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Molecular epidemiology of tuberculosis in northern Australia

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ABSTRACT

Australia has one of the lowest rates of tuberculosis (TB) globally; however, the rates of TB in the Northern Territory (NT) Top End and in Far North Queensland are consistently higher than the national average. Genomic sequencing of *Mycobacterium tuberculosis* (MTB) is increasingly being implemented for transmission surveillance and antimicrobial resistance prediction. Genomic epidemiological studies in northern Australia have demonstrated the utility of sequencing for tracking TB transmission. In the NT Top End, this has demonstrated that most TB transmission is occurring in remote regions, with recent transmission and reactivation from latency contributing to incident TB. In Far North Queensland, genomics has been used to track transmission of a multidrug-resistant MTB clone across the Torres Strait. The next steps include implementation of MTB genomic sequencing in jurisdictional laboratories with real-time cross-jurisdictional analysis to inform public health management of TB.

Keywords: epidemiology, genomics, Mycobacterium, northern Australia, public health, sequencing, surveillance, tuberculosis.

Introduction

Prior to the COVID-19 pandemic, tuberculosis (TB) was the leading infectious cause of death globally.[1] The causative pathogen, *Mycobacterium tuberculosis* (MTB) is transmitted from person to person via droplet aerosols.[2] Humans are the major reservoir, and it is estimated that around a quarter of the world's population are infected.[3] Following infection, MTB can persist in a quiescent state, termed latent TB infection (LTBI).[4] People with LTBI have no symptoms and are considered non-infectious to others. Up to 15% develop active TB disease, with pulmonary disease being the most common manifestation.[5,6] Key components of TB control include timely diagnosis and effective treatment of active TB disease, screening of contacts and high risk groups, and LTBI diagnosis and treatment.[7] The World Health Organization's End TB Strategy 2016–2035 set the goals of 95% reduction in TB deaths and 90% reduction in TB incidence compared with 2015 levels by 2035.[7] The COVID-19 pandemic has had a devastating impact on global TB control, with decreased case ascertainment resulting in a reduction in notified cases from 7.1 million in 2019 to 5.8 million in 2020, and an increase in reported TB deaths.[1]

The rates of TB in Australia are amongst the lowest globally, with annual incidence approximately 5–6 per 100 000 since the 1980s.[8] 86–89% of TB notifications in Australia are in people born overseas.[8] Annual incidence in Australian-born non-Indigenous people is <1 per 100 000 population; however, the rates in Aboriginal and Torres Strait Islander peoples (First Nations Australians) are consistently approximately five-fold higher than this.[8] Much higher rates of TB are seen in countries to Australia's north, including Papua New Guinea, Indonesia, and Timor-Leste.[1] Multidrug-resistant (MDR) TB – defined as resistance to isoniazid and rifampicin – is an increasing challenge in the region.[9,10]

Tuberculosis epidemiology in northern Australia

The Northern Territory (NT) has had the highest overall and childhood TB rates in Australia,[8,11] but has low rates of MDR-TB.[12] Approximately one-third of the population are First Nations Australians, many of whom live in remote regions, and approximately 20% were born overseas.[13] The NT TB rate in First Nations Australians has dropped markedly over the past 30 years, from 114 per 100 000 in 1989 to 5–12 per 100 000 in 2015–2018.[8,14] The number of overseas-born cases has fluctuated: in 1999 there was an increase in cases when >1800 people were evacuated to the NT from Timor-Leste due to conflict associated with the transition to independence,[15] and increases in NT TB notifications have also occurred in association with on-shore detention of fishers from Indonesia and of asylum seekers and crew.[16,17]

To the east, Far North Queensland is in close proximity to Papua New Guinea (PNG). The Torres Strait is the body of water between Cape York, the northernmost tip of Australia, and the Western Province of Papua New Guinea; it is approximately 150 km at its narrowest length and comprises at least 274 islands. The Torres Strait Protected Zone was created after the 1978 treaty between PNG and Australia, allowing cross-border movement without passports or visas for traditional customs and economic activities in the Torres Strait. Rates of TB in Far North Queensland are higher than the national average, at 8.4–12.1 per 100 000 population per year in 2017–2019.[18] Although rates have fallen particularly in the Torres Strait (previously 35.5 per 100 000 in 2014), the rates of TB in First Nations peoples in Queensland remain 8–15 times higher than in the non-Indigenous Australian-born population.[18] The TB incidence in the Western Province of PNG is approximately 2900 per 100 000 with high rates of MDR-TB,[10,19] and approximately 80% of overseas-born cases in Far North Queensland are from PNG.[20]

Genomic sequencing of *Mycobacterium tuberculosis*

Genomic sequencing of MTB is increasingly being implemented as a tool for prediction of antimicrobial resistance, transmission surveillance, and global phylogeographic investigation, and provides much greater resolution than previous typing methods.[21,22] Commonly used sequencing methods include short-read Illumina technology, which has high throughput and high accuracy, and results in reads up to 300 bp in length. Long read sequencing by Oxford Nanopore Technologies results in much longer reads with data produced in real time, but is less accurate than Illumina sequencing.[23] The MTB genome comprises a single chromosome approximately 4.4 Mb in size, with estimated mutation rate 0.3–0.5 single nucleotide polymorphisms (SNPs) per genome per year, and no clear evidence of horizontal gene acquisition.[24,25] Antimicrobial resistance arises from chromosomal point mutations. In 2021 the World Health Organization published its first catalogue of mutations in MTB associated with antimicrobial resistance.[26] To aid phylogeographic analysis, a lineage nomenclature system based on lineage-defining SNPs has been described,[27] with each lineage having distinct geographic distribution linked to human migration history.[28] Transmission surveillance can be done by combining epidemiological data with pairwise SNP distances and phylogenetic analysis.[22,29,30] Core genome multilocus sequence typing can also be used to find possible transmission clusters for further investigation.[31] As genomic sequencing technology moves from research to public health, there is a need for validation and standardisation of wet and dry laboratory methodologies, and for development of processes and platforms for data sharing and analysis.[22]

Genomic epidemiology of tuberculosis in northern Australia

A 2021 study set in the NT Top End combined TB notification data for 741 culture-confirmed cases with genomic sequencing of 497 MTB isolates from 1989 to 2020.[32] There were 359/741 (48%) cases born overseas, and 329/741 (44%) cases were First Nations Australians. There were 235/359 (66%) overseas-born cases from Southeast Asia, with the largest numbers from Indonesia (87 cases) and Timor-Leste (61 cases). Of the 497 sequenced isolates, 52% were lineage 4 (Euro-American lineage), 31% were lineage 1 (Indo-Oceanic lineage), and the remainder belonged to lineages 2 and 3. Of 93 case-contact isolate pairs, 85 were separated by ≤12 SNPs (median 2 SNPs) providing support for using this threshold for defining transmission clusters. There were 28 genomic clusters involving 250 cases; 86% of clustered cases were First Nations Australians and 76% were from a remote region. There was little evidence of transmission arising from overseas-born cases, and no drug-resistant cases clustered together. Genomics was able to link six recent cases not previously identified as part of contact tracing to genomic clusters, and the study findings suggested that both reactivation from latency and recent transmission are contributing to incident TB in the NT Top End. Just seven cases had a second episode of culture-confirmed TB during the study; however, it was difficult to differentiate relapse from reinfection using genomics due to inadequate diversity in circulating MTB.

In the Torres Strait, a genomic epidemiological study included 100 isolates from notified culture-confirmed TB cases among PNG citizens in the Torres Strait Protected Zone between 2010 and 2015, and four isolates from Australian citizens with epidemiologic links to the region.[33] Eighty-three out of 104 isolates belonged to Beijing sublineage 2.2.1.1, of which 49 were closely related to isolates from the PNG Western Province.[9] Thirty-three out of 104 isolates were MDR and an additional two were also resistant to fluoroquinolones and injectable agents (XDR); all 35 MDR and XDR isolates belonged to Beijing sublineage 2.2.1.1. The four isolates from Australian citizens were linked to two separate genomic clusters, suggesting two cross-border MDR-TB transmission events. All 35 MDR or XDR isolates carried the *fabG1-inhA* C15T mutation. Twenty-eight out of 35 had high level isoniazid resistance; 27 had *ndh* (ΔG304) and *inhA* (Ile21Val) mutations, and one had a *katG* mutation (Trp191Arg). All rifampicin-resistant isolates carried *rpoB* (Ser450Leu).

Conclusion

The northern Australian studies described here demonstrate the utility of genomic sequencing for tracking and tracing TB in northern Australia. The Top End study provided evidence that TB transmission is continuing to occur in remote hotspot regions, with evidence that both reactivation from latency and recent transmission are contributing to incident TB. These findings support focus on timely diagnosis of active TB disease and effective treatment of LTBI in those areas, and further work is being undertaken to understand the factors contributing to late TB diagnoses and optimum LTBI treatment regimens. The Torres Strait study tracked the spread of a resistant MTB clone from neighbouring PNG, demonstrating the importance of collaboration with regional neighbours in TB surveillance and control. The next steps in public health implementation of MTB genomics in northern Australia include prospective MTB sequencing in jurisdictional public health laboratories with real-time cross-jurisdictional analysis to inform public health management.

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Data availability. Data sharing is not applicable as no new data were generated or analysed during this study.

Conflicts of interest. The authors declare no conflicts of interest.

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