tuberculosis* WGS of all *M. tuberculosis* isolates can be integrated in current public health TB control programmes. Each country should, taking into account relevant laws and regulations, decide whether or not routine WGS of clinical isolates for surveillance purposes requires individual patient consent
Confidentiality and privacy	To prevent social discrimination on the basis of potentially stigmatising patient diagnoses, all identifiable data should be protected from access outside the public health system (i.e., by employers, the media, immigration officials, etc.) by strong data security, and sharing of identifiable data should be compliant with privacy laws
Two-step data sharing between public health institutions	Within the public health system, anonymous *M. tuberculosis* sequences should be shared routinely between laboratories, countries and regions to help identify *M. tuberculosis* transmission. Only following the identification of a *M. tuberculosis* cluster should socially sensitive meta-data be shared across public health programmes; only those meta-data critical for source identification and public health interventions targeting a particular outbreak should be shared
Building patient trust through partnerships between patients, families, communities and public health institutes	To protect patient privacy and mitigate the intrusion in the rights and liberties of patients and (vulnerable) population groups, disclosure of transmission events to patients and their families and communities should use the least invasive approach possible. Patients should be counselled on how to minimise the psychosocial risks using constructive disclosure models adapted from genetic counseling. Where possible, people with TB should be empowered to help clarify *M. tuberculosis* transmission for the benefit of their own family, friends, social circles and communities through voluntary participation. Every country should, taking into account relevant laws and regulations, decide whether or not individual informed consent is needed for use of relevant meta-data and potentially personal identifying information when using WGS for TB control efforts
Professional transparency and use of non-defaming communication	To prevent inaccurate public attributions of responsibility and to avoid social blame, stigmatisation of locations, communities, or groups, especially those already marginalised or vulnerable to discrimination, public communications about transmission events should be as transparent as possible, explicit about the limitations of WGS, avoid moralising language, and emphasise the permeability of specific locations and communities
Promoting social justice and global solidarity	When possible, the high discriminatory power of WGS should be used to help promote social justice and global solidarity by improving TB control in high-burden countries, including those countries from where people with TB migrate to low-burden countries, in vulnerable groups by acknowledging risk factors and greater incidence of cases in these populations without assigning blame and by discrediting prejudices that portray these groups as disease vectors

WGS = whole-genome sequencing.

TB in families

A retrospective *M. tuberculosis* MIRU-VNTR and WGS analysis in Canada showed that the source of infection was predominantly a non-household community member for children born to Canadian parents or a household member for children born in Canada to foreign-born parents, whereas transmission occurred outside of Canada in most foreign-born children.[30] In one case, WGS and epidemiological data suggested that a visitor transmitted *M. tuberculosis* to both the child and their adult household member.

While real-time availability of this information could have resulted in closure for the parents by answering the lingering question, "Where did my child get TB?", it also raises the question of whether people with TB have the right to know where or from whom they most likely contracted *M. tuberculosis* and how socially sensitive data of transmission should be communicated in ways that safeguard privacy and confidentiality.

Recommendations for ethical practice

The ethics of precision (genomic) medicine and traditional public health ethics were used as the foundation for the development of ethical principles for real-time WGS-guided TB source investigation.[31] Precision medicine ethics focusses on respect for personal control, highlights the importance of professional transparency, aims to protect patients from avoidable harm, and considers the needs and interests of other people that share the patient's (in case of infectious diseases the pathogen's) genetic variants.[32,33] The focus of traditional public health ethics is on public health priority, the prevention of harm, the use of the least intrusive means in achieving the relevant public health priority, and social justice.[34]

Building on these principles, we formulate seven recommendations (Table). These are based on the recognition that, for a sound ethical practice of real-time WGS-driven TB source investigation, the current legislative endorsement of anonymous TB surveil-

lance and contact tracing[35] should be complemented with public engagement, reflect trust and embrace transparency.[16] The promotion and protection of the human rights of affected people should be a legal, ethical and moral imperative and of crucial importance for socially just TB elimination efforts.[36] Furthermore, these recommendations are cognizant of the political and public environment in low-burden societies, which are characterised by increasing attention to protection of privacy and a growing distrust in science.

DISCUSSION

Following consultations with multiple stakeholders and ethical analysis of real-world cases, we identified common themes of concern that result from the speed and precision with which it is possible to associate a specific *M. tuberculosis* strain with socially sensitive information using direct WGS of sputum samples. An important and recurrent theme was social blame and moral responsibility for transmission by vulnerable or marginalised people and communities, resulting in public fear, discrimination, individual or location stigma, moralistic interpretations, and prejudicial and defaming language used by the public, politicians and scientists. Another important theme was the balance between individual and public health rights, including the balance of the right to know who infects whom or where, with the need to safeguard confidentiality and privacy. Implementation of actionable real-time *M. tuberculosis* WGS will require public health programmes to avoid defaming language, move beyond the legal mandate of anonymous surveillance, and embrace transparency, privacy and patient engagement.

Although we involved an international group of experts and stakeholders, this project was limited by the fact that it was focused on the Belgian context, and represents views mainly relevant to other low-burden countries. We also acknowledge the importance of implementing *M. tuberculosis* WGS in regions that suffer high disease burdens; however, real-time WGS of respiratory isolates is unlikely to become a reality in high-burden countries in the near future. Furthermore, although other important challenges were revealed, such as the incidental discovery of other pathogens and the need to remove human DNA, we only focus on the ethical challenges related to WGS of *M. tuberculosis* in the context of real-time TB source investigation.

In conclusion, the future use of real-time *M. tuberculosis* WGS for precision public health surveillance holds considerable promise for TB control but also exemplifies new ethical challenges. The proposed recommendations for ethical practice are a starting point for public health teams who should view the recommendations in the light of their social context and previous TB source investigation experiences.

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RÉSUMÉ

MÉTHODE : Le séquençage complet du génome (WGS) de *Mycobacterium tuberculosis* permet des déductions rapides et précises sur les sources, la localisation et le moment de la transmission. Dans une période de souci croissant de la vie privée et de méfiance vis-à-vis de la science, ces déductions pourraient avoir un effet nocif involontaire et ébranler la confiance du public.

MÉTHODE : Nous avons tenu des discussions interdisciplinaires des parties prenantes et réalisé des analyses éthiques de cas illustratifs de la vie réelle pour identifier les principes qui optimisent les bénéfices et atténuent les effets nocifs d'une investigation des sources de TB grâce au *M. tuberculosis* WGS.

RÉSULTATS : D'importantes préoccupations résultent de la vitesse et de la précision avec lequel le WGS en temps réel associe les souches de *M. tuberculosis* avec des informations sensibles. Une compréhension détaillée des voies de transmission pourrait atténuer les effets nocifs vis-à-vis des patients vulnérables et des communautés quand ils sont blâmés à tort pour des flambées de TB. La précision de WGS peut cependant également identifier les voies de transmission aboutissant à un blâme social, une peur, une discrimination, une stigmatisation individuelle ou géographique et le recours à un langage diffamatoire par le public, les politiciens et les scientifiques. Les programmes de santé publique devraient trouver un équilibre entre le respect de la vie privée et les objectifs de santé publique, la transparence et les droits des individus, notamment celui de savoir qui infecte qui ou à quel endroit.

CONCLUSIONS : Les défis éthiques soulevés par l'investigation en temps réel des sources de TB grâce au WGS exigent que la santé publique aille au-delà de son mandat légal actuel et englobe la transparence, le respect de la vie privée et l'engagement communautaire.