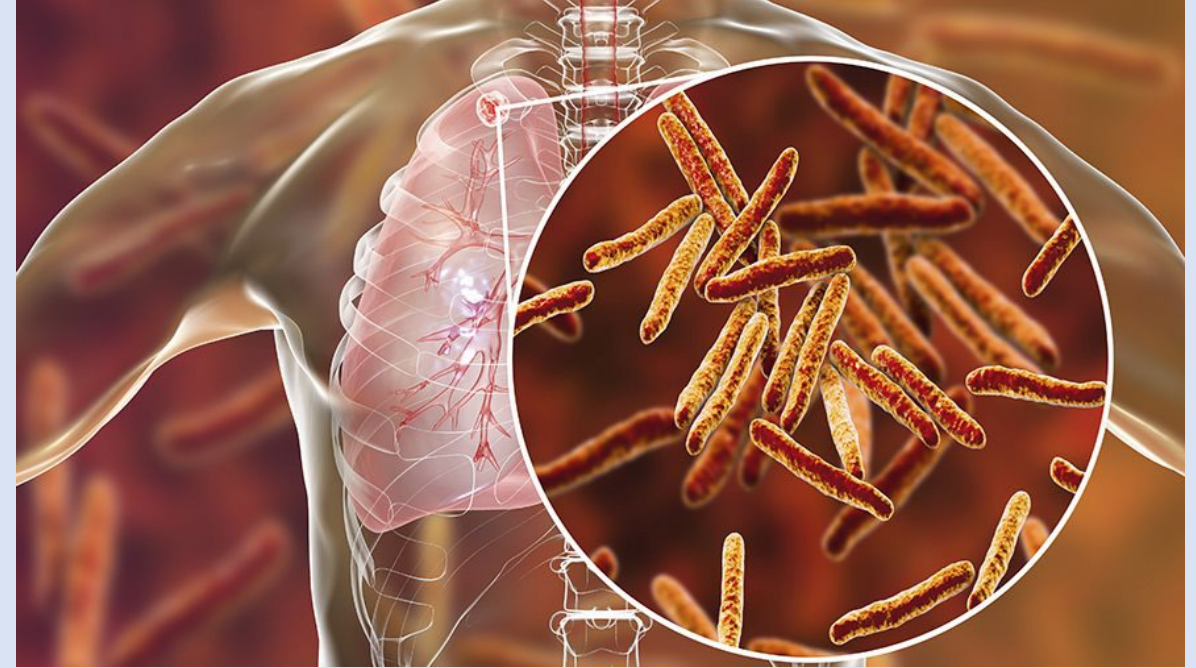
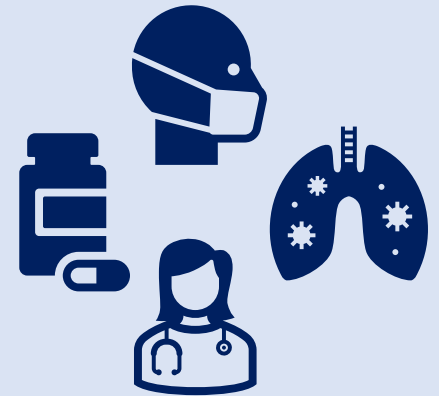


Will Subclinical TB Hinder TB Elimination in North America?



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Learning Objectives

1. Participants will be able to identify how subclinical tuberculosis may impact current approaches to detection and treatment of infection and disease in low-incidence settings.
2. Participants will be able to assess how subclinical tuberculosis may impact elimination efforts within specific populations and epidemiologic settings.

Disclosures

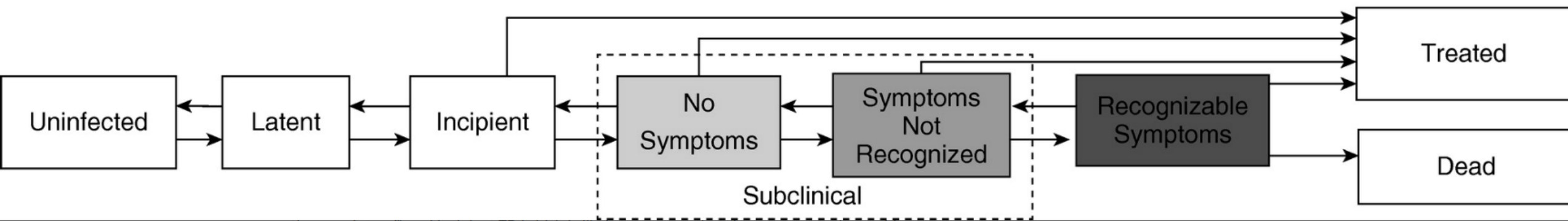
- No direct conflicts of interest related to this talk.
- I receive salary support from the McGill University Health Centre Foundation and McGill Department of Medicine, and research support from the World Health Organization, TDR, and World Bank.
- I am not a clinician. I do not treat tuberculosis. Before stepping up to the microphone after this presentation, please consider this.

What do I mean by North America in this talk?



- 23 countries and over 2 dozen territories in North America with nearly 600 million people.
- My talk will take a limited view and deal only with Canada (primarily) and the USA:
 - 65% of the population
 - 13% of the TB burden
- Really... I will tackle if subclinical TB will hinder elimination in low-incidence settings.

What do I mean by subclinical TB in this talk?



- “Disease due to viable *M. tuberculosis* bacteria that does not cause clinical and/or patient-recognized TB-related symptoms but causes other abnormalities that can be detected using existing radiologic or microbiologic assays”
 - Adapted from: Kendall et al. *AJRCCM* 2021; Drain et al. *Clin Microbiol Rev* 2018.
- Primarily will cover the consequences of subclinical TB on epidemiology and elimination

Outline

- How potentially important is subclinical tuberculosis in USA and Canada?
 - Overview of tuberculosis epidemiology
- Are we doing something wrong?
 - Overview of approaches to diagnosis and treatment of tuberculosis infection and disease
- How bad can it really be?
 - Subclinical tuberculosis and elimination

Potential burden of subclinical tuberculosis may be substantial



1772 notified cases in
2020

TB rate of
4.7 per 100,000



7882 notified cases in
2021

TB rate of
2.4 per 100,000

How many of these cases are subclinical?

- TB prevalence surveys in higher-incidence settings suggest about 50% of all prevalent TB is subclinical (detectable through x-ray).
- The burden of subclinical TB could be as large as the current detected burden of TB in Canada and the USA.

The currently detected burden of subclinical tuberculosis is uncertain

- Tuberculosis case report forms in Canada and USA do not definitively distinguish presence or absence of symptoms.

19. Case finding

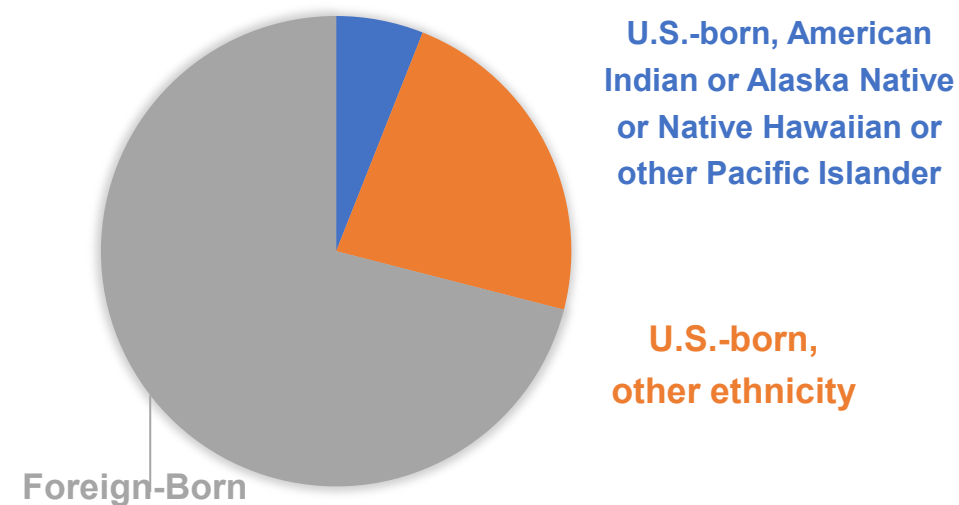
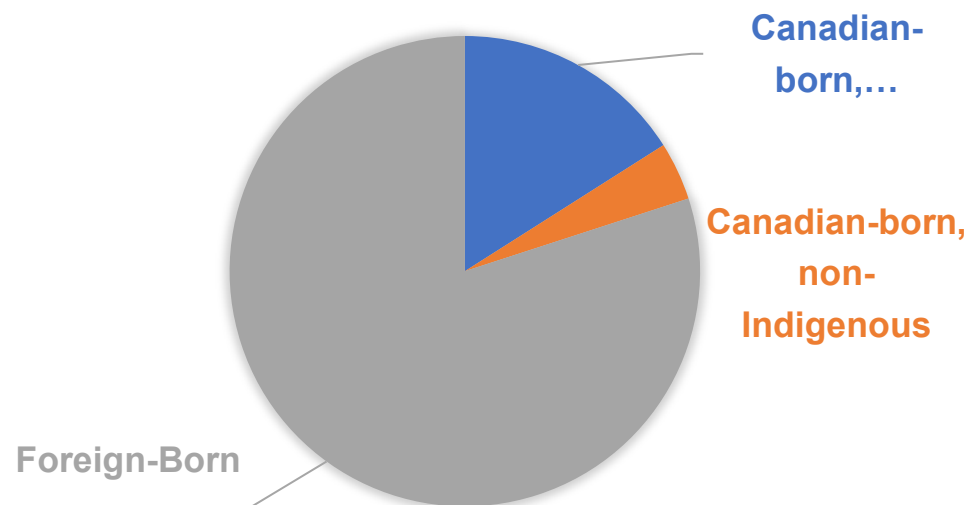
- | | |
|---|---|
| 1 <input type="checkbox"/> Symptoms compatible with site of disease | 2 <input type="checkbox"/> Incidental finding |
| 3 <input type="checkbox"/> Post-mortem | 4 <input type="checkbox"/> Contact investigation |
| 5 <input type="checkbox"/> Immigration medical surveillance | 7 <input type="checkbox"/> Occupational screening |
| 1 <input type="checkbox"/> Initial immigration medical exam done outside Canada | 8 <input type="checkbox"/> Other screening |
| 2 <input type="checkbox"/> Initial immigration medical exam done inside Canada | 9 <input type="checkbox"/> Other (<i>specify</i>) |
| 10 <input type="checkbox"/> Unknown | |

14. Initial Reason Evaluated for TB:

- TB Symptoms
- Screening
- Contact Investigation
- Other
- Unknown

~80% of all cases are flagged with these indicators

The burden of tuberculosis is inequitable



“Drivers” of tuberculosis vary

- The magnitude of local transmission will impact how relevant subclinical tuberculosis is for eventual elimination.

	Foreign-born Persons	Canadian-born, non-Indigenous / U.S.-born	Canadian-born, Indigenous
Proportion of Cases Estimated to be Caused by Recent (Local) Transmission	15% to 40%	30% to 75%	~100%

- Transmission stemming from subclinical tuberculosis may have widely varying impacts depending on population group and other socioeconomic and epidemiological characteristics.

Contribution of local transmission to “detected” tuberculosis burden

Group	TB diagnoses: Canada (2020)	TB diagnoses: USA (2021)
OVERALL DIAGNOSES	1772	7882
Estimated due to local transmission		
Foreign-born persons	196 to 521	818 to 2182
Canadian-born, non-Indigenous / U.S.-born	20 to 51	668 to 1668
Canadian-born, Indigenous	199	--
Total (% of burden)	415 (23%) to 771 (44%)	1486 (20%) to 3850 (49%)

- Approximately one-quarter to one-half of all TB in Canada and USA could be due to local transmission.
- Estimates from high-burden countries suggest 68% (95% prediction interval 27-92) of all transmission is from subclinical TB.
 - Even if less transmissible than clinical disease, people may be infectious **longer**.

So, how potentially important is subclinical tuberculosis?

1

Great deal of uncertainty... but potentially an important driver of the persistence of tuberculosis in certain groups.

2

Surveillance reports do not distinguish specifically “symptomatic” at time of diagnosis versus “asymptomatic”

How much subclinical tuberculosis is being detected at the present is not certain.

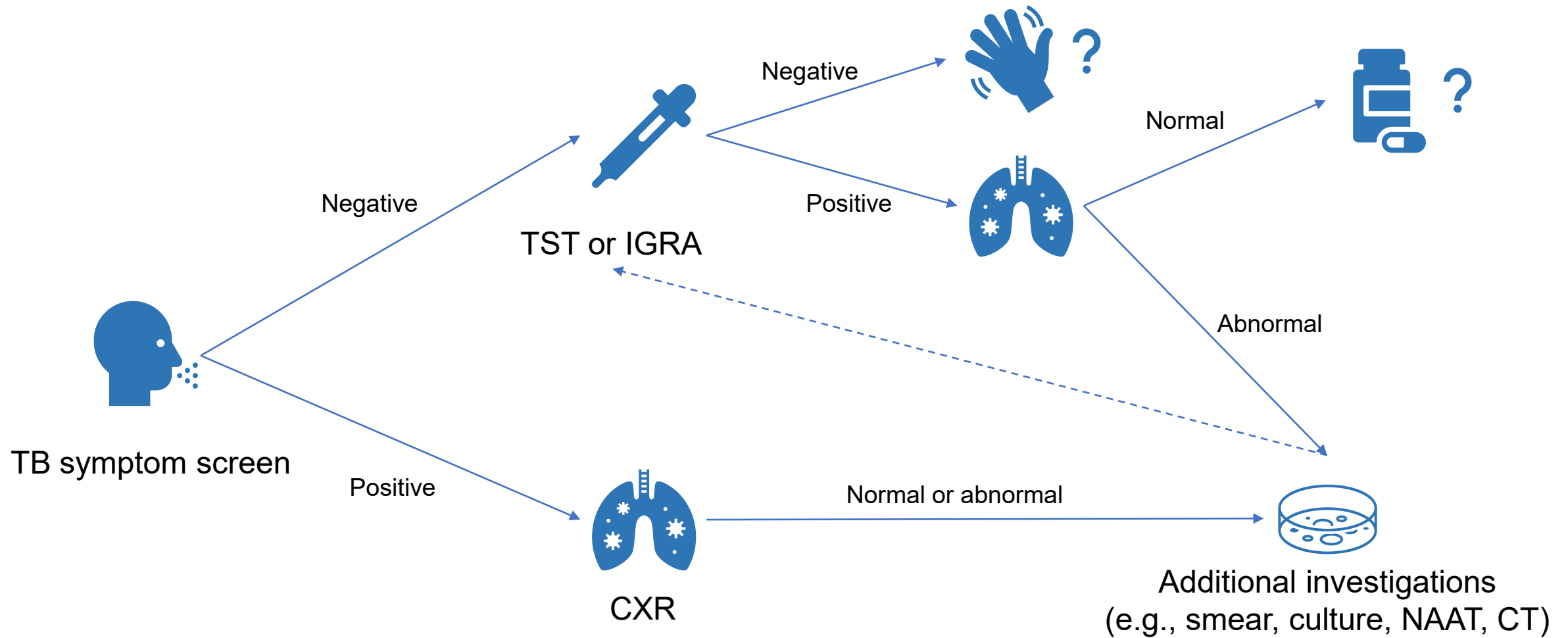
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The burden of tuberculosis may be much higher than what is presently detected if the vast majority of diagnoses occur among symptomatic individuals

4

Though subclinical tuberculosis appears less transmissible, its contribution to overall transmission may be substantial and could be the cause of a proportion of the recent transmission in Canada and the USA

TB assessment during contact investigations



TB assessment during contact investigations

Negative



1. How many people with subclinical TB might be missed due to no symptoms and a negative TST/IGRA?
2. How many people with subclinical TB might be inadvertently treated with tuberculosis preventive treatment?

TB symptoms

Does this matter?



CXR



Additional investigations
(e.g., smear, culture, NAAT, CT)

TB assessment during contact investigations

1

TST and IGRA are reasonably sensitive for disease and a positive test triggers additional investigations to rule out disease prior to tuberculosis preventive treatment.

- Impact uncertain; likely minimal, but greater among immunocompromised.

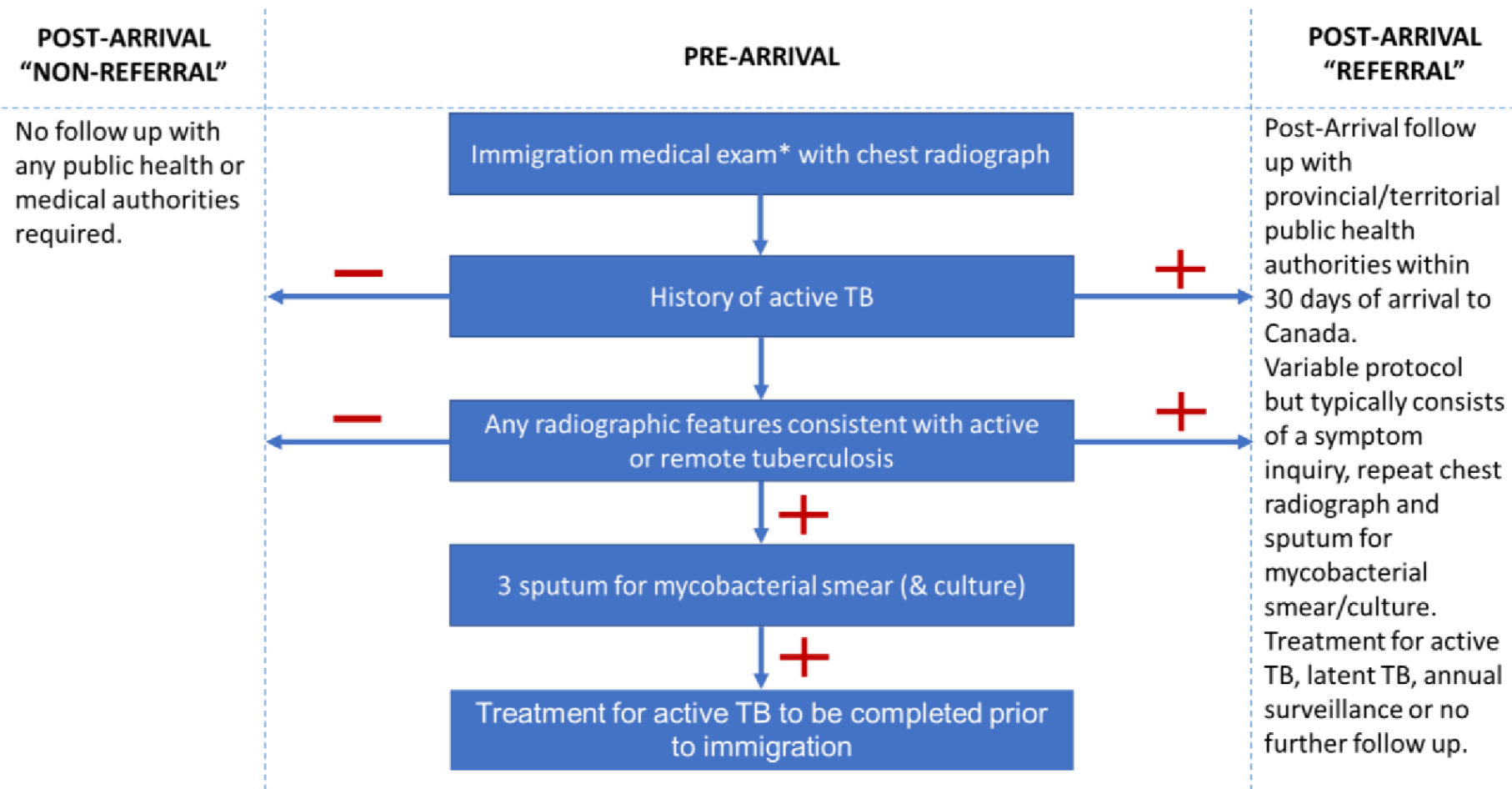
2

Inappropriate treatment of disease might have consequences in terms of drug-resistance, disease progression, and treatment failure.

- No evidence to suggest individuals initiating TPT after ruling out disease with symptoms, plain chest radiograph, and spontaneous sputum develop drug-resistant disease
- In Alberta, ~20% of people with subclinical TB had a normal chest radiograph. Of the 12 people who also received a CT scan, disease was moderate-advanced in only 1 (8%).
- Minimal disease on radiography prior to TPT might be missed in routine practice, but is only ever “recognized” if the patient later presents with disease. How many others are missed and “cured”? **Is TPT largely sufficient for this group?**
- Impact uncertain, but likely minimal.

TB assessment during immigration

In the USA...
your "Class B" referrals



*This examination consists of a medical history, functional inquiry, physical examination, and four age related routine tests: urinalysis, chest radiograph, syphilis serology, and HIV serology.

TB assessment during immigration

Referred for post-arrival surveillance

Approximately 2-3% of new immigrants are requested for post-arrival follow-up and adherence is ~60-70%.

TB rate among those adhering vs. not adhering with surveillance is identical (2 year incidence ~0.7%)

- However... ~75% of TB among those adhering with medical surveillance is subclinical. **How much subclinical TB is being missed among those not adhering with post-arrival surveillance is unclear.**

Not referred for post-arrival surveillance

Comprises 97-98% of new immigrants and 80% of all TB disease (Incidence within 2y of arrival: 0.05%).

In Alberta, 20% of people developing TB in this group were subclinical at diagnosis, but 60% had substantial changes in radiological findings compared to their pre-immigration chest radiograph.

- **A potentially important fraction of disease could have passed through a detectable, subclinical phase.**
- Pre-immigration medicals are good for one-year and subclinical TB may have developed in this timeframe

Subclinical tuberculosis is prevalent in high-risk communities

- The addition of chest radiography to active case finding in outbreaks and/or high-risk communities (people experiencing houselessness, people deprived of liberty, Indigenous communities) is critical to detect TB disease

Study	TB Cases Detected	% Subclinical
People Experiencing Houselessness		
Barry, 1986	3	100%
Capewell, 1986	68	62%
Lau, 1997	9	22%
People Deprived of Liberty		
Pelissari, 2018	181	51%
Bock, 1998	52	74%
Indigenous Communities		
Dion, 2018	3	100%
Uppal, 2021	49	27%

Subclinical tuberculosis may be contributing to the persistence of tuberculosis in Indigenous communities

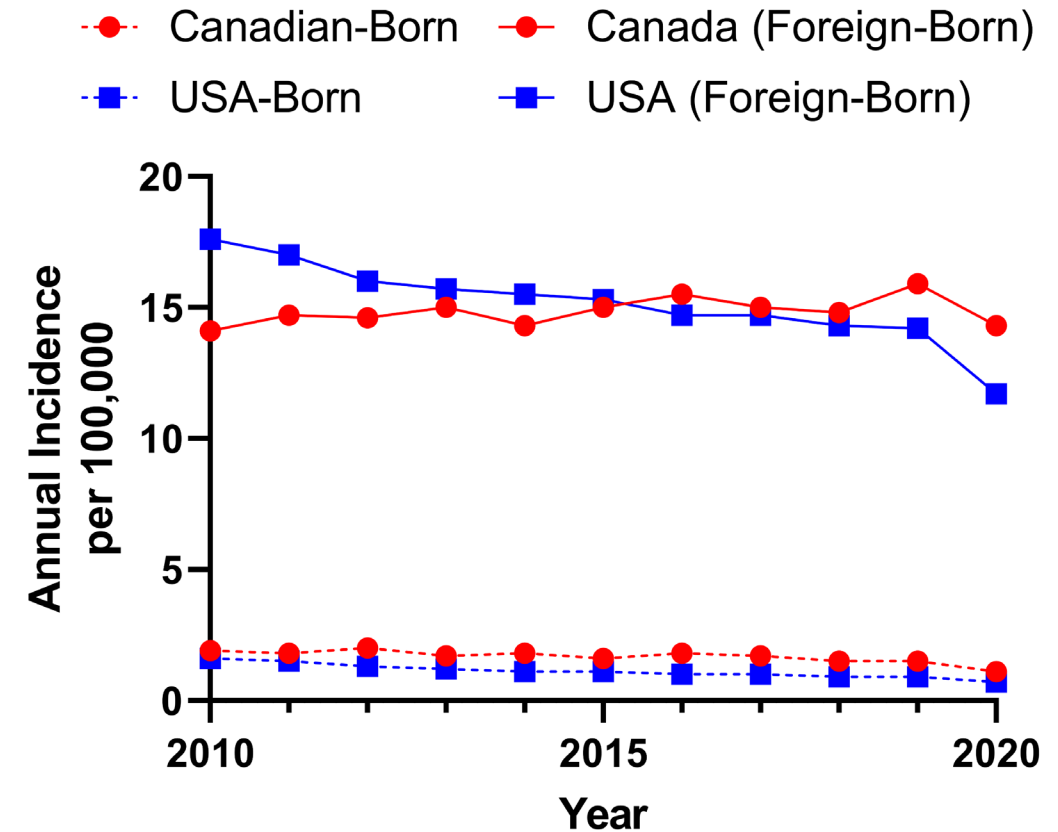
Outbreaks in Nunavut communities: Qikiqtarjuaq (2016-2018); Pangnirtung (2021-present).

- Qikiqtarjuaq—community of 600 people—outbreak contributed to a doubling of the number of people diagnosed with TB in Nunavut between 2016 and 2017.
 - By end of 2017, 10% of the community had been diagnosed with TB disease or infection.
 - Effort undertaken to screen all people in the community: mass screening clinic (symptoms, x-ray, Xpert, TST/IGRA) set up in February 2018.
 - Impact under evaluation, but this effort—which would detect subclinical tuberculosis—appears to have been critical in ending the outbreak.
- Pangnirtung—community of 1500 people—outbreak declared November 2021.
 - January 2021 to November 2022: 37 people diagnosed with TB disease; 147 with TB infection

Is subclinical tuberculosis an important factor in this outbreak?

Subclinical tuberculosis is unlikely a major driver of tuberculosis disease in persons born outside Canada and the USA

- A minority of TB is due to local transmission
- Tuberculosis among people born outside Canada and the USA is largely driven by progression of infection acquired prior to immigration.
- People born outside Canada have lower rates of respiratory (infectious) disease (67.4% vs. 84.6% Canadian-born)
- Effort is (probably?) better placed elsewhere (e.g., prevention, improving care and interrupting transmission abroad)



We can improve detection of subclinical tuberculosis

- In persons at high-risk for tuberculosis (e.g., prolonged close contact with smear-positive TB patient), additional evaluations (sputum collection, CT scan) can be done to improve detection.
- In persons with extrapulmonary TB in close proximity to the respiratory tract (e.g., cervical lymph node TB), subclinical TB is not uncommon (~20% in Alberta) and may present with no lung abnormalities on chest radiography (~50%).
- Active case finding (and development of infrastructure and human resource capacity to support it) with chest radiography among high-risk communities/groups, particularly during outbreaks, can improve detection.
- Scaling testing and treatment for tuberculosis infection (e.g., among persons born outside of Canada/USA) would also contribute to improving detection of subclinical tuberculosis, as it is likely to be identified in work-ups prior to TPT initiation (and TPT may be sufficient for many subclinical cases that are missed).

Is subclinical tuberculosis hindering elimination?

- There have been strong advances towards elimination from 2010-2019 in most population groups using current strategies for prevention and care.

Foreign-born Persons (Canada)	Foreign-born Persons (USA)	Canadian-born, non-Indigenous	U.S.-born	Canadian-born, Indigenous
↑5%	↓19%	↓43%	↓44%	↓20%

- Subclinical tuberculosis may be contributing to the persistence of tuberculosis in some populations—either directly or indirectly—but it is not preventing advances towards elimination.
- There are gaps in our current strategies for tuberculosis prevention and care where subclinical tuberculosis may be missed, but their impact on overall epidemiology is uncertain.
- Subclinical tuberculosis may become increasingly relevant as we approach elimination.

Acknowledgments

The clinical “experts” consulted (and whom we all should hold accountable for any errors)



THANK YOU

