Sustained Intra- and Inter-jurisdictional Transmission of Tuberculosis within a Mobile, Multi-ethnic Social Network: Lessons for Tuberculosis Elimination

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ABSTRACT

Background: A context-specific, spatial-temporal understanding of a chain of tuberculosis (TB) transmission can inform TB elimination strategy.

Methods: Clinical, public health and molecular epidemiologic data were used to: 1) identify and describe a complex cluster of TB cases in Alberta, 2) elucidate transmission sequences, and 3) assess case-patient mobility. Socio-economic indicators in loci of transmission and the province at large were described. Factors seen to be fostering or hampering TB elimination were identified.

Results: Over a 15-year period, 18 TB cases in Alberta and multiple cases in the Northwest Territories were determined to be due to the same strain. One patient was diagnosed at death; all others completed directly-observed therapy (DOT). Case-level analysis revealed that patients were highly mobile with transmission of the strain over 26,569 km², an average of 2.8 different places of residence per patient during treatment, and contacts of sputum smear-positive cases spanning 9 of 17 regional health authorities. The majority of the contacts (57%) were attached to a single infectious case living in a homeless shelter. The three loci of transmission in Alberta were separated geographically but similar in terms of median incomes, rates of unemployment, levels of post-secondary education, and rates of population mobility (p<0.0001).

Conclusion: Upon review of the experience, central oversight, intra- and inter-jurisdictional coordination and DOT were seen as fostering, and the absence of ‘real-time’ DNA fingerprinting, social network analysis, engineering controls in shelters and better determinants of health in loci of transmission were seen as hampering TB elimination.

Key words: Tuberculosis; transmission; molecular epidemiology; socioeconomic indicators


METHODS

This study was performed in Alberta, a province of Western Canada having a population of 2.94 million in 2001 (Statistics Canada) and where the majority of First Nations (66%) are living on-reserve (Indian and Northern Affairs Canada, 2001). In Alberta, initial isolates of M. tuberculosis are DNA fingerprinted in the Provincial Laboratory for Public Health using restriction fragment-length polymorphism (RFLP) supplemented by spoligotyping as necessary.9,10 Over the 17-year period 1991-2007, all large clusters – defined as those having 15 or more case-patients – were identified and described according to the age, sex, population group (Aboriginal [First Nations, Métis, Inuit], Canadian-born non-Aboriginal

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and foreign-born) and place of residence (on-reserve or off-reserve) of their constituent members. One large cluster was selected for study. To assess the inter-jurisdictional spread of this cluster strain, it was compared to all isolates from the Northwest Territories within 2 years of diagnosis, were categorized as ‘Type 1’: clear epidemiologic links, connection based on place of residence at diagnosis, molecular genotyping and diagnosis date within 2 years of another case in the cluster. Results are presented in diagrammatic format to maintain the anonymity of cases and communities.

Case and contact analysis
Public health and hospital records of cluster cases were reviewed retrospectively. Cases were described according to age, sex, population group, date of diagnosis (the start date of treatment), place of residence at diagnosis (city borough, reserve community), disease site (pulmonary or extra-pulmonary), sputum smear status (positive or negative), chest radiograph status (cavitary or non-cavitary), risk factors for reactivation and outcome. Epidemiologic links, defined as likely exposure to another case of TB within 2 years of diagnosis, were categorized as ‘Type 1’: clear epidemiologic links confirmed at the time of diagnosis by traditional contact tracing or review of case records or ‘Type 2’: unclear epidemiologic links, connection based on place of residence at diagnosis, molecular genotyping and diagnosis date within 2 years of another case in the cluster. Results are presented in diagrammatic format to maintain the anonymity of cases and communities.

Mobility analysis
Three indicators were used to assess the mobility of cases: 1) documented out-of-province travel or change of address during treat-
and 2001, there were multiple (>10) NWT cases with the same strain. Between 1995 and 1997, there were no BC, Saskatchewan and Manitoba cases with the same strain. The incidence of TB in Alberta was 6.7 and 3.2 per 100,000 persons in 1991 and 2007, respectively.  

Case and contact analysis
Most of the 18 Cluster “D” cases were young (median age 39 years), male (72.2%), and Aboriginal (72.2%) (Table 2). All had pulmonary or pleuropulmonary TB. Three cases had 1 and five cases had 2 independent determinants of infectiousness (sputum smear positivity and cavitation on chest radiograph).  

Community-level analysis
Loci of transmission were assigned according to address and postal code at diagnosis. The major locus of transmission in Edmonton consisted of three adjoining census areas; in Calgary one census area. Data were obtained from the 2001 census on total population, income, employment, and population mobility for crude comparison of area-based socio-economic measures between loci of transmission and the province at large.

Statistical analysis
The statistical significance of differences between area-level indicators was assessed using chi-squared tests for proportions and t-tests for quantitative variables with STATA, version 9.2. The study was approved by the Health Research Ethics Board of the University of Alberta.

RESULTS
Between 1991 and 2007, there were 1,926 cases of culture-positive TB in Alberta; 404 (21.0%) in Aboriginal peoples, 262 (13.6%) in Canadian-born non-Aboriginal peoples and 1,260 (65.4%) in foreign-born peoples. Initial isolates from 1,880 (97.6%) cases were DNA fingerprinted and 7 large clusters identified (Table 1). Subsets of clusters ‘C’ and ‘G’ had been reported previously.  

Figure 1. Cluster “D” tuberculosis cases by time period and locus of transmission

<table>
<thead>
<tr>
<th>Year</th>
<th>Province or Territory</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reserve Community</td>
</tr>
<tr>
<td></td>
<td>Edmonton Borough</td>
</tr>
<tr>
<td>1991–1994</td>
<td>Calgary Borough</td>
</tr>
<tr>
<td>1995–1998</td>
<td></td>
</tr>
<tr>
<td>1999–2002</td>
<td></td>
</tr>
<tr>
<td>2003–2006</td>
<td></td>
</tr>
</tbody>
</table>

Each number refers to a cluster case (see Table 2). Solid lines refer to ‘Type 1’ transmission links; interrupted lines to ‘Type 2’ transmission links (see text for definitions of transmission links). Open arrows refer to travel to and from the Northwest Territories. The first cluster case was reported in September 1992, the last in February 2006.

Case mobility
On average, the five most infectious cases and all cases changed addresses 4 times and 2.8 times, respectively, during treatment. Five patients had a history of shelter living before and 3 during treatment; shelters were without engineering controls. Three cases (case #s 1, 7, and 14) originated from an NWT band and had a documented history of travel to the NWT either prior to diagnosis or during treatment. Contacts of sputum smear-positive cases were widely distributed, involving 9 of 17 RHAs.

Area-based socio-economic indicators
Median household income and rates of higher education were lower and unemployment rates and population mobility higher in the transmission loci than in the province at large, p<0.0001 (Table 4).
ta and the Northwest Territories. Upon review of the experience, central oversight, integrated case management and DOT were seen as fostering TB elimination. The absence of ‘real-time’ disease control in the context of social networks was seen as sustaining the outbreak and hampering TB elimination.

In contrast to outbreaks in isolated or semi-isolated reserve communities which rely on conventional epidemiology – sometimes to the point of screening ‘community contacts’ – complex outbreaks such as the one reported here rely on molecular epidemiology, geographical-spatial analysis, and the application of unconventional contact-tracing paradigms for investigation.12,16-22 They can be much more challenging. Clearly, it would have been helpful to have recognized the extent of the outbreak earlier. In this regard, newer, polymerase-chain-reaction-based methods of genotyping offer the promise of ‘real-time’ (results in 1 to 2 weeks [national], versus 2 to 12 weeks for RFLP [provincial]) intra- and inter-jurisdictional outbreak detection.23-26 Such genotyping can also unmask the role that social networks play in disease transmission and the extent to which failure to consider unnamed contacts can lead to missed cases. Disease control in the context of social networks requires identification of groups of persons who share similar social settings and mores with infected people. Once these groups are identified, testing and treatment is offered not only to the infected person and the few named contacts, but to the entire network. This approach improves rapport with clientele, helps eliminate stigma, and identifies persons who may have otherwise been missed.27,28

Such strategies might have minimized the effect of case-patient mobility which was substantial. In general, high degrees of mobility are seen in young adults and those with unstable or transient living conditions.29 With respect to the former, migration of First Nations off-reserve is known to have a clear age pattern with young adults being the most mobile. Two of the most infectious First Nations cases were mobile across jurisdictions. With respect to those with unstable or transient living conditions, 57% of the contacts were attached to a single highly infectious shelter resident. Shelter contacts are difficult to assess (30% of this patient’s contacts were unattached) and difficult to treat if infected (only 22.5% of this patient’s newly infected/TST-converted contacts completed treatment of LTBI). Engineering controls such as ultraviolet light might have reduced transmission had they been present in the shelter in question.30 Mandated compliance with TB screening, as a condition of admission, and spot sputum screening in the United States.31,32


ta and the Northwest Territories. Upon review of the experience, central oversight, integrated case management and DOT were seen as fostering TB elimination. The absence of ‘real-time’ DNA fingerprinting (see definition of ‘real-time’ in next paragraph), social network analysis, and engineering controls in shelters and the presence of poor determinants of health in loci of transmission were seen as sustaining the outbreak and hampering TB elimination.

In contrast to outbreaks in isolated or semi-isolated reserve communities which rely on conventional epidemiology – sometimes to the point of screening ‘community contacts’ – complex outbreaks such as the one reported here rely on molecular epidemiology, geographical-spatial analysis, and the application of unconventional contact-tracing paradigms for investigation.12,16-22 They can be much more challenging. Clearly, it would have been helpful to have recognized the extent of the outbreak earlier. In this regard, newer, polymerase-chain-reaction-based methods of genotyping offer the promise of ‘real-time’ (results in 1 to 2 weeks [national], versus 2 to 12 weeks for RFLP [provincial]) intra- and inter-jurisdictional outbreak detection.23-26 Such genotyping can also unmask the role that social networks play in disease transmission and the extent to which failure to consider unnamed contacts can lead to missed cases. Disease control in the context of social networks requires identification of groups of persons who share similar social settings and mores with infected people. Once these groups are identified, testing and treatment is offered not only to the infected person and the few named contacts, but to the entire network. This approach improves rapport with clientele, helps eliminate stigma, and identifies persons who may have otherwise been missed.27,28

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Our crude comparison of socio-economic indicators at the community level suggested a link between TB and social determinants of health. TB cluster size and social disadvantage are known to be associated.33 Substance abuse was a common risk factor among case-patients; excessive alcohol use is known to be disproportionately

### Table 3. Tuberculin Skin Test Results in Contacts of Cluster “D” Patients by Type of Contact and Place of Residence of Contact

<table>
<thead>
<tr>
<th>Tuberculin Skin Test Results</th>
<th>Close</th>
<th>Casual</th>
<th>Other*</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Old Positive</td>
<td>R 18</td>
<td>E 38</td>
<td>C 4</td>
<td>O 3</td>
</tr>
<tr>
<td>New Positive</td>
<td>R 9</td>
<td>E 22</td>
<td>C 2</td>
<td>O 1</td>
</tr>
<tr>
<td>Convert</td>
<td>R 2</td>
<td>E 4</td>
<td>C 1</td>
<td>O 5</td>
</tr>
<tr>
<td>Negative (&gt;8 wks)†</td>
<td>R 8</td>
<td>E 23</td>
<td>C 4</td>
<td>O 3</td>
</tr>
<tr>
<td>Negative (&lt;8 wks)†</td>
<td>R 1</td>
<td>E 11</td>
<td>C 4</td>
<td>O 3</td>
</tr>
<tr>
<td>Unknown</td>
<td>R 1</td>
<td>E 12</td>
<td>C 8</td>
<td>O 2</td>
</tr>
<tr>
<td>Total</td>
<td>R 39</td>
<td>E 123</td>
<td>C 12</td>
<td>O 7</td>
</tr>
</tbody>
</table>

† Refers to reserve community; E=Edmonton, C=Calgary, O=other communities
* Other: refers to those whose contact type (close, casual, etc.) was not specified by the public health department at the time of reporting.
† Refers to ≥8 weeks or <8 weeks after contact with the source case was broken.

### Table 4. Socio-economic Indicators in Communities Where the Cluster “D” Strain Was Transmitted, Compared to Provincial-level Indicators

<table>
<thead>
<tr>
<th>Socio-economic Indicators</th>
<th>Provincial-level</th>
<th>Reserve Community</th>
<th>Edmonton Borough</th>
<th>Calgary Borough</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=18)*</td>
<td>(n=4)</td>
<td>(n=12)</td>
<td>(n=2)</td>
</tr>
<tr>
<td>Total Population</td>
<td>2,941,150</td>
<td>580</td>
<td>12,415</td>
<td>8002</td>
</tr>
<tr>
<td>Income</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence of low income in 2000 (%)</td>
<td>10.5%</td>
<td>Data not available</td>
<td>39.0%</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Median household income ($)</td>
<td>$52,524</td>
<td>$4,724</td>
<td>p&lt;0.0001</td>
<td>$21,920</td>
</tr>
<tr>
<td>Employment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Labour force participation</td>
<td>73.4%</td>
<td>50.0%</td>
<td>p&lt;0.0001</td>
<td>59.2%</td>
</tr>
<tr>
<td>Unemployment rate</td>
<td>4.0%</td>
<td>28.6%</td>
<td>p&lt;0.0001</td>
<td>11.5%</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than high school</td>
<td>6.2%</td>
<td>16%</td>
<td>p&lt;0.0001</td>
<td>18.8%</td>
</tr>
<tr>
<td>High school graduation</td>
<td>31.5%</td>
<td>46%</td>
<td>p&lt;0.0008</td>
<td>36.1%</td>
</tr>
<tr>
<td>Trades school</td>
<td>14.0%</td>
<td>6%</td>
<td>p=0.013</td>
<td>8.9%</td>
</tr>
<tr>
<td>≥1 year of college or university</td>
<td>51.0%</td>
<td>32%</td>
<td>p&lt;0.0001</td>
<td>36.3%</td>
</tr>
<tr>
<td>Population Mobility</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persons who moved, 2000-2001</td>
<td>17.6%</td>
<td>11%</td>
<td>p=0.052</td>
<td>34.4%</td>
</tr>
</tbody>
</table>

* Number of individuals in chain of transmission.
† Chi-squared tests comparing proportion at community level to proportion at regional level.
high in clustered patients. Substance abuse is the most commonly reported modifiable behaviour impeding TB elimination efforts in the United States. Poor socio-economic conditions and substance abuse have been linked; together they may contribute to delayed diagnosis and more advanced disease (greater transmission) at presentation.

The major limitation of this study is its retrospective design, requiring the use of proxies for mobility analysis and aggregate data for area-based analysis.

In conclusion, as TB rates continue to decline, an increasing proportion of cases are likely to occur in difficult-to-reach populations. New technology and better understanding of complex chains of transmission can expose barriers to TB elimination.

REFERENCES


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RéSUMÉ

Conteste : La connaissance spatio-temporelle et contextuelle d’une chaîne de transmission de la tuberculose pourrait éayer la stratégie d’élimination de cette maladie.

Méthode : A l’aide de données cliniques, de santé publique et d’épidémiologie moléculaire, nous avons : 1) mis en évidence et décrit une concentration complexe de cas de tuberculose en Alberta, 2) éluclidé les séquences de transmission et 3) évalué la mobilité des cas patients. Nous décrivons les indicateurs sociocinématiques sur les lieux de transmission et dans le reste de la province. Les facteurs qui semblent favoriser ou entraver l’élimination de la tuberculose sont indiqués.

Résultats : Sur une période de 15 ans, il a été déterminé que 18 cas de tuberculose relevés en Alberta et plusieurs cas dans les Territoires du Nord-Ouest avaient la même souche. L’un des patients a été diagnostiqué après sa mort; tous les autres ont reçu un traitement directement observé (TDO). L’analyse par cas montre que les patients étaient très mobiles : la souche s’est propagée sur 26 569 km², chaque patient a eu en moyenne 2,8 lieux de résidence durant son traitement, et les contacts des cas dont les frottis de crachat étaient positifs couvraient 9 des 17 régies régionales de la santé. La majorité des contacts (57%) étaient rattachés à un même lieu infectieux hébergé dans une maison pour sans-abri. Les trois lieux de transmission en Alberta étaient éloignés géographiquement, mais semblables pour ce qui est des revenus médians, des taux de chômage, des niveaux d’études postsecondaires et des taux de mobilité de la population (p<0.0001).

Conclusion : Selon notre analyse, les facteurs favorisant l’élimination de la tuberculose sont la surveillance centrale, la coordination intra- et interprovincial et le TDO. Les facteurs entravant l’élimination de la tuberculose sont l’absence (1999:6,1%); ‘en temps réel’ par code génétique, l’absence d’analyse des réseaux sociaux, l’absence de mesures techniques dans les maisons de refuge et l’absence de meilleurs déterminants de la santé dans les lieux de transmission.

Mots clés : tuberculose; transmission; épidémiologie moléculaire; indicateurs sociocinématiques