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Title	Intercontinental translocation of latent multidrug-resistant tuberculosis to Australia demonstrated by whole genome sequencing

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Intercontinental translocation of latent multidrug-resistant tuberculosis to Australia demonstrated by whole genome sequencing

TO THE EDITOR: In 2016, there were an estimated 490 000 cases globally of multidrug-resistant (MDR) tuberculosis exhibiting resistance to isoniazid and rifampicin.[1] The first case of MDR tuberculosis diagnosed in Tasmania occurred in 2016 in a Vietnamese-born person. Vietnam was the second highest reported country of birth for overseas-born patients with tuberculosis notified in Australia in 2014.[2] The patient had previously tested positive for tuberculosis infection in an interferon-γ release assay test performed in Tasmania in early 2016, but at the time, the patient was asymptomatic, had a normal chest x-ray and was sputum culture negative. After an episode of colitis, a colon tissue biopsy specimen isolated *Mycobacterium tuberculosis*. Whole genome sequence of the isolate (TASMDR1), identified high confidence mutations for isoniazid, rifampicin, ethambutol and pyrazinamide, in accordance with the culture-based drug susceptibility testing, and, in addition, it identified a mutation associated with streptomycin resistance.[3]

We became aware that a household contact of the Tasmania-located patient with MDR tuberculosis had been diagnosed with pulmonary tuberculosis in Vietnam in 2012 and requested the drug susceptibility testing data for this isolate (VTB1) from the treating hospital in Ho Chi Minh City. VTB1 was resistant to isoniazid, rifampicin, ethambutol, pyrazinamide and streptomycin in culture-based drug susceptibility testing. We therefore obtained a genomic DNA preparation of VTB1 to enable direct comparison with the TASMDR1 isolate collected in Tasmania. Next generation sequencing of VTB1 was performed on an Illumina platform and paired-end reads were mapped to the *M. tuberculosis* H37Rv reference genome (NC_000962.3). The Box shows variants associated with drug resistance.

In addition to drug resistance mutations, VTB1 shared all previously described variants in TASMDR1 with respect to H37Rv[3] and, therefore, the two isolates were genetically indistinguishable. This is strongly indicative of transmission involving the two patients based on established single nucleotide polymorphism thresholds.[4] It is most probable that the patient diagnosed in Tasmania contracted the MDR strain of *M. tuberculosis* during the episode of pulmonary disease diagnosed in the household contact in 2012 and that the infection remained latent until reactivating as extrapulmonary MDR tuberculosis in 2016.

In conclusion, the global burden of latent tuberculosis infection has been estimated to be 23% of the world's population, which corresponds to about 1.7 billion people.[5] Despite the immense prevalence of latent tuberculosis infection, there are few reports in the literature that confirm using genome variant analyses for the translocation of the MDR form of tuberculosis from one jurisdiction to another as a latent infection and its subsequent emergence as active MDR tuberculosis in a new host country. This type of transit of tuberculosis is difficult to detect with pre-immigration screening practices that are reliant upon a diagnosis of pulmonary tuberculosis based on a chest x-ray. The international movement of MDR tuberculosis in latent form, as has been determined in this case, is an area of concern and could be a significant challenge for future tuberculosis eradication. The growing application of genome sequencing in tuberculosis diagnostics and surveillance will help establish the level of MDR tuberculosis cases due to reactivation of latent tuberculosis infection.

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[Insert box]

Drug resistance determining mutations in a contact who presented with tuberculosis in Vietnam in 2012 (VTB1) and in the first confirmed patient with multidrug-resistant (MDR) tuberculosis in Tasmania in 2016 (TASMDR1). The isolate from VTB1 and TASMDR1 share identical drug resistance mutations

Isolates	Drug	Gene	Function	Mutation	Substitution
VTB1 and TASMDR1	Rifampicin	*rpoB (Rv0667)*	RNA polymerase β-subunit	gAc/gGc, tCg/tTg	D435G, S450L
	Isoniazid	*katG (Rv1908c)*	Catalase-peroxidase	aGc/aCc	S315T
	Pyrazinamide	*pncA (Rv2043c)*	Pyrazinamidase/nicotinamidase	cCg/cTg	P62L
	Ethambutol	*embB (Rv3795)*	Arabinosyltransferase B	Atg/Gtg	M306V
	Streptomycin	*rrs (MTB000019)*	16S ribosomal RNA	a/c	a514c*

* Substitution located in a non-protein coding gene.

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