

2017 AMMI Canada Medical Student Research Award Proposal

Molecular Epidemiology of *Mycobacterium tuberculosis* in Newfoundland and Labrador

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Background:

Although the incidence of Tuberculosis (TB) in Canada is among the lowest in the world, unacceptably high rates of TB persist among the Aboriginal population [1]. According to the 2014 report on TB from the Public Health Agency of Canada, Canadian-born aboriginals made up 4% of the total population but accounted for 21% of TB cases in Canada [1]. The incident rate of TB among Aboriginals is about five times higher than the overall Canadian average and particularly endemic to the Inuit population [1]. The Inuit span four regions in Canada that constitute Inuit Nunangat (Inuit Homeland): Inuvialuit (Northwest Territories), Nunavut, Nunavik (Northern Québec) and Nunatsiavut (Labrador) [2].

Nunatsiavut is an autonomous area governed by the Inuit in Newfoundland and Labrador, that includes territory in Labrador extending to the Quebec border. Nunatsiavut is one of the regions in Canada with an ongoing TB epidemic. Newfoundland and Labrador reported 30 cases of active TB in 2015, with a majority coming from the Nunatsiavut region [4]. TB control among First Nations is a priority of the Public Health Agency, based on the health and economic burden among these populations caused by TB [1].

Although the factors associated with a high TB incidence among Aboriginals are not fully understood, one of the objectives of TB control is targeting populations at greatest risk of active TB. Achieving better understanding of the epidemiology of TB in this location may contribute to more effective TB control.

A previous study by Marcel Behr from the McGill International TB Centre performed whole-genome sequencing (WGS) on 163 *Mycobacterium tuberculosis* isolates from Nunavik to track TB transmission over space and time [3]. The analysis revealed that TB was first introduced into that region in the early 20th century, and despite a genomic profile that lacks features of a hypervirulent strain, TB thrives and continues to cause outbreaks [3]. Within village transmission was identified. The result of their analysis suggest that the virulence of a TB strain may not be as important as the host or social factors conducive to transmission that contribute to the ongoing TB epidemic in Nunavik and possibly other high-incidence areas [3].

WGS is a powerful tool for investigation of epidemiology of TB, which offers additional greater resolution for strain typing compared to conventional methods [5]. WGS is being used to answer fundamental TB control questions in combination with clinical records, as demonstrated in a most recent publication on the transmission of drug resistant TB in South Africa [6]. The information that may be gained from our

study includes identifying when TB entered Labrador, where it came from, how Labrador TB is related to TB in other regions and provinces, and how TB moved through villages and households in Nunatsiavut. This

information may inform future interventions for TB control in this population.

Research Question: How does the clinical epidemiology map correlate to the genomic pattern analysis of the confirmed TB cases in Labrador?

Study Design:

Mycobacterium tuberculosis isolates from Newfoundland and Labrador are stored at the National Microbiology Laboratory (NML) in Winnipeg. An agreement has been made with the NML to forward these strains to the McGill International TB Centre where Dr. Marcel Behr's research team has the appropriate biosafety level laboratory for safe handling of the bacteria, and the expertise to perform the DNA extraction and whole genome sequencing. The testing and bioinformatics analysis will be funded by Dr. Marcel Behr, who offers these services in-kind, though a CIHR Foundation Grant.

Unique strains will be included, from both pulmonary and non-pulmonary active TB cases, including years 2004-2016 and collected from patients diagnosed in Newfoundland and Labrador, both Aboriginal and non-Aboriginal (Figure 1). If additional strains are available from prior to 2004, these will also be included. Strains isolated since 2014 have been typed using Mycobacterial Interspersed Repetitive Units (MIRU), and this analysis has revealed a high rate of clonal spread, suggestive of ongoing transmission as opposed to reactivation of previous latent infections.

DNA extraction will be performed followed by sequencing using MiSeq 250 (Illumina) [3]. Reads will be aligned with a control genome, and single nucleotide polymorphisms (SNP) identified. Phylogenetic trees will be created using Molecular Evolutionary Genetics Analysis, and divergence times estimated using Bayesian Markov chain Monte Carlo methods, as previously described [3,5].

Clinical, demographic, and geographic data will be collected from medical records and local health care workers. Contact between TB cases and risk factors for TB infection will be analyzed. This conventional epidemiology will be completed by Lucy Smith and used to strengthen the conclusions of the molecular epidemiology.

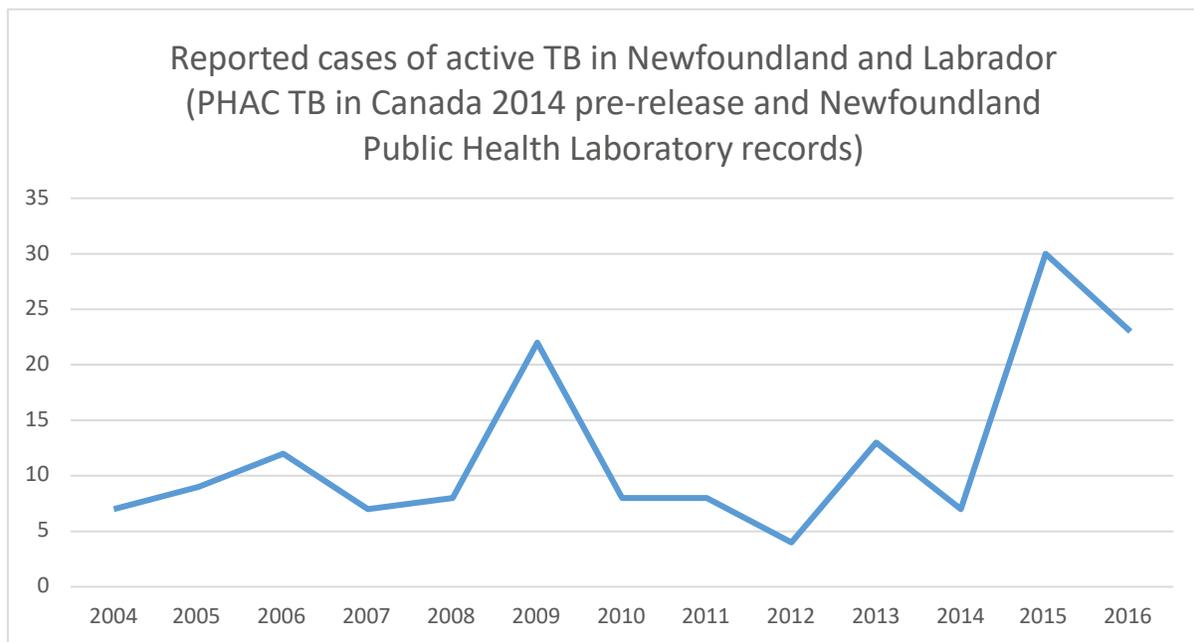
Ethics committee approval will be required. Patient consent will be waived as secondary use of data. Aboriginal research committee approval will be required. Open communication with the Nunatsiavut government will continue throughout the project.

Significance:

TB represents a significant social and economic burden among Aboriginal communities such as Nunatsiavut, Labrador [7]. Preventing cases of active TB may significantly improve public health among Aboriginal communities [7]. The epidemiological conclusions from this study may contribute to future TB control initiatives in Newfoundland and Labrador, and in other epidemic regions in Canada. This project aligns with the strategic planning goals and initiatives listed in the AMMI 2015 Annual Report, such as infection prevention and control, knowledge translation, promotion and support of research in infectious diseases and microbiology in Canada [8]. In addition to gaining scientific knowledge, this project may strengthen inter-provincial research collaborations.

Figure 1. Reported cases of active TB in Newfoundland and Labrador
 (PHAC TB in Canada 2014 pre-release and Newfoundland Public Health Laboratory records)

Year	Number of TB strains available
2004	7
2005	9
2006	12
2007	7
2008	8
2009	22
2010	8
2011	8
2012	4
2013	13
2014	7
2015	30
2016	23
Total	158



References

1. *Tuberculosis prevention and control in Canada - a federal framework for action*. Ottawa: Health Canada and the Public Health Agency of Canada, 2014.
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4. Newfoundland and Labrador Communicable Disease Surveillance. Monthly Disease Report: December 2015. Government of Newfoundland and Labrador, St. John's, 2015.
5. Lee, R. S. and M. A. Behr. "The Implications of Whole-Genome Sequencing in the Control of Tuberculosis". *Therapeutic Advances in Infectious Disease*, vol 3, no. 2, 2015, pp. 47-62. *SAGE Publications*, doi:10.1177/2049936115624630.
6. Shah, N. Sarita et al. "Transmission of Extensively Drug-Resistant Tuberculosis in South Africa". *New England Journal of Medicine* 376.3 (2017): 243-253.
7. Health Canada's Monitoring and Performance Framework for Tuberculosis Programs for First Nations On-Reserve. Health Canada, Ottawa, 2015.
8. Association of Medical Microbiology and Infectious Disease Canada, Annual Report. Vancouver, 2015, http://ammi.com.my/storage/upload/ammi/files/AMMI_Annual_Report_2015.pdf.