Determinants of tuberculosis trends in six Indigenous populations of the USA, Canada, and Greenland from 1960 to 2014: a population-based study

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Summary

Background Tuberculosis continues to disproportionately affect many Indigenous populations in the USA, Canada, and Greenland. We aimed to investigate whether population-based tuberculosis-specific interventions or changes in general health and socioeconomic indicators, or a combination of these factors, were associated with changes in tuberculosis incidence in these Indigenous populations.

Methods For this population-based study we examined annual tuberculosis notification rates between 1960 and 2014 in six Indigenous populations of the USA, Canada, and Greenland (Inuit [Greenland], American Indian and Alaska Native [Alaska, USA], First Nations [Alberta, Canada], Cree of Eeyou Istchee [Quebec, Canada], Inuit of Nunavik [Quebec, Canada], and Inuit of Nunavut [Canada]), as well as the general population of Canada. We used mixed-model linear regression to estimate the association of these rates with population-wide interventions of bacillus Calmette-Guérin (BCG) vaccination of infants, radiographic screening, or testing and treatment for latent tuberculosis infection (LTBI), and with other health and socioeconomic indicators including life expectancy, infant mortality, diabetes, obesity, smoking, alcohol use, crowded housing, employment, education, and health expenditures.

Findings Tuberculosis notification rates declined rapidly in all six Indigenous populations between 1960 and 1980, with continued decline in Indigenous populations in Alberta, Alaska, and Eeyou Istchee thereafter but recrudescence in Inuit populations of Nunavut, Nunavik, and Greenland. Annual percentage reductions in tuberculosis incidence were significantly associated with two tuberculosis control interventions, relative to no intervention, and after adjustment for infant mortality and smoking: BCG vaccination (–11%, 95% CI –6 to –17) and LTBI screening and treatment (–10%, –3 to –18). Adjusted associations were not significant for chest radiographic screening (–1%, 95% CI –7 to 5). Declining tuberculosis notification rates were significantly associated with increased life expectancy (–37·8 [95% CI –41·7 to –33·9] fewer cases per 100 000 for each 1-year increase) and decreased infant mortality (–9·0 [–9·5 to –8·6] fewer cases per 100 000 for each death averted per 1000 livebirths) in all six Indigenous populations, but no significant associations were observed for other health and socioeconomic indicators examined.

Interpretation Population-based BCG vaccination of infants and LTBI screening and treatment were associated with significant decreases in tuberculosis notification rates in these Indigenous populations. These interventions should be reinforced in populations still affected by tuberculosis, while also addressing the persistent health and socioeconomic disparities.

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Introduction

Indigenous populations in the USA, Canada, and Greenland have had some of the highest recorded rates of tuberculosis morbidity and mortality. Annual mortality from tuberculosis reached a peak of 9·3% in 1886 in the population of the Qu'Appelle Agency in western Canada.[1] In the 1950s, tuberculosis notification rates ranged between 1500 per 100 000 and 2500 per 100 000 among Inuit populations in Greenland, the Northwest Territories of Canada, and Alaska.[2–5] After implementation of population-based tuberculosis control interventions, including bacillus Calmette-Guérin (BCG) vaccination of infants, active case finding through periodic chest radiography screening, and treatment of latent tuberculosis infection (LTBI), notification rates declined by as much as 15–20% per year.[3,6–8] This decline is commonly referred to as evidence of the effectiveness of tuberculosis control measures.[3,7,8] However, given the known link between tuberculosis and malnutrition,[9,10] general health,[11] and socioeconomic factors,[12,13] this decline could also have been due to the coincident improvements in general health and socioeconomic conditions in these populations.

In the past 25 years, tuberculosis morbidity notification rates have markedly increased among several Indigenous

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Research in context

Evidence before this study

Indigenous populations in the USA, Canada, and Greenland have had some of the highest recorded rates of tuberculosis morbidity and mortality. Introduction of several population-based tuberculosis control interventions was associated with substantial declines in these rates, and cessation of these interventions has been associated with resurgence in these rates over the past 25 years among several of these populations. Although this tuberculosis recrudescence might also be explained by ongoing unfavourable general health and socioeconomic conditions, the causes for this resurgence and the most effective strategies to reverse it are not clear. We did not do a formal literature search before undertaking this study. However, on the basis of available reviews, including the global burden of tuberculosis among Indigenous populations by Tollefson and colleagues (2013), and the burden and causes of poor health among Indigenous peoples by Gracey, Smith, and King (2009), we concluded that there was a paucity of data to indicate whether the recrudescence was due to withdrawal of tuberculosis-specific control interventions or worsening in general health and socioeconomic conditions in these populations.

Added value of this study

In the six Indigenous populations of the USA, Canada, and Greenland considered for this population-based study, we found that annual tuberculosis notification rates declined much more rapidly in the years when the tuberculosis-specific interventions of bacillus Calmette-Guérin (BCG) vaccination in infants and population-based screening and treatment of latent tuberculosis infection were implemented, than in years when they were not. This observation was found in unadjusted analyses and also after accounting for confounding changes in selected health, lifestyle, and socioeconomic status indicators between 1960 and 2014. Although both BCG vaccination of infants and latent tuberculosis treatment have well established individual benefits, this study is, to our knowledge, one of the few to have detected a benefit at the population level. This observation might reflect the intensity of these programmes, which reached a large proportion of the intended populations, often for several successive years.

Implications of all the available evidence

The outcomes of this study suggest that population-based tuberculosis-specific control interventions might have important benefits in groups with a substantial burden of tuberculosis. As such, premature cessation of these interventions might have contributed to the recrudescence of tuberculosis in some Indigenous populations. However, acceptability, feasibility, and cost are major potential barriers to successful re-introduction of these measures. Hence operational research will be needed to develop acceptable and effective interventions, as well as investigative research to define the optimum coverage and duration of these programmes to achieve lasting reductions in tuberculosis incidence in these and similarly at-risk populations.

populations of the USA, Canada, and Greenland.[14–17] It has been speculated that this resurgence in tuberculosis might be explained by unfavourable general health and socioeconomic conditions, or suboptimal tuberculosis control interventions, or a combination of these factors.[18] The WHO strategy to eliminate tuberculosis in high-income countries emphasises the importance of tuberculosis prevention and control in Indigenous populations.[19] However, the most effective strategies to achieve this objective are not clear. We aimed to investigate whether population-based tuberculosis-specific interventions, changes in general health and socioeconomic indicators, or a combination of these factors, were associated with changes in tuberculosis notification rates in six Indigenous populations in the USA, Canada, and Greenland.

Methods

Study design

In this population-based study we examined associations of annual notification rates of all forms of tuberculosis infection, from 1960 to 2014, with changes in selected health and socioeconomic indicators, and with use of tuberculosis-specific interventions among six Indigenous populations in the USA, Canada, and Greenland. Trends in tuberculosis and other health and socioeconomic indicators were also compared with the general population of Canada. The tuberculosis control measures assessed were defined as mass (population-wide) or community-based if offered to the general public, rather than on the basis of individual risk factors such as recent close contact with a person with tuberculosis. The interventions were BCG vaccination administered in infancy; active tuberculosis case finding by use of periodic chest radiography; and tuberculin skin test (TST) screening, followed by chest radiography (to exclude active tuberculosis) for those with a positive TST, and LTBI treatment with adequate regimens, as defined by WHO.[20]

The other health and socioeconomic indicators selected for this analysis represented potential determinants for which we could find adequate, publicly accessible information in all populations (preferably since 1960 and for at least two decades from 1960 to 2014). We examined general health indicators of average life expectancy at birth (for men and women), infant mortality, and suicide rate (mental health indicator); other health indicators of obesity and diabetes; lifestyle habits of cigarette smoking and alcohol use; health system indicators, of total health expenditures or health budgets (ie, not specific to tuberculosis), and number of physicians per 1000 population; socioeconomic indicators of crowded housing, education, and unemployment; a cultural continuity indicator as defined by an Indigenous language spoken at home; and incidence of HIV infection and multidrug-resistant tuberculosis (MDR-TB). Detailed information on health determinants and socioeconomic indicators for each jurisdiction is provided in the appendix (pp 5–21). Initially we considered numerous potential indicators in these categories. However, after extensive searching of all possible data sources and discussions with collaborators working with the six Indigenous populations, some indicators were dropped because the information available was either inadequate or not comparable over time and between populations because of methodological differences (see appendix p 5).

Study populations

The six Indigenous populations considered were located in Greenland (Inuit), the US state of Alaska (American Indian and Alaska Native), the Canadian provinces of Alberta (First Nations) and Quebec (Cree of Eeyou Istchee or Cree Territory of James Bay, and Inuit of Nunavik), and the Canadian territory of Nunavut (Inuit; part of the Northwest Territories before 1999). For comparison, we considered the general population of Canada.[21]

Search strategy and selection criteria

All information was obtained with population-level data that were already published, presented in conference proceedings, or publicly available from census or national, provincial or state, and regional surveys. A structured electronic database search in PubMed, Embase, and Web of Science was done to find indexed papers with keywords of "Indigenous" (or "indigen*"), "tuberc*", "population interventions"; "BCG", "latent tuberculosis", "screening", "case-finding", "radiographic screening", as well as the names of the Indigenous populations, and the names of all covariates. We identified further papers by reviewing references of identified publications. We also searched government websites for information. Additional published or publicly available information and public health reports from local health jurisdictions were identified by collaborating public health practitioners, other health officials, librarians, and investigators working with the six Indigenous populations (collaborators are listed at the end of this Article). All sources and data obtained were verified by co-authors and collaborators. Information about when each tuberculosis control intervention was started and stopped in the selected populations was gathered from regional public health reports and the published literature, and was corroborated by public health officials in each jurisdiction.

Data analysis

We estimated the associations of tuberculosis-specific interventions and general health, lifestyle, and socioeconomic indicators with changes in annual notification rates of all forms of tuberculosis from 1960 to 2014. Given the observed increased incidence of tuberculosis since the late 1980s in the Indigenous populations of Nunavik, Nunavut, and Greenland, these three populations were considered together as recrudescent populations. The other three Indigenous populations of Alberta, Alaska, and Eeyou Istchee were grouped together as non-recrudescent populations, given the continued decline in tuberculosis incidence observed in these populations in the past 25 years.

See Online for appendix

The average annual percentage change and associated 95% CI were calculated for each general health and socioeconomic indicator and the tuberculosis notification rate in each population, from 1960 to 2014. We tested differences for statistical significance, using *t* tests, between the mean values of these indicators in the recrudescent versus non-recrudescent populations, in three time periods: 1960–79, 1980–99, and 2000–14. Data on life expectancy, infant mortality, suicide rate, and number of physicians per population were generally available from 1960 to 2014, allowing analysis of these covariates throughout the study period. The remaining independent variables were available consistently in all populations only from 1980 onwards, and hence could be analysed only from 1980 to 2014.

The association between annual percentage change in tuberculosis notification rates and changes in each of the general health and socioeconomic indicators was estimated by use of mixed-model linear regression with random intercept to account for clustering effects within each population. Regression was done in all six Indigenous populations and in the recrudescent and

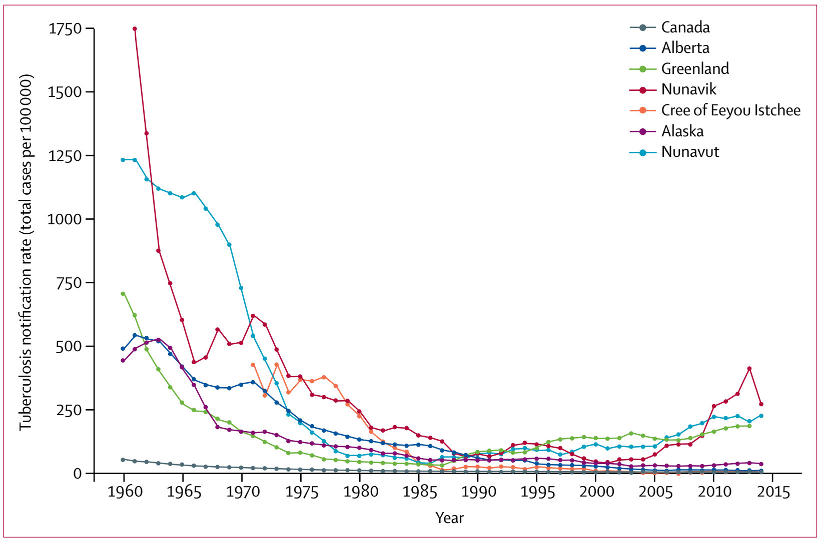

Figure 1: **Tuberculosis notification rates (per 100 000 population) from 1960 to 2014 in six Indigenous populations and the general population of Canada**

	TB incidence per 100 000	HIV incidence per 100 000	MDR-TB incidence per 100 000	Life expectancy, years at birth	Infant mortality per 1000 livebirths
1960–79					
Recrudescent populations	536 (434·9)	..	0 (0·0)	60 (4·8)	75 (42·2)
Non-recrudescent populations	310 (135·5)	..	..	65 (4·4)	40 (14·5)
General population of Canada	26 (13·5)	0·5 (0·7)	..	73 (1·2)	19 (6·1)
p value for recrudescent *vs* non-recrudescent populations*	0·262	..	..	0·021	0·028
p value; general population *vs* non-recrudescent populations†	0·001	..	..	0·006	0·023
1980–99					
Recrudescent populations	90 (40·5)	10 (8·0)	0·0 (0·0)	65 (2·1)	27 (8·1)
Non-recrudescent populations	62 (38·6)	..	0·6 (1·2)	71 (3·2)	16 (4·6)
General population of Canada	8 (1·5)	12 (3·2)	0·0 (0.0)	77 (1·2)	7 (1·5)
p value for recrudescent *vs* non-recrudescent populations*	0·104	..	0·18	<0·0001	0·0005
p value for general population *vs* non-recrudescent populations†	0·004	..	0·299	0·002	0·003
2000–14					
Recrudescent populations	157 (74·3)	4 (5·1)	0·7 (1·0)	69 (3·1)	16 (5·4)
Non-recrudescent populations	18 (12·5)	17 (17·4)	0·4 (0·6)	73 (3·2)	10 (2·2)
General population of Canada	5 (0·4)	7 (0·8)	0·0 (0·0)	80 (0·7)	5 (0·2)
p value for recrudescent *vs* non-recrudescent populations*	<0·0001	0·036	0·636	0·008	0·031
p value for general population *vs* non-recrudescent populations†	0·052	0·405	0·374	0·012	0·002

Data are mean (SD) unless otherwise stated. TB=tuberculosis. MDR-TB=multidrug-resistant tuberculosis. The three Indigenous non-recrudescent populations comprised all registered First Nations in Alberta, the Alaska Native population, and the Cree population of Eeyou Istchee or the Cree territory of James Bay in Quebec. The three Indigenous recrudescent populations were the Inuit populations of Nunavut, Nunavik (Northern Quebec), and Greenland. *Differences between recrudescent and non-recrudescent populations tested for statistical significance by use of *t* tests for normal distribution or Wilcoxon Mann Whitney *U* test if not normally distributed. †Differences between Canadian general population and non-recrudescent populations tested for statistical significance by use of *t* tests for normal distribution or Wilcoxon Mann Whitney *U* test if not normally distributed.

Table 1: **Comparison of three non-recrudescent populations with the three recrudescent populations and the general population of Canada (data available from 1960 onwards)**

non-recrudescent populations separately. The average annual percentage change in the tuberculosis notification rate in years when each of the three tuberculosis specific interventions were used versus when they were not used was compared with *t* tests. Covariates significantly associated with changes in tuberculosis incidence in the univariable analysis (infant mortality, smoking, and diabetes) or associated with tuberculosis incidence in other studies (infant mortality, smoking, diabetes, and overcrowded housing) were included in linear mixed-model regression, with random intercept to account for clustering by population,[22] to estimate the effect of each tuberculosis control intervention on the annual percentage change in tuberculosis notification rates.

Missing values were imputed with Proc MI by fully conditional specification with 20 imputations in SAS version 9.4; this approach uses the values of other determinants to estimate missing values by use of multivariable regression.[23] The average value from the 20 imputations was then used in multivariable analysis to obtain an estimate of the effect of population-based tuberculosis control interventions adjusted for those covariates. Imputed values were used only for adjustment and were not used for estimation of the association of these independent variables with tuberculosis notification rates.

This study was reviewed and approved by the Research Committee of the Cree Board of Health and Social Services of James Bay (Montreal, QC, Canada) and the Ethics Committee of McGill University (Montreal, QC, Canada). For jurisdictions outside Canada, the study was approved by the Scientific Ethics Committee for Greenland, the Alaska Area Institutional Review Board, and the Alaska Native Tribal Health Consortium Research and Ethics Committee.

Role of the funding source

Funding for this project was provided by the Public Health Department of the Cree Board of Health and Social Services of James Bay. McGill University Library supported cost recovery for access to certain data. These funding sources had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

Results

In all six Indigenous populations, tuberculosis notification rates declined substantially from the 1960s to 1980s, but remained higher than rates in the general population of Canada (figure 1). After 1980, tuberculosis notification trends diverged, with continued decline for the First Nations population in Alberta, American Indian and Alaska Native population in Alaska, and Cree of Eeyou Istchee (the non-recrudescent populations), but a resurgence in the Inuit populations of Nunavut, Nunavik, and Greenland (the recrudescent populations; table 1). The proportion of bacteriologically confirmed tuberculosis increased between 1960 and 1980 in all jurisdictions,[2,24] and since 1990 has been 80% for all of Canada,[25] 70–80% in Nunavut,[26] more than 80% in Nunavik,[27–30] 100% in Eeyou Istchee,[28–30] 80–90% in Alaska,[31] 80–90% in adults (>14 years) in Alberta,[24,25] and 50–80% in Greenland[32] (appendix pp 5, 6, 9, 10, 12, 14, 16, 18).

As summarised in the appendix pp2–4, many indicators of general health and socioeconomic status improved over time in all Indigenous populations. Total health expenditures (not tuberculosis-specific) increased substantially for many of these populations, including the recrudescent populations. However, health and socioeconomic disparities have persisted between the different Indigenous populations, and especially between all Indigenous populations and the general population of Canada, including for infant mortality and life expectancy (figures 2A, B). Crowded housing (figure 2C) and cigarette smoking (figure 2D) have also been more prevalent among Indigenous populations than among the general population of Canada for decades. Although educational attainment (appendix p 24) has improved since 1980, unemployment rates have remained high with little improvement (appendix p 23) in Indigenous populations.

Smoking prevalence and educational attainment differed significantly in recrudescent versus non-recrudescent populations, but other indicators such as overcrowded housing, heavy (binge) alcohol use, and number of physicians per 1000 population did not significantly differ, even as tuberculosis incidence diverged between these groups after 1980 (table 2). Diabetes prevalence was higher and increased more in the three non-recrudescent populations than in the recrudescent populations, suggesting that diabetes is unlikely to have had a role in the resurgence of tuberculosis. Excessive alcohol use (binge drinking) was more prevalent in five Indigenous populations than in the general population of Canada (data not available for Greenland), but this difference was not significant between recrudescent and non-recrudescent populations. Limited available data (summarised for each population in the appendix) suggest that use of hard drugs such as opioids or cocaine is not common in recrudescent populations, and is a rare cause of deaths from drug toxicity in the Indigenous populations in this study (with the exception of the First Nations population of Alberta, a non-recrudescent population).[33–36] This observation suggests that use of alcohol or hard drugs is unlikely to have had a major role in the recrudescence of tuberculosis. Incidence of HIV infection in 2000–14 was lower in the recrudescent populations than the non-recrudescent populations (table 1). MDR-TB has been non-existent in Eeyou Istchee, Nunavut, and Nunavik, and is rare among the American Indian and Alaska Native population of Alaska, First Nations of Alberta, and the Inuit population in Greenland (population-specific data not shown; mean values for recrudescent and non-recrudescent populations summarised in table 1). In summary, it seems unlikely that HIV and MDR-TB had any role in the recrudescence, hence these indicators were not considered in further analyses.

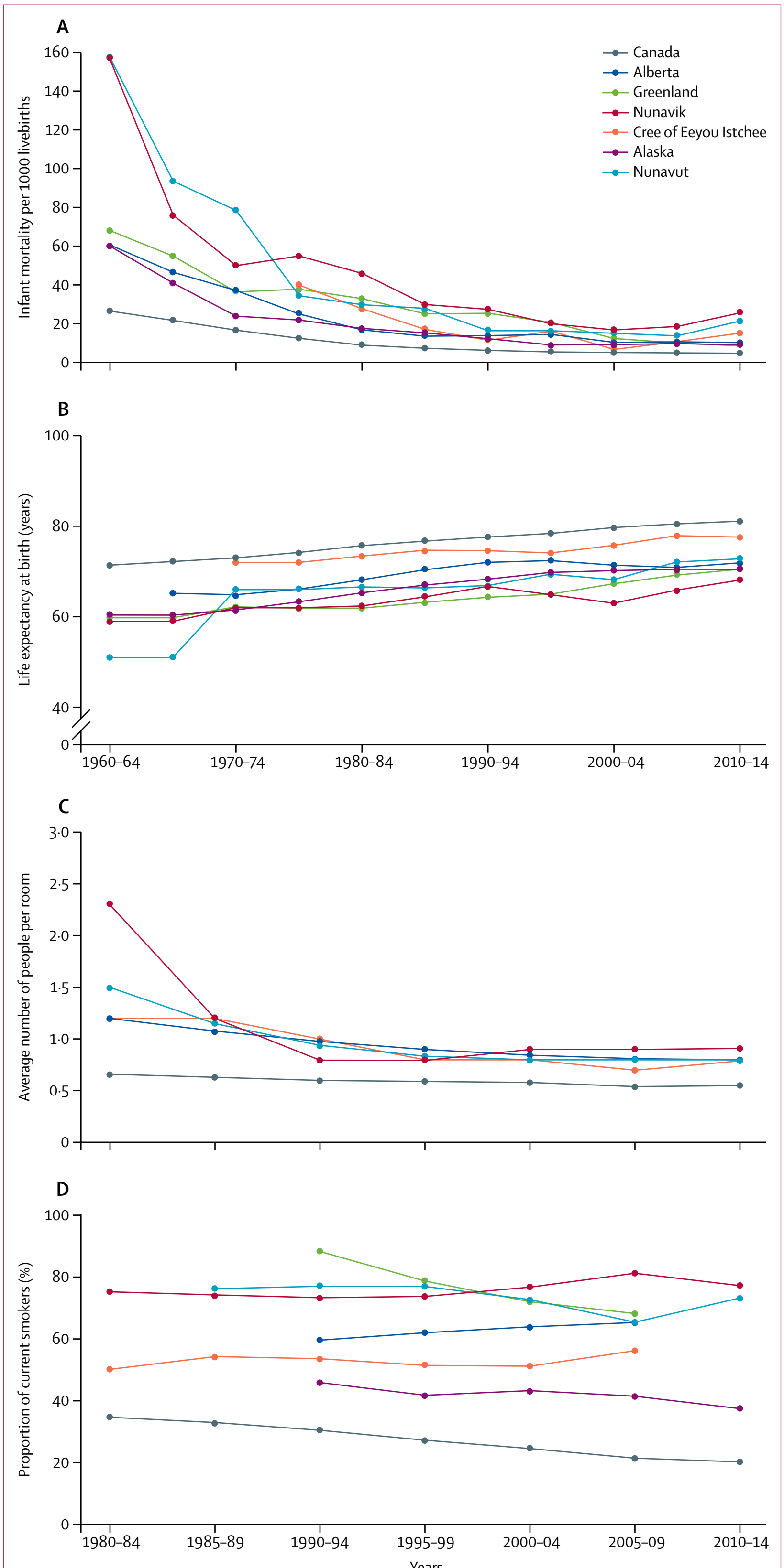

Figure 2: Trends of selected health and socioeconomic indicators in the six Indigenous populations under study
(A) Infant mortality (per 1000 livebirths) from 1960 to 2014 in six Indigenous populations and the general population of Canada. (B) Life expectancy at birth from 1960 to 2014 in six Indigenous populations and the general population of Canada. (C) Overcrowded housing (average number of persons per room) from 1980 to 2014 in five Indigenous populations and the general population of Canada (no data for Alaska). (D) Prevalence of current smokers among adults from 1980 to 2014 in six Indigenous populations and the general population of Canada.

	1980–99					2000–14				
	Recrudescent populations	Non-recrudescent populations	General population of Canada	p value; recrudescent *vs* non-recrudescent*	p value; general *vs* non-recrudescent†	Recrudescent populations	Non-recrudescent populations	General population of Canada	p value; recrudescent *vs* non-recrudescent*	p value; general *vs* non-recrudescent†
Diabetes prevalence	4% (3·3)	9% (2·8)	5% (1·1)	0·036	0·247	6% (3·6)	12% (7·5)	7% (0·9)	0·086	0·435
Obesity prevalence	14% (6·3)	33% (13·1)	13% (1·9)	0·002	0·016	24% (3·5)	41% (15·5)	17% (1·9)	0·002	0·031
Proportion of adults currently smoking	77% (4·5)	52% (6·6)	31% (3·2)	<0·0001	0·0002	72% (5·6)	51% (11·0)	22% (2·2)	0·0003	0·002
Proportion of adults reporting heavy (binge) alcohol use	36% (12·3)	22% (3·6)	16% (3·3)	0·081	0·111	33% (14·3)	28% (9·9)	17% (1·1)	0·519	0·028
Housing; number of persons per room	1·2 (0·5)	1·0 (0·1)	0·4 (0·0)	0·846	0·004	0·8 (0·1)	0·8 (0·1)	0·4 (0·0)	0·455	0·012
Education; proportion of adults who completed high school	22% (11·9)	41% (15·8)	57% (7·2)	0·017	0·073	37% (7·2)	60% (14·1)	77% (7·2)	0·0004	0·080
Proportion of adults unemployed	18% (8·9)	23% (6·2)	9% (1·4)	0·147	0·0009	16% (6·3)	18% (2·5)	7% (0·6)	0·596	<0·0001
Number of physicians per 1000 population	1 (0·4)	1 (0·6)	2 (0·1)	0·869	0·148	1 (0·7)	2 (0·7)	2 (0·1)	0·238	0·613
Proportion speaking native language at home	88% (10·5)	57% (32·5)	..	0·083	..	84% (15·5)	50% (31·4)	..	0·021	..

Data are mean (SD). The three Indigenous non-recrudescent populations comprised all registered First Nations in Alberta, the Alaska Native population, and the Cree population of Eeyou Istchee or the Cree territory of James Bay territory in Quebec. The three Indigenous recrudescent populations were the populations of Nunavut, Nunavik (Northern Quebec), and Greenland. Health budget expenditures could not be combined as data reporting methods and definitions were too different in each population. *Differences between recrudescent and non-recrudescent populations tested for statistical significance by use of *t* tests for normal distribution or Wilcoxon Mann Whitney *U* test if not normally distributed. †Differences between Canadian general population and non-recrudescent populations tested for statistical significance by use of *t* tests for normal distribution or Wilcoxon Mann Whitney *U* test if not normally distributed.

Table 2: **Comparison of the three non-recrudescent populations with the three recrudescent populations and the general population of Canada (data available from 1980 onwards)**

In unadjusted analyses (table 3), we observed that tuberculosis notification rates declined significantly as life expectancy increased and as infant mortality decreased. In all Indigenous populations, each 1-year increase in life expectancy resulted in a fall in tuberculosis notification rates of 37·8 per 100 000, and each decrease in infant mortality of one death per 1000 livebirths decreased tuberculosis notification by nine per 100 000. By contrast, we observed no consistent associations of tuberculosis incidence with the other health and socioeconomic indicators (table 3).

Population coverage of tuberculosis-specific interventions was different for each Indigenous population (appendix). On the basis of available data, at least 80% of infants received BCG vaccination in all programme years in Greenland, Eeyou Istchee, Nunavik, and Nunavut; this coverage was at approximately 50–60% in most years for the First Nations population of Alberta. Limited data indicate that coverage of chest radiography for active case finding was high in all populations during the programme years. The available data indicate that at least 10% of the total Indigenous populations in Nunavut, Eeyou Istchee, and Alaska finished LTBI treatment during the programme years, and at least 10% of the population of Nunavik were offered this treatment during the programme years. These tuberculosis-specific interventions were usually stopped when tuberculosis incidence was perceived to be low, although these decisions were not well documented.[27,37,38]

During the years when each of the population-based tuberculosis-specific interventions were applied, tuberculosis notification rates in the six Indigenous populations decreased significantly more rapidly than in years when interventions were not applied, according to unadjusted analyses (table 4); this decrease did not significantly differ between recrudescent and non-recrudescent populations (table 4). As shown in table 5, when adjusted for infant mortality, or for infant mortality plus smoking or crowded housing, the decline in tuberculosis incidence was 10–11% greater with routine BCG vaccination of infants than without routine BCG vaccination. Similarly, tuberculosis incidence declined by 10% more during years when population based TST screening and LTBI therapy were implemented than in years without mass LTBI therapy. In these adjusted analyses, population-based chest radiography for active case finding was not significantly associated with changes in tuberculosis notification rates.

Discussion

In all six Indigenous populations studied, tuberculosis notification rates were high or very high in the 1960s and declined rapidly in all populations until the 1980s, when population-wide tuberculosis-specific interventions of chest radiography as well as LTBI screening and treatment were largely stopped. Thereafter, trends diverged. The three Inuit populations in Canada and

	Three non-recrudescent populations	Three recrudescent populations	Six Indigenous populations	General population of Canada
Based on data from 1960 to 2014				
Life expectancy at birth, for each increase of 1 year	–32·8 (–36·9 to –28·7)	–39·8 (–45·6 to –34·0)	–37·8 (–41·7 to –33·9)	–3·1 (–3·6 to –2·6)
Infant mortality for each decrease of 1 death per 1000 livebirths	–9·9 (–10·2 to –9·5)	–8·9 (–9·6 to –8·3)	–9·0 (–9·5 to –8·6)	–1·6 (–1·7 to –1·5)
Based on data from 1980 to 2014				
Diabetes prevalence, per 1% increase in prevalence	–1·3 (–1·6 to –1·0)	..*	..*	..*
Obesity prevalence, per 1% increase in prevalence	–2·0 (–2·5 to –1·5)	4·2 (1·6 to 6·7)	–0·3 (–1·6 to 1·1)	–0·6 (–0·8 to –0·4)
Smoking, per 1% increase in adults currently smoking	–0·8 (–1·6 to 0·0)	–2·3 (–5·2 to 0·6)	–2·0 (–4·1 to 0·1)	0·3 (0·3 to 0·3)
Alcohol, per 1% increase in adults reporting binge drinking	0·9 (–0·1 to 1·9)	–6·5 (–10·9 to –2·1)	–5·1 (–7·9 to –2·3)	–0·2 (–0·5 to 0·1)
Housing, per increase by 0·1 persons per room	15·0 (12·6 to 17·5)	–1·2 (–6·9 to 4·6)	3·5 (–0·1 to 7·1)	3·6 (3·2 to 4·0)
Education, per 1% more adults with a high school diploma	–1·5 (–1·8 to –1·2)	1·7 (0·2 to 3·1)	–0·1 (–0·8 to 0·5)	–0·1 (–0·1 to –0·1)
Employment, per 1% increase in unemployed adults	2·4 (1·7 to 3·1)	–1·5 (–3·6 to 0·6)	0·8 (–0·7 to 2·4)	0·6 (0·4 to 0·9)
Per-capita health budget and expenditures per $1000 increase	–6·2 (–8·9 to –3·5)	11·1 (7·5 to 14·8)	5·3 (2·4 to 8·3)	–1·3 (–1·5 to –1·1)
Physicians, per increase of 1 MD per 1000 population	–35·9 (–51·8 to –20·0)	19·4 (–7·3 to 46·1)	3·4 (–24·2 to 31·0)	–11·2 (–13·2 to –9·2)
Native language, per 1% increase in individuals speaking native language at home	–0·2 (–0·4 to –0·0)	–4·4 (–6·7 to –2·1)	–1·8 (–3·1 to –0·5)	NA

Data are annual changes in notification rates per 100 000 population (95% CI). Changes estimated by use of mixed-model linear regression with a random intercept to account for clustering by population. Models with random intercepts and slopes did not converge, so only random intercept models were used. The three non-recrudescent populations comprised all registered First Nations in Alberta, the Alaska Native population, and the Cree population of Eeyou Istchee or the Cree territory of James Bay in Quebec. The three recrudescent populations were the populations of Nunavut, Nunavik (Northern Quebec), and Greenland. The population of Canada refers to the entire population of Canada. Number of missing observations as a percentage of total possible observations (1960–2014): life expectancy, 12%; infant mortality, 6%; (1980–2014); diabetes, 63%; obesity, 31%; smoking, 27%; alcohol consumption, 56%; housing, 32%; education, 20%; employment, 14%; budget, 29%; number of physicians, 20%; language, 29%. *Too many missing observations. Estimates unstable from the regression model. NA=not applicable to the general population.

Table 3: **Estimated changes in tuberculosis notification rate for each unit change in health indicators, habits, and socioeconomic and health-system indicators**

Greenland showed recrudescence, whereas rates continued to decline in the other three Indigenous populations. On the basis of the information amassed in this study, there have been substantial improvements in health and socioeconomic indicators in all six Indigenous populations. However, important disparities remain between the recrudescent and non-recrudescent populations, and between all Indigenous populations and the general population of Canada. In adjusted analyses, and after adjustment for potentially confounding changes in infant mortality, and smoking or overcrowded housing, BCG vaccination of infants and population-based LTBI treatment were associated with significant declines in tuberculosis in the Indigenous populations studied.

We believe this study had several strengths. We included, evaluated, and analysed a wealth of detailed information about tuberculosis notification rates, implementation of tuberculosis-specific interventions, and more than a dozen indicators of general health, lifestyle, health systems, and socioeconomic status gleaned from over 250 sources, for six distinct Indigenous populations for the past three to six decades. This effort enabled analysis of a wide range of factors that could have affected long-term epidemiological trends in tuberculosis in different Indigenous populations.

Nevertheless, these findings should be interpreted with caution, because of the ecological design of this study. This design can result in exposure misclassification—individuals

	Three Indigenous non-recrudescent populations*	Three Indigenous recrudescent populations*	Six Indigenous populations
Routine BCG vaccination in infancy			
BCG administered	–8 (–12 to –3)	–3 (–6 to 0)	–5 (–7 to –2)
BCG not administered	–1 (–5 to 3)	4 (–6 to 13)	0 (–4 to 4)
Population-wide chest x-ray screening			
X-ray screening	–8 (–13 to –3)	–7 (–11 to –4)	–7 (–10 to –4)
No x-ray screening	–3 (–7 to 0)	1 (–3 to 4)	–1 (–4 to 1)
Population-wide isoniazid therapy for latent tuberculosis (with or without TST)			
Population-wide LTBI therapy†	–15 (–25 to –5)	–14 (–20 to –7)	–14 (–20 to –9)
No population-wide LTBI therapy	–3 (–7 to 0)	0 (–3 to 3)	–2 (–4 to 0)

Data are average annual percentage change in notification rates per 100 000 population (95% CI), from univariate ordinary least squares (OLS) model. BCG=bacillus Calmette-Guérin. TST=tuberculin skin test. LTBI=latent tuberculosis infection. *The three Indigenous non-recrudescent populations comprised all registered First Nations in Alberta, the Alaska Native population, and the Cree population of Eeyou Istchee or the Cree territory of James Bay in Quebec. The three Indigenous recrudescent populations were the populations of Nunavut, Nunavik (Northern Quebec), and Greenland. No datapoints are missing in this analysis. The differences in the estimated percentage change in tuberculosis notification rates between the two population groups were tested for significance, by putting the interaction terms for group with each of the independent variables into the model and testing whether the coefficients for the two populations were different. Based on this approach, none of the differences was statistically significant ($p>0·05$). †Population-wide LTBI screening and treatment in this study included TST screening of all persons, regardless of risk factors, followed by chest x-ray examinations of those who were TST positive, followed by isoniazid therapy.

Table 4: **Average annual percentage change in tuberculosis notification rates during years when three tuberculosis-specific interventions were used versus when they were not used**

with tuberculosis might not have had the average values for the health and socioeconomic determinants measured. However, this study design is considered to be appropriate to assess the effect of population-wide tuberculosis control

	Three Indigenous non-recrudescent populations*	Three Indigenous recrudescent populations*	Six Indigenous populations
Univariable analysis			
BCG in infancy (given *vs* not given)	−11 (−18 to −3)	−7 (−14 to 1)	−7 (−12 to −2)
X-ray (screening *vs* no screening)	−4 (−11 to 3)	−8 (−14 to −2)	−6 (−11 to −2)
TST plus isoniazid (mass *vs* individualised)	−12 (−23 to −1)	−14 (−23 to −4)	−13 (−20 to −6)
Multivariable analysis, adjusted for infant mortality			
BCG in infancy (given *vs* not given)	−11 (−19 to −3)	−14 (−21 to −7)	−11 (−16 to −5)
X-ray (screening *vs* no screening)	−8 (−21 to 4)	1 (−7 to 8)	−1 (−7 to 5)
TST plus isoniazid (mass *vs* individualised)	−13 (−25 to −1)	−8 (−18 to 0)	−10 (−18 to −3)
Multivariable analysis, adjusted for infant mortality and smoking†			
BCG in infancy (given *vs* not given)	−11 (−20 to −3)	−13 (−20 to −6)	−11 (−17 to −6)
X-ray (screening *vs* no screening)	−9 (−21 to 4)	2 (−5 to 10)	−1 (−7 to 5)
TST plus isoniazid (mass *vs* individualised)	−15 (−28 to −2)	−12 (−21 to −3)	−10 (−18 to −3)
Multivariable analysis, adjusted for infant mortality and crowded housing‡			
BCG (given *vs* not given)	−8 (−14 to −1)	−13 (−20 to −6)	−10 (−15 to −5)
X-ray (screening *vs* no screening)	−8 (−21 to 4)	5 (−3 to 13)	−1 (−7 to 6)
TST plus isoniazid (mass *vs* individualised)	−14 (−27 to −1)	−9 (−19 to 2)	−10 (−18 to −3)

Data are average annual percentage change in notification rate per 100 000 (95% CI) during the years when interventions were applied versus when they were not applied. Changes estimated by use of mixed-model linear regression with random intercept to account for clustering by population. Models with a random intercept and slope did not converge, so only random intercept models were used. BCG=bacillus Calmette-Guérin. TST=tuberculin skin test. *The differences in the estimated percentage change in tuberculosis notification rates between the two population groups were tested for significance by putting the interaction terms for group with each of the independent variables into the model and testing whether the coefficients for the two populations were different. Based on this approach, none of the estimates for the population groups was significantly different (p>0·05). †For smoking, an average of 67 (32%) missing values were obtained from 20 imputations estimated by use of Proc MI with fully conditional specification, in a model using infant mortality, suicide, education, and diabetes. ‡For crowded housing, 32 (15%) missing values were imputed by use of Proc MI model with life expectancy, suicide, obesity, education, employment, and alcohol. Limited adjustment was possible, since models could include only two parameters at a time. Infant mortality was selected since this parameter was most strongly associated with tuberculosis notification rates. Other parameters were selected on the basis of significant association with tuberculosis notification rate in univariate analysis, or known association with tuberculosis incidence in other published studies (see Methods).

Table 5: **Adjusted effect of tuberculosis control interventions on tuberculosis notification rates, 1960 to 2014**

interventions on population measures of tuberculosis incidence.[39]

There were also important limitations in the data. Certain covariates were measured differently in different populations. To minimise this potential for error, we tried to restrict our analysis to parameters that were defined and measured in similar ways as much as possible. Some data about lifestyle and socioeconomic indicators were missing for certain populations or in certain years. However, the random misclassification due to differences in measurement methods and missing information would be expected to have reduced our ability to detect significant associations and underestimated, if anything, the associations between tuberculosis incidence and indicators of general health, lifestyle, and socioeconomic risk factors.

Another potential concern might be the accuracy of diagnosis of tuberculosis infection, which could have differed in different regions over time. To address this concern, we collected information on bacteriological confirmation of tuberculosis. As detailed in the appendix, the percentage of bacteriologically confirmed tuberculosis increased between 1960 and 1980 in all jurisdictions,[2,24] and since 1990 has been more than 80% in all populations except for Greenland in some years.[2,24–32] Hence, although some of the initial decline from 1960 to 1980 could have been due to more precise diagnostic criteria, it seems unlikely that the resurgence since 1980 can be explained by misdiagnosis or overdiagnosis.

We found that improvements in infant mortality and life expectancy were associated with declining tuberculosis incidence, as has been documented elsewhere in the modern era[11] and in the pre-antibiotic era.[11,40] Yet the recrudescence of tuberculosis among three Inuit populations of Canada and Greenland occurred despite improvements in infant mortality and life expectancy during the same years. We also observed no associations between tuberculosis incidence and overcrowded housing, education, and employment indicators—all of which improved in all six Indigenous populations. HIV and MDR-TB incidence were also unlikely to have had any role in the observed recrudescence. On the basis of the scarce available data, use of hard drugs or alcohol is similarly unlikely to have had a major role. The association of increased prevalence of diabetes with decreased tuberculosis incidence is contrary to published reports of the association of diabetes with tuberculosis[12] but might reflect the protective effect of obesity,[10,41] which was highly correlated with diabetes in this study (data not shown).

In the populations studied, the three tuberculosis control interventions were mostly applied together, making it difficult to ascertain their independent effect. However, in multivariable analysis, BCG vaccination of infants and mass tuberculin screening with treatment of LTBI were significantly associated with decreased tuberculosis incidence. This observation might reflect high population coverage of these resource-intensive programmes in several jurisdictions. For example, of the total population aged younger than 35 years in Eeyou Istchee, 39% were tested for LTBI in 1981, 63% in 1982, and 43% in 1983, with isoniazid provided to all tuberculin reactors by Cree lay health workers, and 57% completing LTBI therapy[42,43] (see the appendix for more detailed information on coverage of these interventions in all jurisdictions). The finding that mass LTBI diagnosis and treatment was associated with significant reductions in tuberculosis incidence could have important implications for other tuberculosis-affected populations beyond Indigenous communities. This finding would support recommendations by WHO for enhanced diagnosis and treatment of LTBI in high-risk populations in low-incidence countries,[19] as well as the importance of LTBI therapy for the WHO END-TB strategy.[44] Our findings contrast with those of a study among mine workers in South Africa, which showed no significant effect of mass LTBI treatment.[45] However, unlike the Indigenous populations of our study, these miners had high prevalence of HIV infection and silicosis, and extraordinarily high rates of tuberculosis transmission—all of which would be expected to severely reduce the benefits of mass LTBI therapy.

In 1986, Grzybowski and Enarson[8] reported that the intensive tuberculosis control programme for the Inuit population of the Northwest Territories in Canada resulted in the fastest rate of decline ever recorded for tuberculosis.[2] However, they observed: "It is admittedly worrisome that the rate of decline of tuberculosis in the Inuit appears to have levelled off during the last few years of the study period. This suggests that the impetus to fight tuberculosis in the [Inuit population of Canada] is waning".[8] 30 years later we believe their concerns were justified, given the resurgence witnessed in three populations following discontinuation of the most intensive aspects of their tuberculosis control programmes.

However, in the other three Indigenous populations, these mass tuberculosis control programmes were discontinued at approximately the same time, yet tuberculosis notification rates continued to decline. The general health status (life expectancy, infant mortality, and suicide rates), and certain lifestyle and socioeconomic indicators (smoking and education) of the three non-recrudescent populations were significantly better than those of the recrudescent populations. This combination of multiple factors could have resulted in increased susceptibility to tuberculosis[10–12] in the recrudescent populations. Because the rates of tuberculosis were higher in the recrudescent populations before 1985, compared with the non-recrudescent populations, this resulted in a larger reservoir in members of the recrudescent populations born before 1985. Therefore, we speculate that the recrudescence of tuberculosis seen in these populations after the reduction in population-wide tuberculosis control interventions might have resulted from the synergistic problems of a large reservoir of LTBI and heightened susceptibility due to overall less favourable general health and certain socioeconomic conditions.

In conclusion, major health disparities continue to exist in the six Indigenous populations studied, in comparison with the general population of Canada. There are also important disparities between the three Indigenous populations that have had a recrudescence of tuberculosis and the three populations that have not. After adjustment for potentially confounding changes in general health and other indicators, two population-wide (mass) tuberculosis-specific interventions were associated with reductions in tuberculosis incidence. Our results emphasise the need to strengthen tuberculosis-specific control interventions in Indigenous populations with continued high incidence while also addressing the persistent underlying health disparities.

Contributors

KD and DM were responsible for the initial study conception and design. KD, ZL, DM, SWM, SW, PLe, JT, ER, BV, DR, MC, AF, WY, GGA, BS, and RL were responsible for data gathering. KD, PLi, MM, AB, and DM were responsible for data analysis. KD prepared the initial draft of manuscript. All authors contributed to critical review of manuscript drafts and reviewed and approved the final manuscript.

Declaration of interests

We declare no competing interests.

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