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 km^2, 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

La traduction du résumé se trouve à la fin de l'article.

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The World Health Organization *Global Plan to Stop TB: 2006-2015* aims to halve by 2015 the prevalence of TB reported in 1990.[1] Consistent with this goal, the Canadian Tuberculosis Committee of the Public Health Agency of Canada set a target Canadian TB incidence rate of 3.6 per 100,000 persons (one-half the incidence rate in Canada in 1990) for 2015.[2] So far, the achievement of this goal has been hampered by sustained high rates of TB in Aboriginal peoples and the foreign-born. Strategies aimed at eliminating TB focus on interrupting transmission and preventing TB in persons already infected.[2]

This study is focused on the Canadian-born and describes in detail and places into context a complex cluster (chain of transmission) of TB cases in Alberta. Further, it uses the exercise to inform TB elimination strategy. A cluster of TB cases is one whose causative isolates of *Mycobacterium tuberculosis* share a common DNA fingerprint, suggesting a transmission link between them.[3] In instances where housing is unstable and patients may not know the names and locations of contacts, studies that incorporate DNA fingerprinting of isolates have provided insight into spatial and temporal patterns of transmission as well as factors that might contribute to rapid progression of disease.[4-8] In addition to DNA fingerprint data, contact tracing, mobility and socio-economic data were used to further describe the chain of transmission and interpret its implications for TB elimination.

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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Table 1. Large (≥15 Members) Chains of Tuberculosis Transmission (Clusters) in Alberta by Age, Sex, Population Group and Place of Residence (On-reserve/Off-reserve) at Diagnosis, 1991-2007

Cluster*	Number of Cluster Members	Age of Cluster Members (Years)			Male	Population Group of Cluster Members					Residence On-/Off-reserve†
		<15	15-64	>64		CBA			CBO	FB	
						FN	Métis	Inuit			
A	15	1	14	0	8	6	2	1	6	0	3/12
B	15	0	9	6	7	10	4	0	0	1	10/5
C	18	7	11	0	7	18	0	0	0	0	18/0
D	18	1	17	0	13	8	4	0	5	1	4/14
E	23	0	20	3	11	21	0	0	0	2	20/3
F	25	1	12	12	15	0	0	0	0	25	0/25
G	43	3	34	6	28	30	6	0	6	1	30/13

Shaded cluster = study cluster
CBA=Canadian-born Aboriginal, CBO=Canadian-born 'Other', FN=First nation, FB=foreign-born
* Cluster member's *M.tuberculosis* isolates had 100% identical DNA fingerprint patterns. The number of IS*6110* bands in each cluster strain, a measure of the power to discriminate one strain from another, was 12, 9, 13, 11, 11, 1, 10, respectively. Subsets of cluster 'C' and 'G' had been reported previously.[12]
† Of the 85 persons listed as on-reserve at the time of diagnosis, 78 were First Nations and 7 were Métis.

Table 2. Demographic, Clinical and Epidemiological Features of Cluster "D" Members

Case No.*	Demographic			Clinical			Epidemiologic				
Date of Diagnosis (mo/yr)	Age (yrs)	Sex	Population Group	Sputum Smear Positive	Cavity on CXR	Risk Factors†	Links Between Cases	Number of Contacts‡			
								Past TST Positive	Not Assessed	TST Negative	New TST Positive/ Converter
1 (09/92)	24	F	FN	Y	Y	1,2	Source #'s 2,5,8,11, possibly #3,4	18	1	18	15
2 (10/92)	9	F	FN	N	N		Household contact of #1	13	1	90	19
3 (05/93)	32	M	FN	N	N	1	Unknown			1	
4 (08/93)	27	M	FN	N	N	1	Unknown	8	–	11	8
5 (09/94)	44	M	CBO	Y	Y	1	Lived with #1 for two weeks	–	1	4	–
6 (04/95)	46	M	Métis	Y	Y	1,3	Probable source case of #7,10	11	7	33	7
7 (05/95)	37	M	FN	Y	Y	1,2	Roommate of #6	2	–	–	1
8 (05/96)	45	M	CBO	Y	Y	1,2	Probable source #'s 9,12,13,16	150	186	209	71
9 (08/96)	48	M	CBO	N	N	1	Co-worker contact of #8	1	1	5	2
10 (08/96)	46	M	Métis	N	N	1	Roommate of #6, contact of #8	–	–	–	–
11 (06/97)	38	M	FN	N	N	3,4	Contact of #1	10	11	9	6
12 (12/97)	46	M	CBO	N	N	1,2	Contact of #8	33	36	15	12
13 (06/98)	49	F	FN	N	N	1	Contact of #8	–	–	1	1
14 (12/98)	63	M	FN	Y	N	1	Unknown	2	2	–	2
15 (01/99)	31	M	Métis	N	N		Visited Edmonton in near past	2	1	5	–
16 (08/02)	42	M	CBO	Y	N	1,3	Contact of #8	4	7	9	9
17 (07/04)	29	F	FB	N	N		Customer at #16's workplace	–	–	1	
18 (02/06)	40	F	Métis	N	Y	1	Unknown	–	–	8	

M=male, F=female; FN=First Nation, CBO=Canadian-born 'Other', FB=foreign-born; Y=yes, N=no; CXR=chest x-ray; TST=tuberculin skin test
* Cases are numbered according to their order of occurrence (see figure). Case #14 had a past history of TB; case # 1, 5, 6, 10, 11, 13, and 18 had a past history of a positive TST.
† Risk Factors: 1=Alcohol abuse defined as patient-reported alcoholism or disclosure of excessive alcohol use, 2=injection drug use, 3=substance abuse, unspecified or other, 4=severe malnutrition.
‡ Contacts who were 'not assessed' were those with no past positive TST and, either a negative TST that was performed at less than 8 weeks post-contact, or no TST. TST negative contacts are those who were negative ≥8 weeks post-final contact with the source case. A TST converter was defined according to the Canadian Tuberculosis Standards.[2]

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 (NWT) in 1993-2001 (n=122) and all isolates from British Columbia (BC), Saskatchewan and Manitoba in 1995-1997 (n=944).[11]

Case and contact analysis

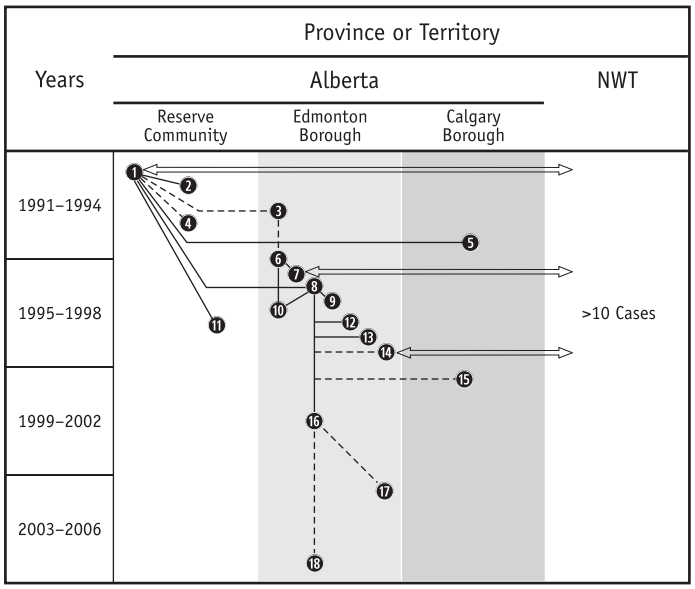
Public health and hospital records of cluster cases were reviewed retrospectively. Cases were described according to age, sex, population group, date of diagnosis (the start date of treatment), place of residence at diagnosis (city borough, reserve community), disease site (pulmonary or extra-pulmonary), sputum smear status (positive or negative), chest radiograph status (cavitary or non-cavitary), risk factors for reactivation and outcome.[2] Epidemiologic links, defined as likely exposure to another case of TB within the cluster 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.

Contact summary reports for each case were reviewed to identify potential linkages within the cluster (contact tracing had been performed by public health nurses in accordance with the recommendations of the *Canadian Tuberculosis Standards*).[2] Data extracted from contact tracing included total number of contacts, the nature of their association to the source case (close, casual, or other) and geographical location. Contacts were assigned to one of 17 geographical locations based on residence and Regional Health Authority (RHA) divisions used in the province up until 2003. Locations of contacts were tabulated by patient, and average distances of contact locations from source locations were calculated, based on residence at diagnosis.

Mobility analysis

Three indicators were used to assess the mobility of cases: 1) documented out-of-province travel or change of address during treat-

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



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.

ment for active TB, 2) history of homelessness evidenced by record of residence in a publicly operated shelter in the 12 months preceding diagnosis or during treatment for active TB and 3) geographical location of contacts.

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.[12] Cluster 'D' was chosen as being the most likely to inform TB elimination strategy. It involved four different population groups and a drug-susceptible strain; its extent was unrecognized at the time (routine and catch-up [historical isolates] RFLP typing did not begin until later). All cluster cases occurred within 2 years of each other. Between 1993 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.[13]

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 pleuro-pulmonary TB. Three cases had 1 and five cases had 2 independent determinants of infectiousness (sputum smear positivity and cavitation on chest radiograph).[14] Fourteen patients were HIV tested and negative; non-tested patients had no record of a positive HIV test result in the provincial HIV database up to the end of 2007. Substance abuse was very common (88.2% of the adult cases). Intra- and inter-jurisdictional management was well coordinated and all but one case (#4 who was diagnosed at death) completed directly observed treatment (DOT).[15] Three loci of transmission were identified: a reserve community, an Edmonton borough, and a Calgary borough, spanning 26,569 km^2 (Figure 1). Ten cases had 'Type 1' and 7 cases had 'Type 2' transmission links.

Most contacts (57.0% of 1,080) were attached to a single highly infectious homeless shelter resident (#8). Many (24.4%) of this case's contacts were already known to be tuberculin skin test (TST) positive. Most of the 254 non-assessed case contacts (186 or 73.2%) were contacts of this case. Of the 71 new TST positive/TST converted contacts of this patient, 58 (81.7%) were recommended, 30 (42.3%) accepted, and 16 (22.5%) completed treatment of latent tuberculosis infection (LTBI). Close contacts were more likely than those who were casual or 'other' to have a new positive TST or TST conversion, 51.3% versus 31.3% versus 20.4%, respectively (Table 3).

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).

DISCUSSION

At a time when the overall incidence of TB in Alberta was falling, sustained transmission was occurring in a difficult-to-reach population. Cluster cases were from multiple population groups, occurred over an extended period of time, and with few exceptions were not connected one with another at the time. Though cluster cases were HIV negative and the cluster strain drug-susceptible, there was ongoing intra-jurisdictional transmission between three loci in Alberta and inter-jurisdictional transmission between Alber-

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

Tuberculin Skin Test Results	Type of Contact												Total
	Close				Casual				Other*				
	R	E	C	O	R	E	C	O	R	E	C	O	
Old Positive	18	38	4	3	7	27		3	18	108	4	24	254
New Positive	9	22	2	1	10	19	1		13	39		7	123
Converter	2	4			3	2			11	7		1	30
Negative (≥8 wks)†	8	23	4	3	5	70		2	93	192	1	18	419
Negative (<8 wks)†	1	11			4	15		3	2	53		6	95
Unknown	1	25	2			12			5	109	1	4	159
Total	39	123	12	7	29	145	1	8	142	508	6	60	1080

R=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

Socio-economic Indicators	Provincial-level	Community-level					
		Reserve Community		Edmonton Borough		Calgary Borough	
	(n=18)*	(n=4)	p-value†	(n=12)	p-value†	(n=2)	p-value†
Total Population	2,941,150	580	–	12,415	–	8002	–
Income							
Incidence of low income in 2000 (%)	10.5%	Data not available	–	39.0%	p<0.0001	27.5%	p<0.0001
Median household income ($)	$52,524	$4,724	p<0.0001	$21,920	p<0.0001	$40,396	p<0.0001
Employment							
Labour force participation	73.4%	50.0%	p<0.0001	59.2%	p<0.0001	70.8%	P=0.019
Unemployment rate	4.0%	28.6%	p<0.0001	11.5%	p<0.0001	7.6%	p<0.0001
Education							
Less than high school	6.2%	16%	p<0.0001	18.8%	p<0.0001	43.4%	p<0.0001
High school graduation	31.5%	46%	p=0.0008	36.1%	p<0.0001	16.3%	p<0.0001
Trades school	14.0%	6%	p=0.013	8.9%	p<0.0001	16.5%	P=0.004
≥1 year of college or university	51.0%	32%	p<0.0001	36.3%	p<0.0001	24.0%	p<0.0001
Population Mobility							
Persons who moved, 2000-2001	17.6%	11%	p=0.052	34.4%	p<0.0001	29.7%	p<0.0001

* Number of individuals in chain of transmission.
† Chi-squared tests comparing proportion at community level to proportion at regional level.

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 *M. tuberculosis* (for example, "mycobacterial interspersed repetitive-unit-variable number tandem repeats" [MIRU-VNTR]) 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 went unassessed), subject to re-infection (8 of the cluster cases had a history of TB or a positive TST) 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 are strategies that have been used with success in homeless shelters in the United States.[31,32]

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

high in clustered patients.[23] Substance abuse is the most commonly reported modifiable behaviour impeding TB elimination efforts in the United States.[34] 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.

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RÉSUMÉ

Contexte : La connaissance spatio-temporelle et contextuelle d'une chaîne de transmission de la tuberculose pourrait étayer la stratégie d'élimination de cette maladie.

Méthode : À 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) élucidé les séquences de transmission et 3) évalué la mobilité des cas patients. Nous décrivons les indicateurs socioéconomiques 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 km^2, 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 cas 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 interprovinciale et le TDO. Les facteurs entravant l'élimination de la tuberculose sont l'absence d'identification « en temps réel » par le 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 socioéconomiques