

Molecular Epidemiology of *Mycobacterium tuberculosis* To Describe the Transmission Dynamics Among Inuit Residing in Iqaluit Nunavut Using Whole-Genome Sequencing

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Background. In the last decade, tuberculosis (TB) incidence among Inuit in the Canadian Arctic has been rising. Our aim was to better understand the transmission dynamics of TB in this remote region of Canada using whole-genome sequencing.

Methods. Isolates from patients who had culture-positive pulmonary TB in Iqaluit, Nunavut, between 2009 and 2015 underwent whole-genome sequencing (WGS). The number of transmission events between cases within clusters was calculated using a threshold of a ≤ 3 single nucleotide polymorphism (SNP) difference between isolates and then combined with detailed epidemiological data using a reproducible novel algorithm. Social network analysis of epidemiological data was used to support the WGS data analysis.

Results. During the study period, 140 *Mycobacterium tuberculosis* isolates from 135 cases were sequenced. Four clusters were identified, all from Euro-American lineage. One cluster represented 62% of all cases that were sequenced over the entire study period. In this cluster, 2 large chains of transmission were associated with 3 superspreading events in a homeless shelter. One of the superspreading events was linked to a nonsanctioned gambling house that resulted in further transmission. Shelter to nonshelter transmission was also confirmed. An algorithm developed for the determination of transmission events demonstrated very good reproducibility (κ score .98, 95% confidence interval, .97–1.0).

Conclusions. Our study suggests that socioeconomic factors, namely residing in a homeless shelter and spending time in a gambling house, combined with the superspreading event effect may have been significant factors explaining the rise in cases in this predominantly Inuit Arctic community.

Keywords. Inuit; molecular epidemiology; tuberculosis; whole-genome sequencing.

In Canada, tuberculosis (TB) incident rates are low but remain elevated among indigenous populations, which include First Nations, Inuit, and Métis. Tuberculosis incidence rates are the highest among Inuit when compared with all Canadian indigenous peoples. In Inuit Nunangat (Inuit homeland), which spans 4 regions in the Canadian arctic, the TB incidence rate was 205 per 100 000 compared with 0.5 per 100 000 in the

nonindigenous Canadian-born population in 2017 [1]. The incidence rates have been steadily climbing over the past 10 years in Inuit Nunangat [1]. As a result of these findings in 2018, the Government of Canada and Inuit Tapiriit Kanatami (The National Inuit Advocacy Organization) committed to reducing active TB cases by at least 50% by 2025 and to the elimination of TB among Inuit communities by 2030 [2].

Strains of *Mycobacterium tuberculosis* (Mtb) in Nunavut are extremely homogenous, with only 2 strain types currently circulating as identified by standard genotyping methods [3, 4]. Standard genotyping is not sufficiently discriminatory to provide enough information to track transmission links in these regions [5, 6]. Whole-genome sequencing (WGS) of Mtb isolates provides higher resolution to understand transmission dynamics [7, 8]. However, WGS alone using routine sequencing depth is limited in terms of the resolution needed to understand

Received 9 December 2019; editorial decision 16 March 2020; accepted 10 April 2020; published online April 13, 2020.

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Clinical Infectious Diseases® 2021;72(12):2187–95

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DOI: 10.1093/cid/ciaa420

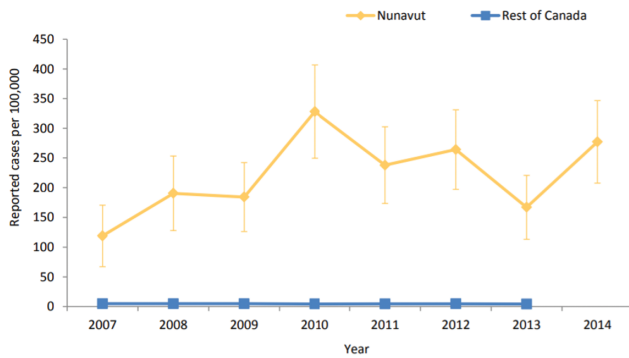


Figure 1. Age-standardized incidence rates of active TB in Nunavut, Canada [15]. Yellow vertical bars represent standard error. Abbreviation: TB, tuberculosis.

transmission dynamics in this part of the world [9] since multiple transmission events can occur with no detectable single nucleotide polymorphism (SNP) acquisition [10]. While environmental and social conditions are conducive to spread [11–13], host and bacterial factors could also influence transmission patterns. However, previous WGS studies done in these arctic regions among Inuit suggest that bacterial virulence factors are not likely to be the driving force of transmission, and instead the high rate of transmission is more likely associated with environmental conditions [5, 14].

The rise in TB cases seen in Nunavut since 2007 peaked in 2010 and was maintained for several years (Figure 1). In 2010, there were 100 incident TB cases in 25 Nunavut communities, 50% of which were concentrated in the capital Iqaluit (Figure 2). Deciphering transmission dynamics by integrating WGS and epidemiologic data, including social network analysis, offers an optimal approach to deriving putative transmission pathways to better understand TB outbreaks [8, 10, 11]. Furthermore, the development of reproducible algorithms to identify these transmission networks will assist health departments in focusing resources where interventions will have the greatest impact, benefiting individual patients and the larger community [15]. We set out to determine the proportion of transmission events

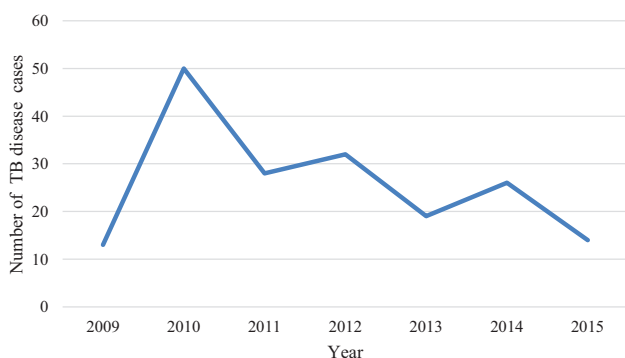


Figure 2. TB disease cases per year in Iqaluit, Nunavut. Abbreviation: TB, tuberculosis.

linked to specific epidemiological risk factors, individual(s) or location(s), to better understand transmission dynamics among this unique population residing in a remote region of Canada, using a reproducible transmission algorithm integrating WGS and epidemiological data.

METHODS

Study Population and Design

In 2016, the population of Nunavut in the Canadian Arctic was 37 082, of whom 84% were Inuit [15]. Iqaluit is the capital of Nunavut (n = 7590 in 2016, 55% Inuit) and the largest community in Inuit Nunangat [15]. Iqaluit is situated on Baffin Island, accessible by plane or ship during the brief summer and by plane only during the winter months. No roads link the communities on Baffin Island. In 2010, Iqaluit had the highest proportion of TB cases in Inuit Nunangat. The peak of cases seen in Iqaluit that year represented approximately 50% of the total number of Nunavut cases and 43% of TB cases in Inuit Nunangat [2].

Consecutive incident cases of culture-positive pulmonary TB were identified between the years 2009 and 2015 in Iqaluit (Supplementary Appendix 1). Clinical cases (treated empirically without culture confirmation) were not included in the analysis. Contact-tracing data were obtained from Iqaluit public health nurses who collected the data in accordance with the Canadian TB standards [16] and the Nunavut TB manual [17]. The Strengthening the Reporting of Molecular Epidemiology for Infectious Diseases (STROME-ID) statement [18] was used to guide reporting of this study. Laboratory methods are described in Supplementary Appendix 2.

Epidemiology Methods

Social Network Analysis

The contact network was constructed in Pajek (Batagelj, Mrvar, 2016) from a list of links between people and exposed contacts who were also cases, and between people and places they frequented.

Determination of Transmission

The following base principles were used to determine transmission: (1) SNP difference of 3 or less, (2) epidemiological links were based on named contact or common location (definitions in Supplementary Appendix 3), (3) biological plausibility ([a] timing = date of diagnosis/start of treatment, [b] clinical infectiousness = smear status), and (4) only one likely source was identified as the source for the spread case. The following further assumptions were made: (1) SNPs are acquired in an additive manner, (2) the direction of transmission is to the case with the additional SNPs, and (3) each spread case has a single source case. A superspreading event was defined as a starlike phylogenetic topology with at least 6 secondary cases branching directly from a common node [8]. Detailed methods of the

algorithm and definitions used are provided in [Supplementary Appendices 3 and 4](#).

Determination of Transmission and Reproducibility of the Novel Algorithm

To identify putative transmission events, the SNP difference between all isolates was identified. We applied a threshold of 3 or fewer SNPs to rule out unlikely transmission events (rationale shown in [Supplementary Appendix 3](#)). Following the application of the threshold, putative transmission events were further restricted by excluding any events that occurred due to an SNP reversion or went “backwards” to a common ancestor. The resulting putative transmission events were then further restricted by applying a set of rules and transmission definitions ([Supplementary Appendices 3 and 4](#)) based on the principles outlined above. The rules were applied independently by 2 of the investigators (D. V., K. S.) and adjudicated by another 2 investigators (G. G. A., A. A. Z.). Transmission maps of clusters were constructed. Each isolate was placed in the year that the person was diagnosed. Arrows pointing backwards in time in the map were allowed if the two isolates were separated by 2 years or less, representing a reasonable estimate of the time a person could go undiagnosed [19, 20].

Statistical Analysis

We calculated the proportion of transmission events by dividing the number of transmission events linked to an individual(s) or location(s) over the total number of transmission events. We used the “n” method, which compares the number of people involved in transmission chains compared with those not involved in transmission chains [21]. A κ score was calculated between 2 independent investigators (D. V. D., K. S.) that applied the rules for the novel algorithm used to develop transmission maps. We used univariable and multivariable logistic regression modeling to estimate odds ratios (ORs) between key risk factors and being identified as a source case in a transmission event. Risk factors for inclusion in the model were selected a priori based on expert knowledge and existing literature. These included the following: homeless shelter residence, presenting to the emergency department as opposed to being diagnosed through contact screening or employment screening, reporting a cough that lasted more than 2 weeks, age, and sex. All analyses were done using SAS version 9 (SAS Institute Inc).

RESULTS

Between 2009 and 2015, 185 TB cases were reported in Iqaluit (178 patients), including culture-confirmed and clinical cases (not culture-confirmed but treated) cases ([Supplementary Appendix 1](#)). The majority of the patients included in the study were male Inuit adults. None were human immunodeficiency virus (HIV) positive and all had pulmonary TB susceptible to

all first-line drugs, except for 1 case with monoresistance to rifampin ([Table 1](#)).

We sequenced 140 culture-confirmed TB isolates from 135 patients collected between March 2009 to November 2015. Contact tracing was done for 178 patients residing in Iqaluit and diagnosed between 2009 and 2015. The culture sampling fraction was 95% (140 WGS-obtained/147 culture-confirmed cases) and the overall sampling fraction of all cases in Iqaluit

Table 1. Demographic and Clinical Characteristics of Tuberculosis Cases, by Culture Status

Characteristics	Cases with WGS Data Included in Analysis (N = 140)
Mean age (range), years	41.8 (7–91) [n = 139]
Female, n (%)	43/137 (31)
Inuit ethnicity, n (%)	134/137 (98)
Year diagnosed, n (%)	
2009	9 (6)
2010	31 (22)
2011	27 (19)
2012	25 (18)
2013	14 (10)
2014	21 (15)
2015	13 (9)
History of BCG, n (%)	
Yes	99 (71)
No	4 (3)
Unknown	37 (26)
Smear, n (% positive)	60 (43)
Radiograph, n (% cavitations present)	36 (26)
Place where diagnosis was made, n (%)	
Contact investigation	59 (42)
Emergency room	32 (23)
Employment screening	2 (1)
Rehabilitation	1 (1)
Surveillance	10 (7)
Taima TB project	3 (2)
Walk-ins	23 (17)
Unknown	10 (7)
Clinical presentation (presenting with each symptom), n (%)	
Cough	70 (50)
Sweats	37 (27)
Fatigue	26 (19)
Fever	2 (23)
Hemoptysis	18 (13)
Weight loss	36 (26)
Prior active TB treatment, n (%)	
Yes	24 (17)
No	110 (79)
Unknown	6 (4)
Place of residence, n (%)	
Residential address	120 (86)
Homeless shelter	10 (7)
Unstable housing	5 (4)
Missing data or unknown address	5 (4)

Abbreviations: BCG, bacille Calmette-Guérin; TB, tuberculosis; WGS, whole-genome sequencing.

during the study period was 76% (135 [number of patients with culture-confirmed TB in the study]/178 [all culture-confirmed and clinical individual patients occurring in the population during the study period]).

Average depth of coverage was 231 times (range, 95–672X) across 99.7% (range, 99.3–99.8%) of the H37Rv reference genome (GenBank NC_000962.3). Average base quality of reads was 30.1 (range, 24.7–35.9). All 154 genomes were identified as Euro-American lineage 4.8 based on the regions of difference [22] and lineage-specific SNPs [23]. A total of 657 single nucleotide variant sites were included in the final analysis. Four distinct genomic clusters were observed from the topology of the maximum likelihood phylogenetic tree (Figure 3). The maximum SNP distance between all isolates within a cluster was 12 (Table 2).

Social Network Maps

We used social network graphs to first identify “location hotspots” or “superspreading events” (Figure 4). As 108 locations were nominated, for simplicity of reading the diagrams, we graphed only those people who nominated at least 1 other person, and

only the 2 most common locations named by 36% of people, representing 13% of all locations. One hundred thirteen individuals named 1 to 12 confirmed cases as contacts. The graph of only individuals who had named each other formed 1 large component of 107 people connected by at least 1 link and 3 other dyads. The structure identified the homeless shelter and the nonsanctioned gambling house as possible “location hotspots.”

Transmission Maps

The algorithm developed to generate the transmission maps was tested for its reproducibility by having 2 investigators not involved in the work apply the rules independently to generate transmission maps (Figures 5–7). The κ score between the 2 investigators was very good (.98; 95% confidence interval [CI], .97–1.0) (Supplementary Appendix 5).

Cluster 1 contained 87 isolates from 140 (62%) that were examined during the study period. In this cluster, 2 large chains of transmission were associated with 3 superspreading events in the homeless shelter. The first chain accounted for 17 transmissions, linked by 2 superspreading events (study #1193 and #1051), both of whom were found to be a contact of the

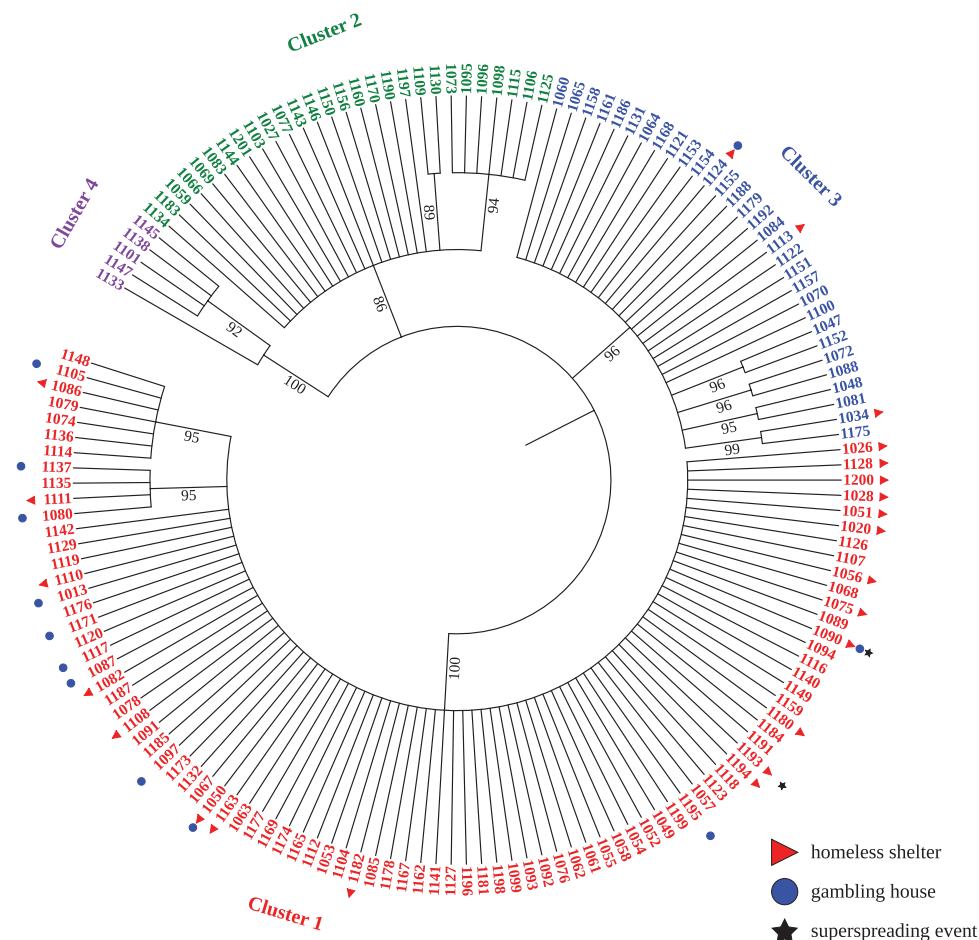


Figure 3. Bootstrap consensus tree depicting 154 Mtb isolates collected from March 2003 to November 2015. Evolutionary history inferred using the maximum likelihood method and bootstrapping with 1000 replicates. Branches with <80% support were collapsed. Abbreviation: Mtb, *Mycobacterium tuberculosis*.

Table 2. Number of Isolates and Single Nucleotide Polymorphisms Between Isolates per Cluster

Cluster	Number of Isolates (2009–2015)	Number of Historical Isolates (2003–2008)	Number of SNPs Between Isolates in the Cluster
1	87	3	0–12
2	25	3	0–9
3	23	8	0–11
4 ^a	5	0	0–11

Abbreviation: SNP, single nucleotide polymorphism.

^aThese isolates clustered with the Mn sublineage from Nunavik, a region in Inuit Nunangat located in the northern tip of the province of Quebec [3] (Supplementary Appendix 8).

other and were housed at the same homeless shelter. Clinically, these cases were highly contagious with a significant bacillary load and cavitation observed on imaging. In addition, a third superspreading event (study #1090) from the homeless shelter was diagnosed 1 year later and accounted for a transmission chain with 12 additional transmissions.

The number of primary transmission events (definite, probable, and possible) linked to these 3 superspreading events that presented in consecutive years from the homeless shelter were as follows: 6 for the first, 7 for the second, and 6 for the third. A further 10 transmission events were noted in the chains associated with these 3 superspreading events. The total number of transmissions in chains attributed to these 3

superspreading events was 29 out of a possible 44 transmissions that were identified in cluster 1. Importantly, 3 cases attributed to the third superspreading event from the shelter were linked by a nonsanctioned residential gambling house. The gambling house cases added another 7 transmissions in a separate chain. The proportion of transmission events from shelter to nonshelter individuals (including secondary and tertiary cases and gambling-house cases) related to these 3 superspreading events from the homeless shelter was 14 of 29 (48%). Clusters 2 and 3 were considerably smaller in number (Supplementary Appendix 6). Cluster 3 did demonstrate shelter and gambling house cases, but no transmission chains were found. No transmission events could be determined in cluster 4, which was the smallest cluster. There were 4 cases that had more than 1 isolate sequenced during the study period, 3 were thought to be reinfections and 1 a relapse (Supplementary Appendix 7).

In multivariable logistic regression analysis, presentation to the emergency department (adjusted OR [aOR], 4.16; 95% CI, 1.10–15.72) was associated with being identified as a source case in a transmission event after adjusting for possible confounders (Table 3). Residence in the homeless shelter (aOR, 3.03; 95% CI, .37–24.6), reporting a prolonged cough at diagnosis (aOR, 2.05; 95% CI, .42–9.93), and being 25–34 years old (aOR, 2.28; 95% CI, .19–26.37) all showed an association with being a source case but were not statistically significant.

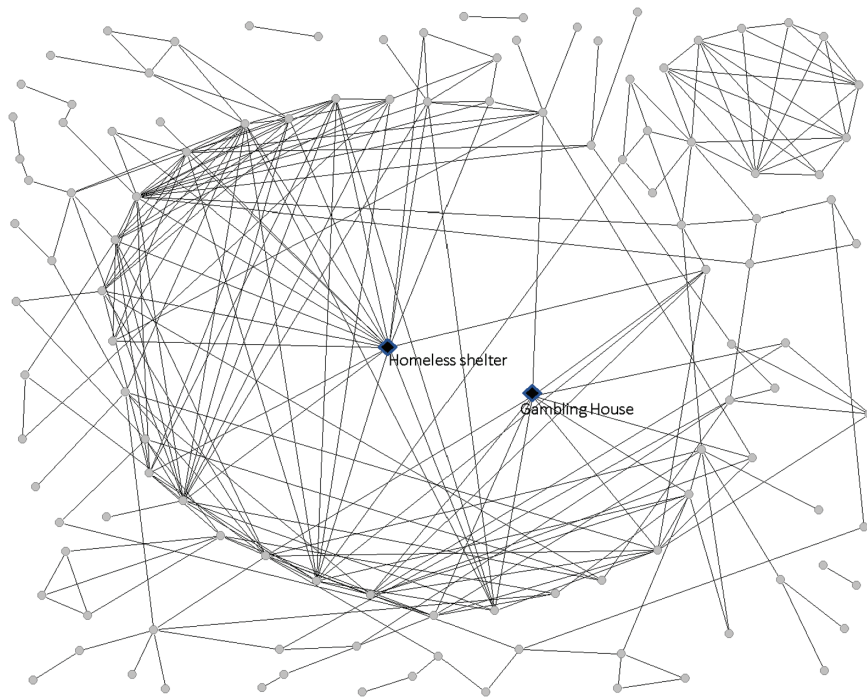


Figure 4. Social network based on 114 named cases and 2 key locations most commonly frequented. Gray dots represent people, and black diamonds represent places. Lines between a person and a place show that the person had spent time at that place. For example, a person may have spent time at both locations, in which case there would be a black line from that person to the shelter and another line from that person to the gambling house. Additional black lines may link that person to other people with whom they may have been in contact.

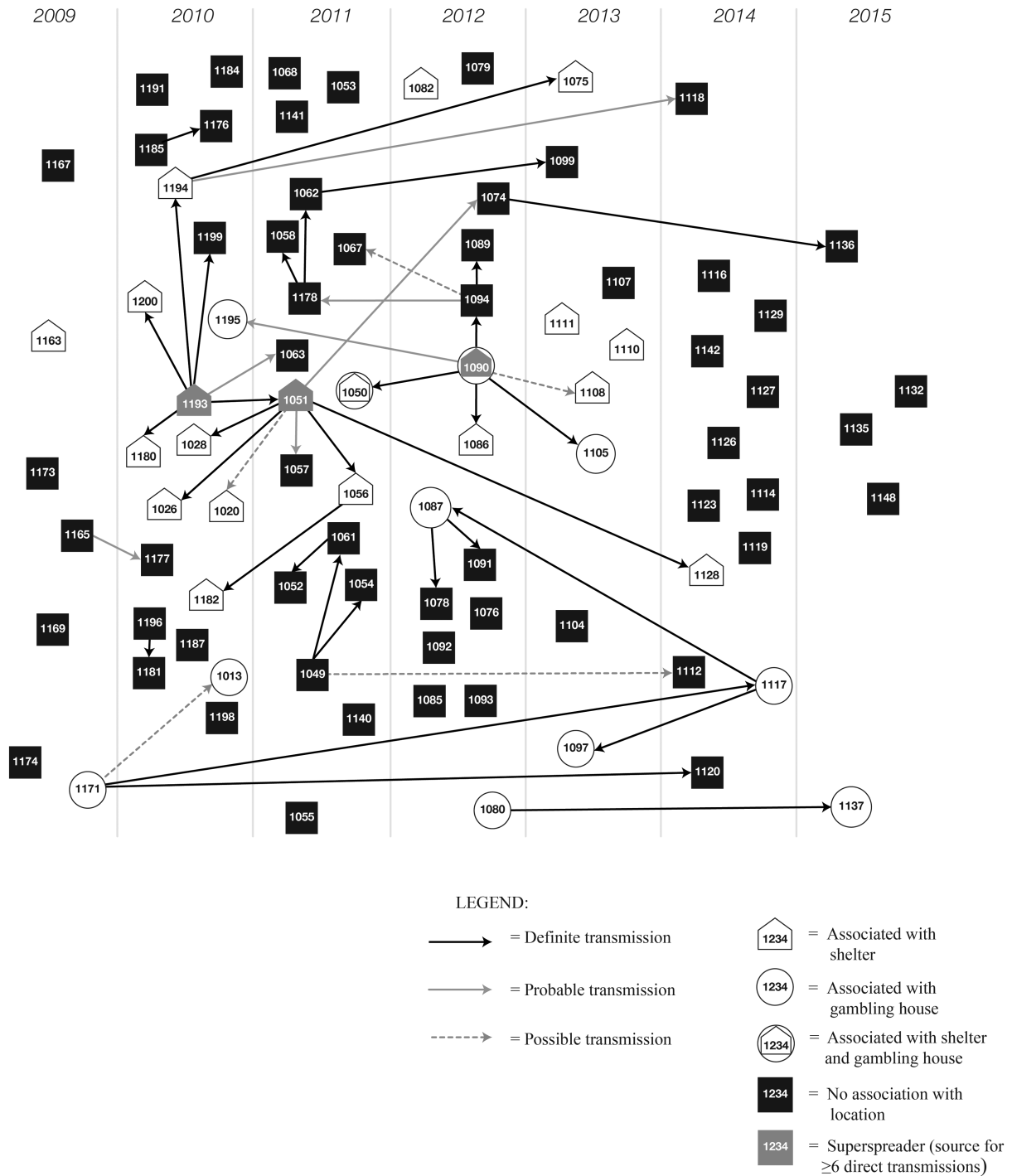


Figure 5. Transmission events between sequenced Mtb isolates from cluster 1. Abbreviation: Mtb, *Mycobacterium tuberculosis*.

DISCUSSION

In this remote and predominantly Inuit Canadian arctic community, WGS of Mtb isolates from active TB cases in Iqaluit between 2009 and 2015 provided further resolution of the common endemic strain identified by standard genotyping, revealing a large cluster of cases where transmission was amplified within the setting of a homeless shelter.

The data suggest that a homeless shelter was the epicenter of the outbreak in 2010 in Iqaluit, which led to the peak of active TB disease observed the following year. Four distinct clusters were identified, with 1 cluster containing 62% (87/140) of all Mtb isolates analyzed, and 3 superspreading events linked to the shelter were noted. Clinically, these cases were highly contagious, with significant bacillary load,

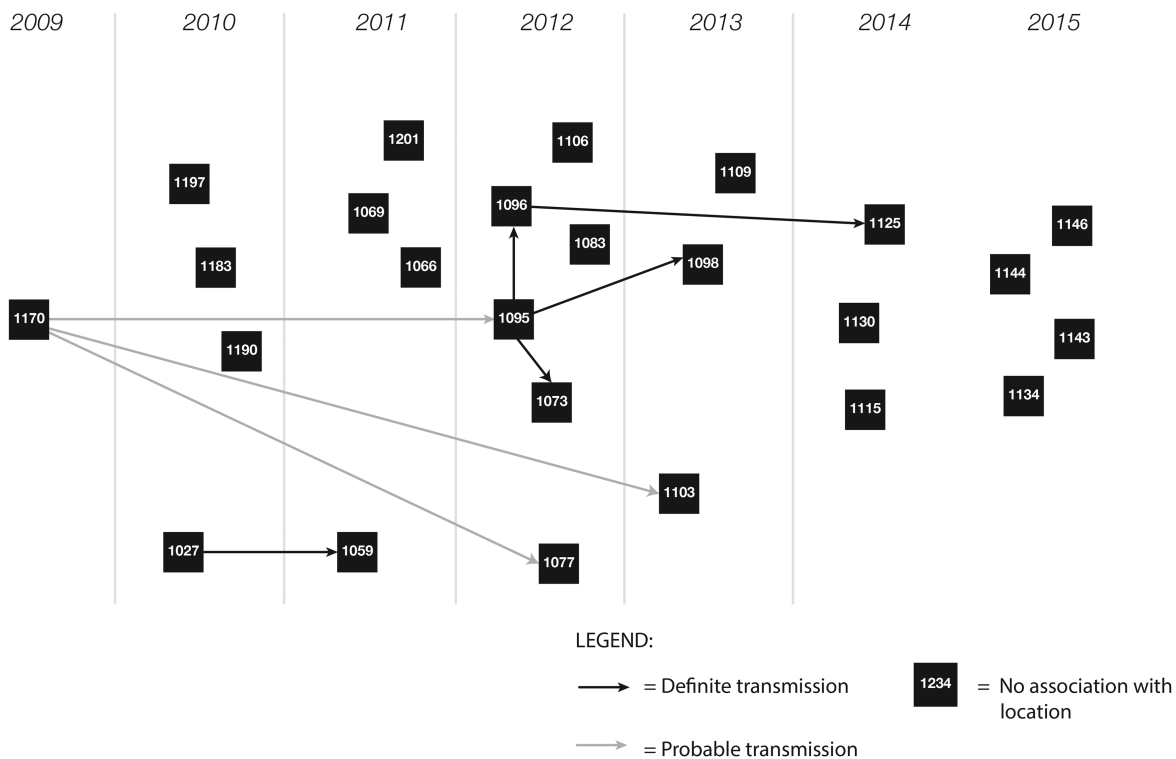


Figure 6. Transmission events between sequences Mtb isolates from cluster 2. Abbreviation: Mtb, *Mycobacterium tuberculosis*.

and had pulmonary cavities suggesting they may have been sick for an extended period of time. After adjusting for possible confounders, presentation to the emergency department was associated with being identified as a source case (aOR, 4.16; 95% CI, 1.10–15.72). This association could hypothetically reflect the fact that patients were quite sick at the time of presentation due to high bacillary loads, which likely increased the risk of transmission. It is hypothesized that further spread of TB occurred at a nonsanctioned residential gambling house. Additional evidence of the role the shelter played in TB transmission is demonstrated by the observation that almost half (14/29) of the cases in the 2 largest transmission chains identified within the shelter-associated cluster 1 were not shelter residents, and active TB cases in this cluster continued to be identified well beyond the initial peak of cases in 2010. Ongoing evidence of TB transmission post-2010 was an unexpected finding and greater than anticipated.

The peak of the TB outbreak in Nunavut was in 2010–2011. In 2011, the Nunavut Housing Needs Survey (NHNS) reported that 5% of Iqaluit’s population was in immediate need of housing and living temporarily in another person’s dwelling [24]. Iqaluit has 2 shelters with a total of 34 beds that often operate well over capacity. The available beds would have only been able to house a very small proportion of those needing immediate shelter [25]. In fact, 30% of dwellings in Iqaluit housed temporary residents without a home elsewhere in the 12 months prior to the NHNS [24]. This practice is often referred to as “couch surfing.” The NHNS survey findings may help to explain our

results, such that couch surfing likely contributed to significant transmission between homeless individuals and the community. Due to the arctic climate, homeless individuals cannot remain outdoors and will seek shelter wherever it is available, resulting in crowding of existing housing. In a recent study done in the same community during the same period of study, we observed crowding as the key predictor of TB infection after adjusting for several key social determinants of health [26]. In addition, Inuit social structure and community unity in the context of an intense climate may result in more time spent together in crowded dwellings [12, 26, 27], which are often in need of repair, with poor air circulation [28], compared with southern urban regions. Strategies to tackle the chronic housing shortage to alleviate homelessness and the invisible homeless population or couch surfers are paramount. The development of active case-finding programs in this vulnerable population has been shown to be effective [29] in addition to implementation of targeted preventive treatment programs and environmental infection-control measures in the shelters. These infection-control measures would include improved air circulation [28] with HEPA filters, installation of ultraviolet germicidal irradiation lights, and a reduction of the number of people housed per room [16].

Mycobacterium tuberculosis isolates in the study were identified as belonging to the Euro-American lineage (lineage 4), in keeping with other studies from this part of the world [5, 14]. The isolates were most likely circulating in the community prior to 2009, as all of the pre-2009 isolates sequenced were linked to

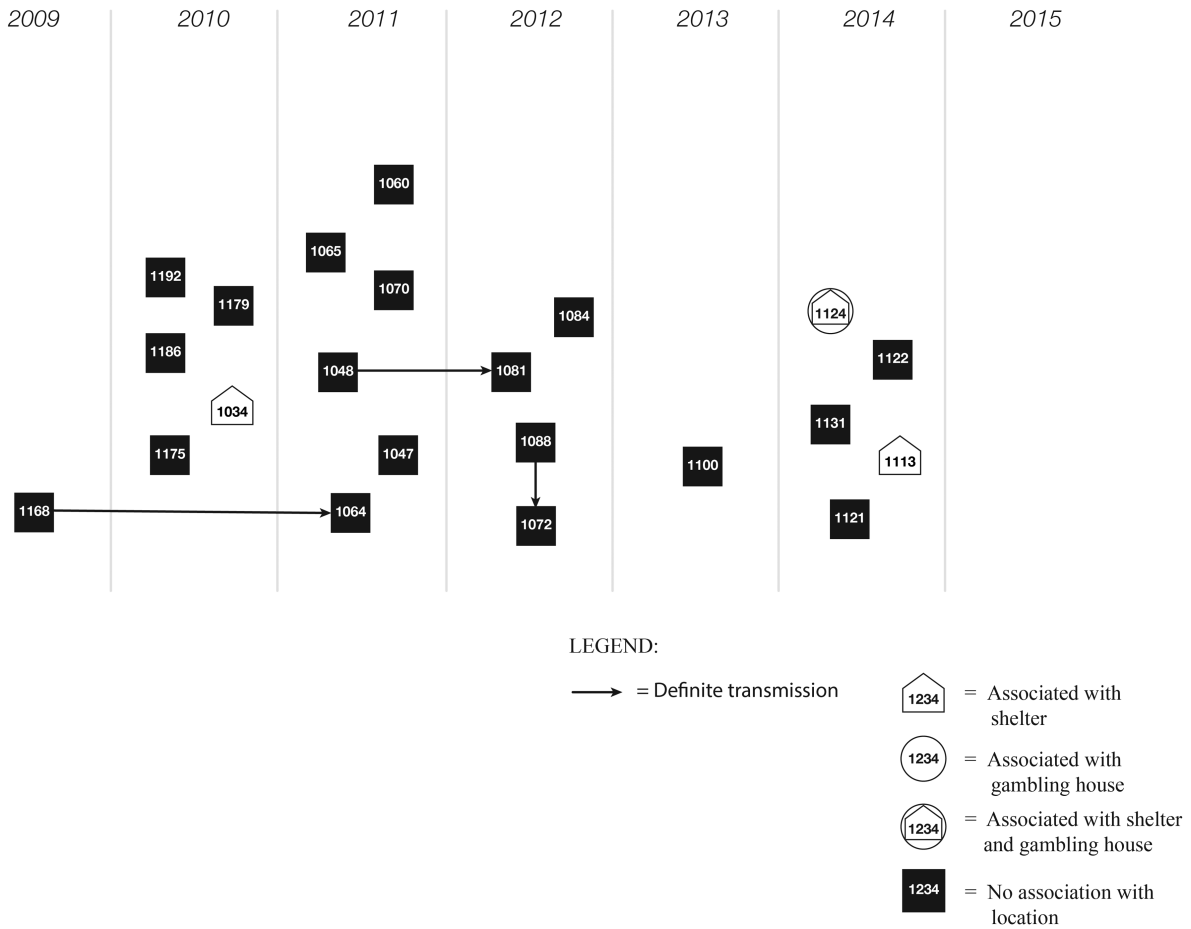


Figure 7. Transmission events between sequenced Mtb isolates from cluster 3. Abbreviation: Mtb, *Mycobacterium tuberculosis*.

clusters 1, 2, and 3. Other studies have identified a similar circulation of endemic Mtb strains in this region [5, 14]. Strains from this study were also found to cluster with strains from Nunavik,

Table 3. Factors Associated With Being Identified as a Source Case in a Transmission Event: Logistic Multivariable Regression Analysis

Index Source	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Sex (female)	1.02 (.38–2.72)	1.14 (.31–3.92)
Age		.98 (.94–1.02)
15–24 years	(Ref)	(Ref)
25–34 years	2.82 (.27–28.52)	2.28 (.20–26.33)
35–44 years	2.11 (.23–19.43)	1.15 (.11–12.11)
45–54 years	3.23 (.35–29.27)	1.41 (.13–15.25)
≥ 55 years	1.09 (.06–19.62)	.87 (.03–19.60)
Homeless shelter	2.59 (.81–8.30)	3.03 (.37–24.61)
Presentation to the emergency department	3.63 (1.39–9.48)	4.16 (1.10–15.72)
Prolonged cough	2.2 (.73–6.57)	2.05 (.42–9.93)

Outcome: being a source case (binary 0, 1). All of the variables used in the regression analysis are listed in the table. Abbreviations: CI, confidence interval; Ref, reference.

another region in the Nunangat (Supplementary Appendix 8). This finding supports previous observations [4] that intervillage transmission can occur.

The present study has several strengths. Previous studies have been difficult to reproduce due to challenges faced in the algorithms applied to determine transmission events. In this study, we present a reproducible algorithm combining genomic and epidemiological data. The existence of additional unrecognized cases is quite unlikely in this remote arctic setting with a stable population compared with other populations because there is minimal population turnover [15]. These features allow for more precise estimation of TB transmission causing disease. Further, our sample of isolates was not a convenience sample [21] but a true reflection of TB incidence in this community over a 7-year period.

Limitations of the study include that it is a retrospective analysis. Although data were collected in real time, they were analyzed at the end of the study period. We did not look at within-host diversity, which could have affected the interpretation of transmission pathways. However, we excluded heterogeneous

SNPs from our analysis, reducing the risk of missing transmission events due to within-patient SNP variability. In addition, we looked for heterogeneity at cluster-defining SNPs and did not see any evidence of mixed-cluster infections. We also used a very stringent threshold to determine a transmission event of a 3 or fewer SNP difference as the first filter for the algorithm. The threshold has been used by others [30] and was validated in 1 study in a similar region [14]. It is possible that there are cases not identified for analysis in this study because the patient died of TB or moved out of the community before diagnosis. The clinical data were limited in that we could not determine with certainty the exact date of symptom onset; therefore, the period of infectiousness was an estimate, a limitation that is found in similar studies. While environmental and social conditions are conducive to spread, host and bacterial factors could also influence transmission patterns; however, these factors have not been identified in past studies as being significant influencers of transmission [5, 14].

The homeless shelter was the epicenter of the outbreak in 2010 in Iqaluit, which led to the peak of active TB disease observed the following year. The extensive spread of TB transmission after the initial peak was an unexpected finding and greater than anticipated. Our study highlights the combined effect of an amenable socioeconomic factor, namely homelessness, and superspreading events in the shelter environment, which contributed to a significant increase in active TB cases within this remote region of Canada.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgments. The authors thank the National Reference Centre for Mycobacteriology and the Public Health Ontario Laboratory staff for performing whole-genome sequencing of study isolates. We also thank the Taima Tuberculosis steering committee members and the staff at Iqaluit Public Health.

Financial support. This study was supported by grants from the Canadian High Arctic Research Station; The Ottawa Hospital, Division of Respiratory; the Ontario Thoracic Society; the Canadian Institutes of Health Research (fellowship 152448); and the Genomic Research Development Initiative.

Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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