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Genomic Epidemiology of Tuberculosis in Ontario (2023–2025)

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PHO Microbiology Rounds

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Disclosure

The author has no conflicts of interest to declare.

Learning Objectives

By the end of this session, participants will be able to:

- Describe the role of genomic epidemiology in TB surveillance
- Recognize TB genomic epidemiology trends in Ontario
- Explain the genomic analysis pipeline for WGS data and its use in public health surveillance of MTB

Outline

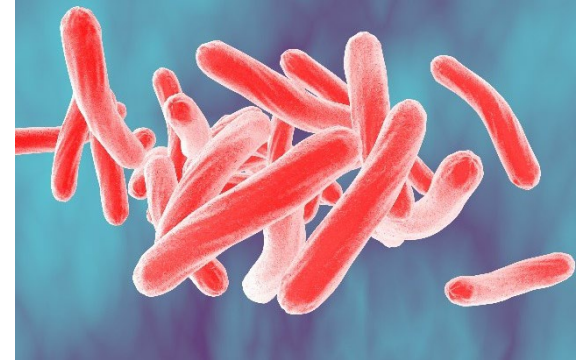
- TB epidemiological trends in Canada and Ontario
- Overview of the research-use bioinformatics pipeline for TB whole genome sequencing (WGS) data
- Genomic insights from 2023–2025 surveillance
- Transmission and drug resistance patterns

Tuberculosis in Canada

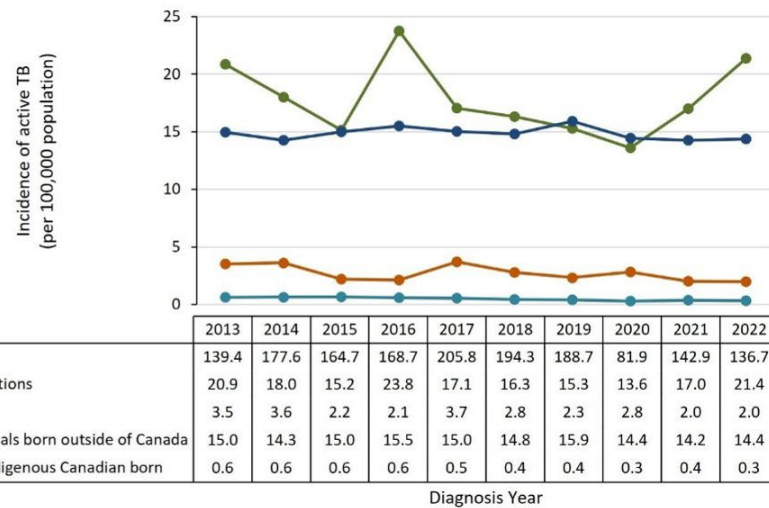
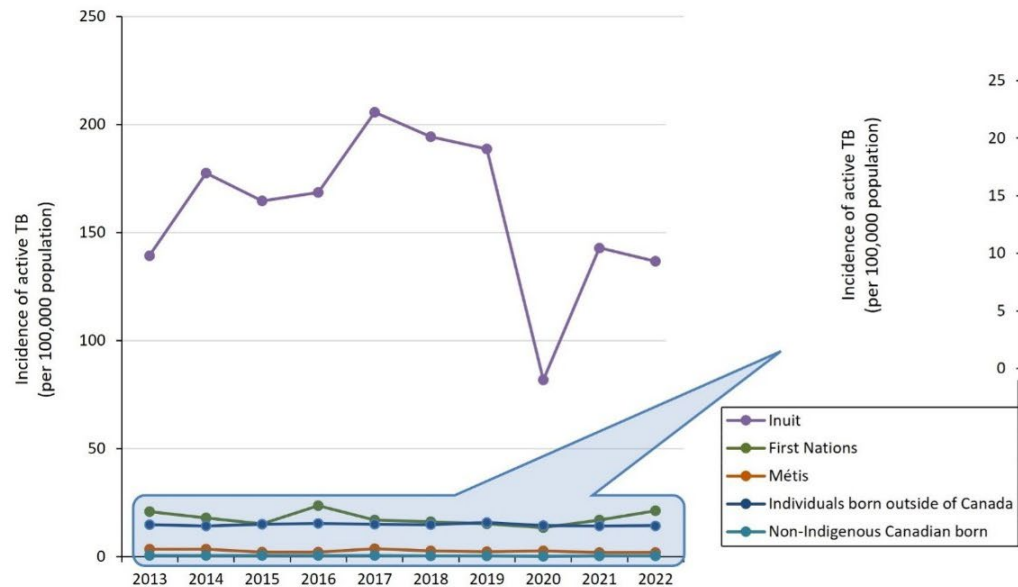
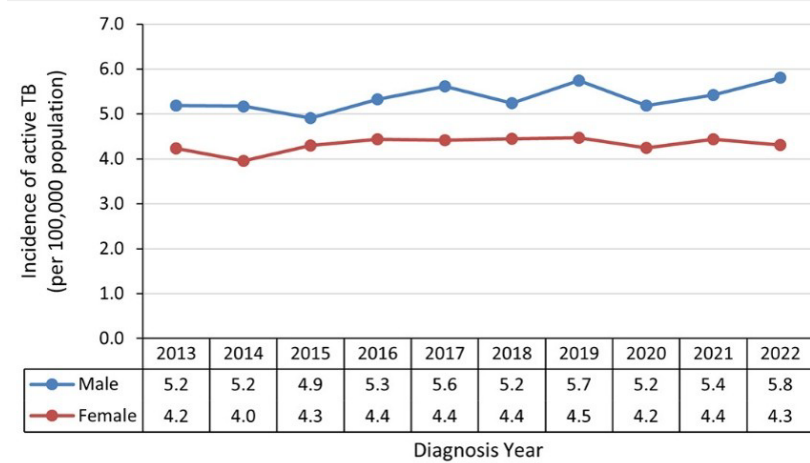
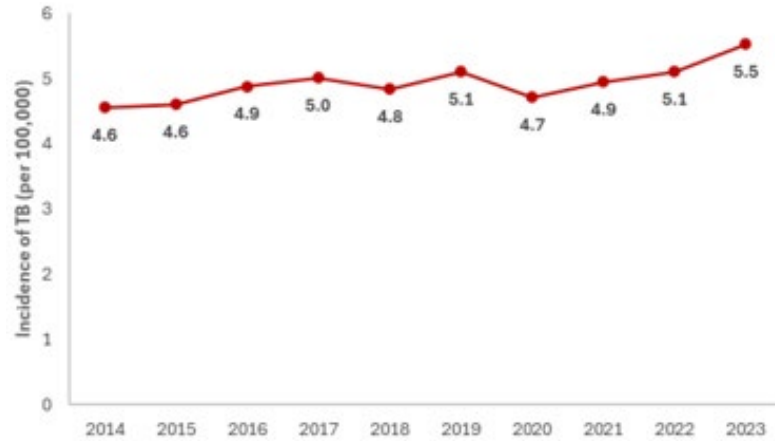
- Tuberculosis (TB) is an airborne respiratory disease, caused by bacterial pathogen *Mycobacterium tuberculosis* complex (MTBC)
- In Canada, TB incidence remains low overall but disproportionately affects specific populations
- Lineage 1-4 are the major lineages circulating in Canada
- Canada has committed to the WHO End TB Strategy, aiming to eliminate TB by 2035

The Role of WGS in TB Surveillance ^{1,2}

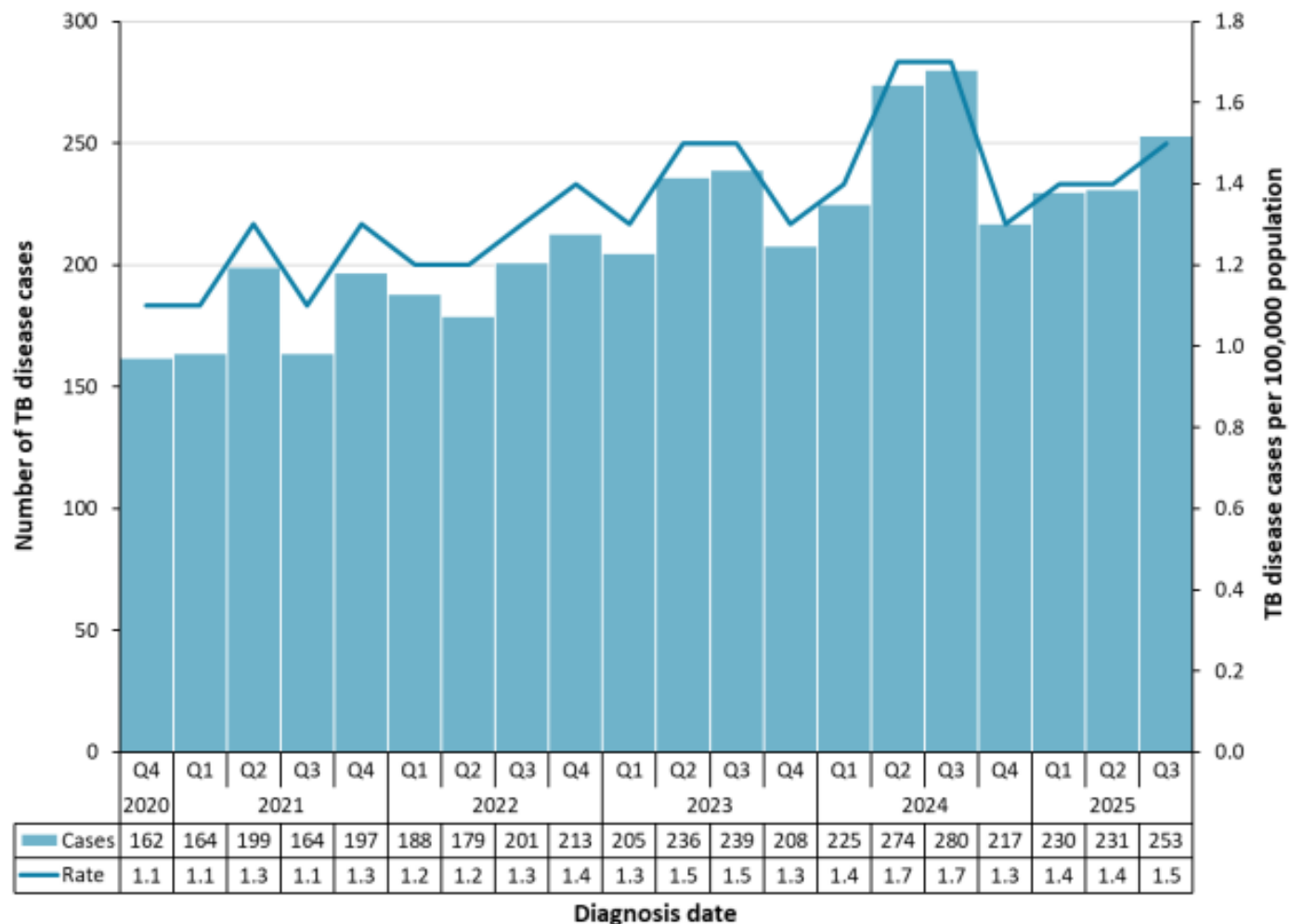
- Whole genome sequencing (WGS) of MTBC cases from Ontario is routinely sequenced at PHO for public health surveillance
- WGS enables identification of recent transmission events and prediction of drug resistance. Epidemiological data confirms who, where, and when transmission occurred
- Genomic Epidemiology integrates epidemiological and WGS data, further enhances TB surveillance and control



Tuberculosis in Canada ^{3,4}



TB in Ontario ⁵



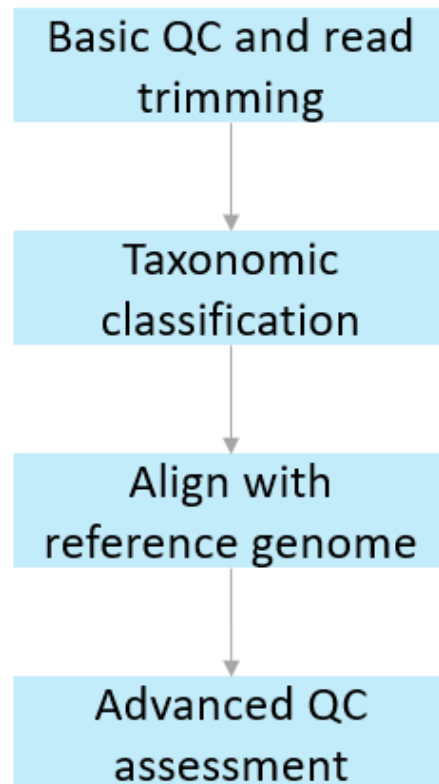
TB Disease Cases and Rates Per 100,000 Population by Diagnosis Date: October 1, 2020, to September 30, 2025



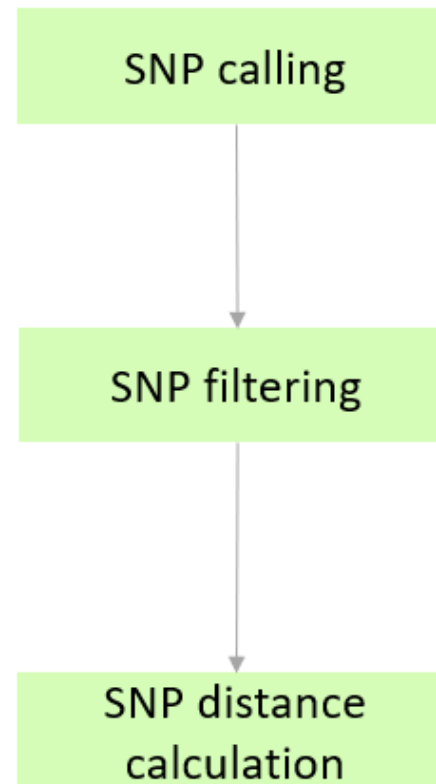
Genomic Epidemiology of Tuberculosis in 2023-2025

Bioinformatics analysis pipeline

Data Processing



Variant Analysis

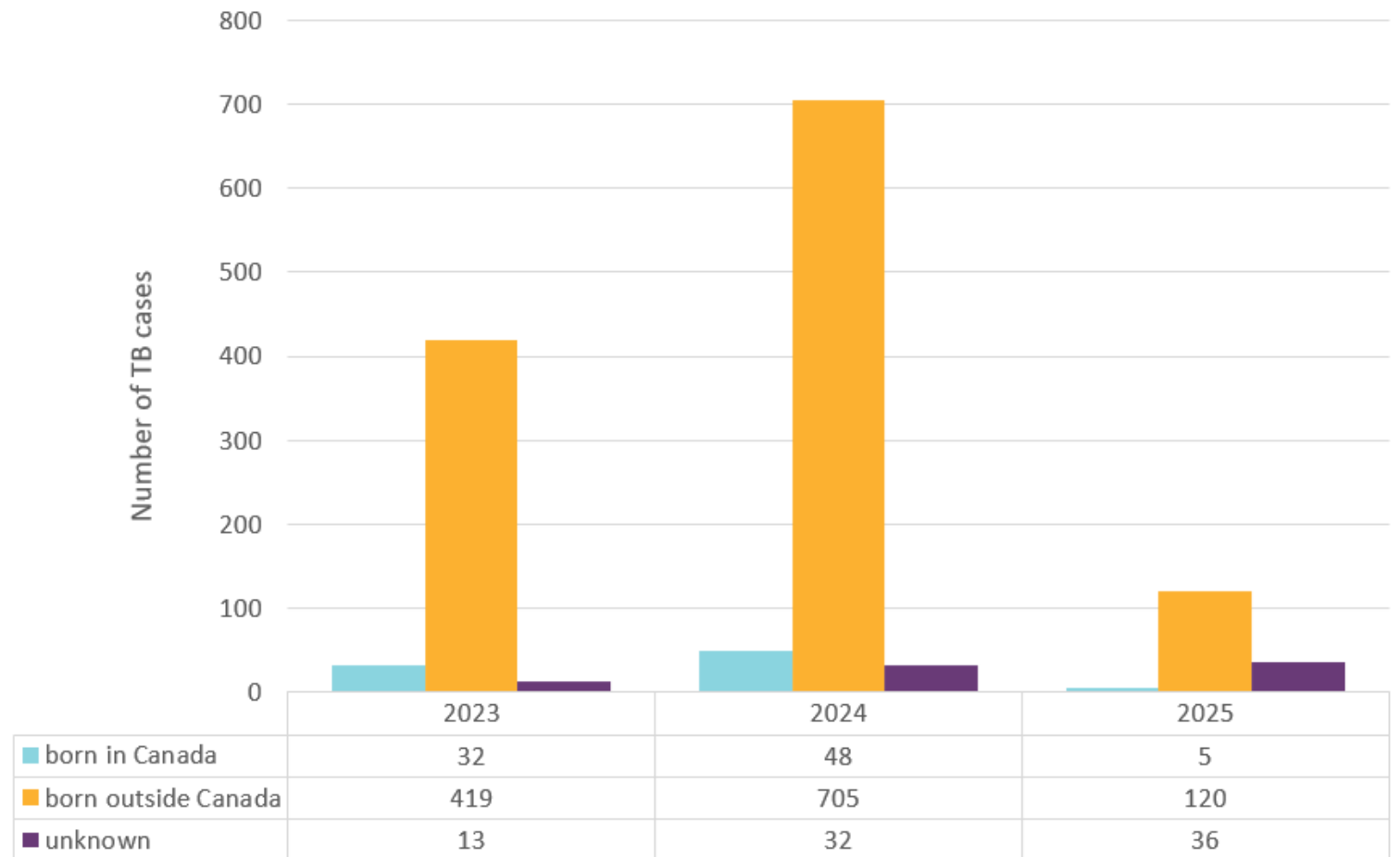


Outputs

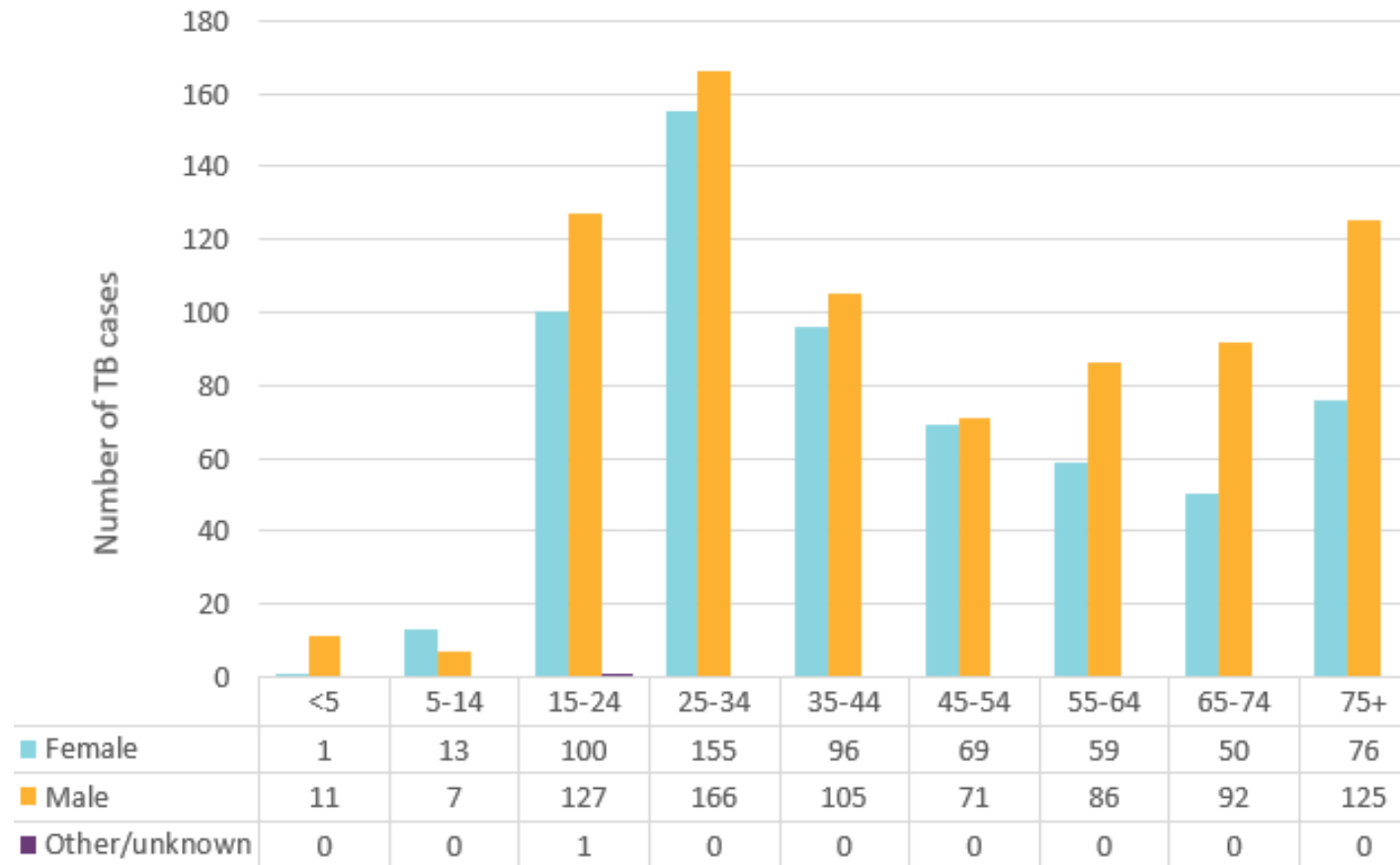


TB cases by year and immigration status

- Dataset
 - 2023-01-03 to 2025-03-31
 - N = 1,410
- TB cases are primarily among individuals born outside Canada (88.23%)



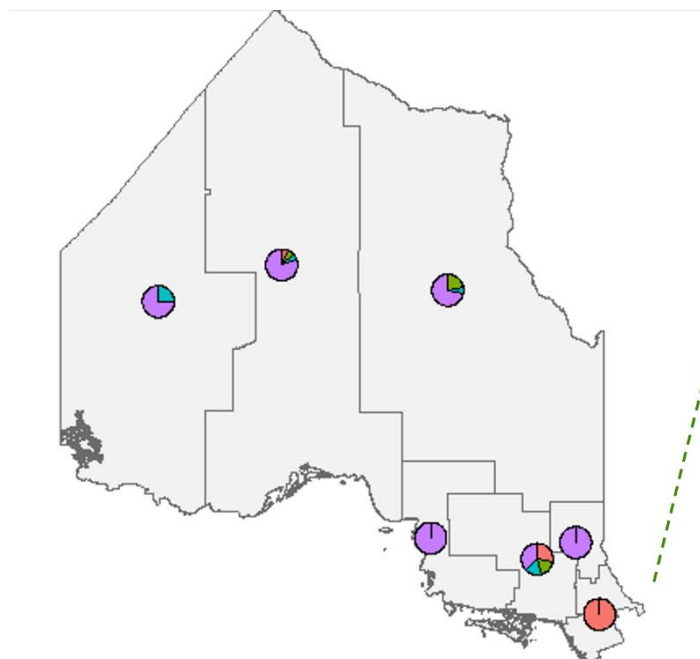
TB cases by age groups and sex



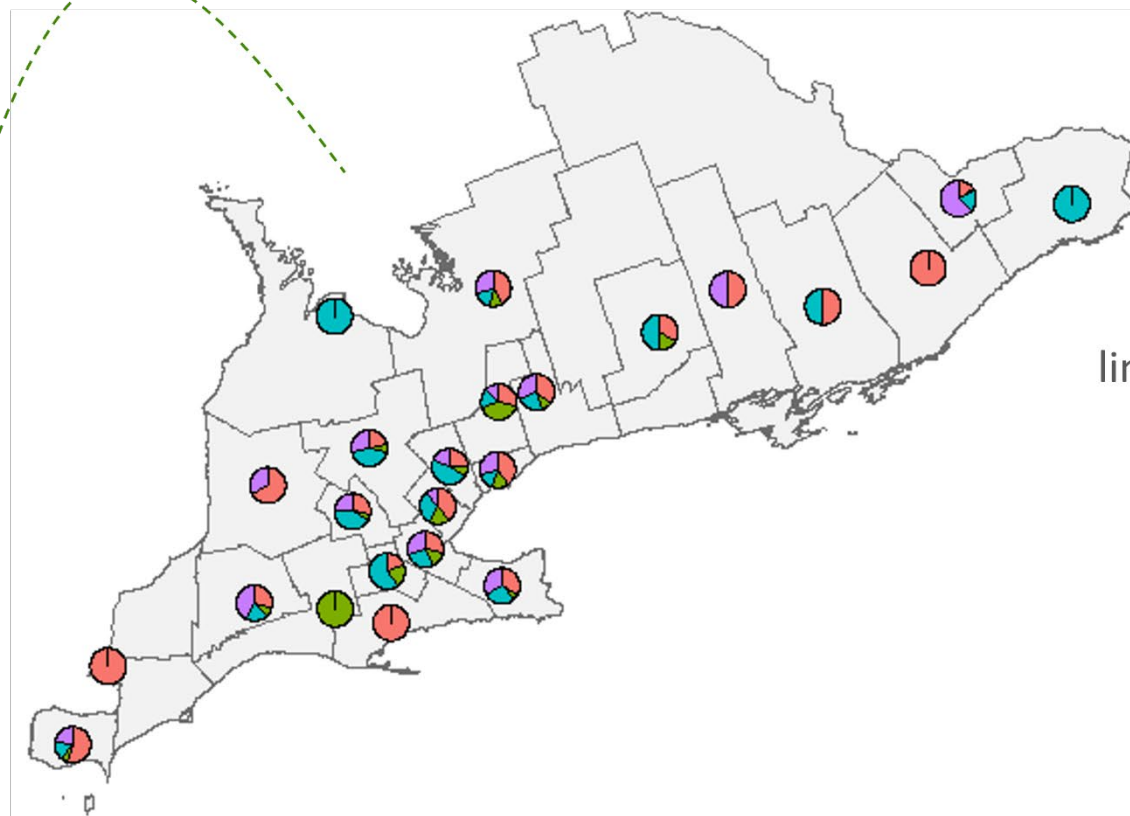
TB incidence is highest in 25–34 age group. Males (56.10%) are more affected than females (43.90%).

TB lineage distribution varies across Ontario

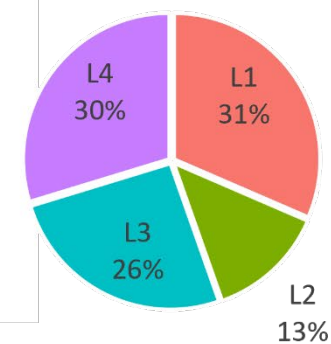
Northern Ontario



Southern Ontario

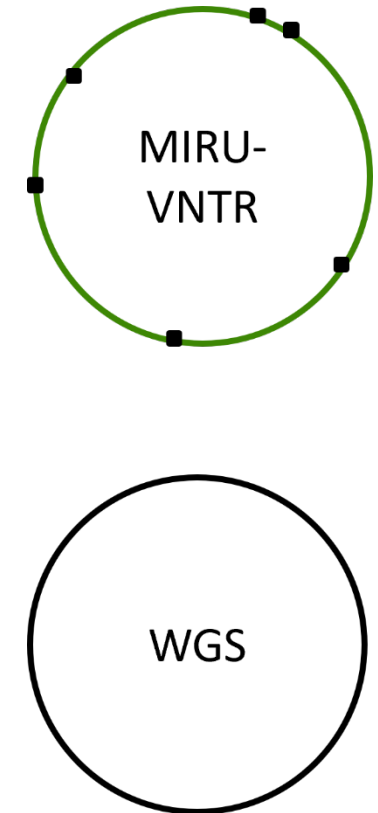


lineage distribution of all samples



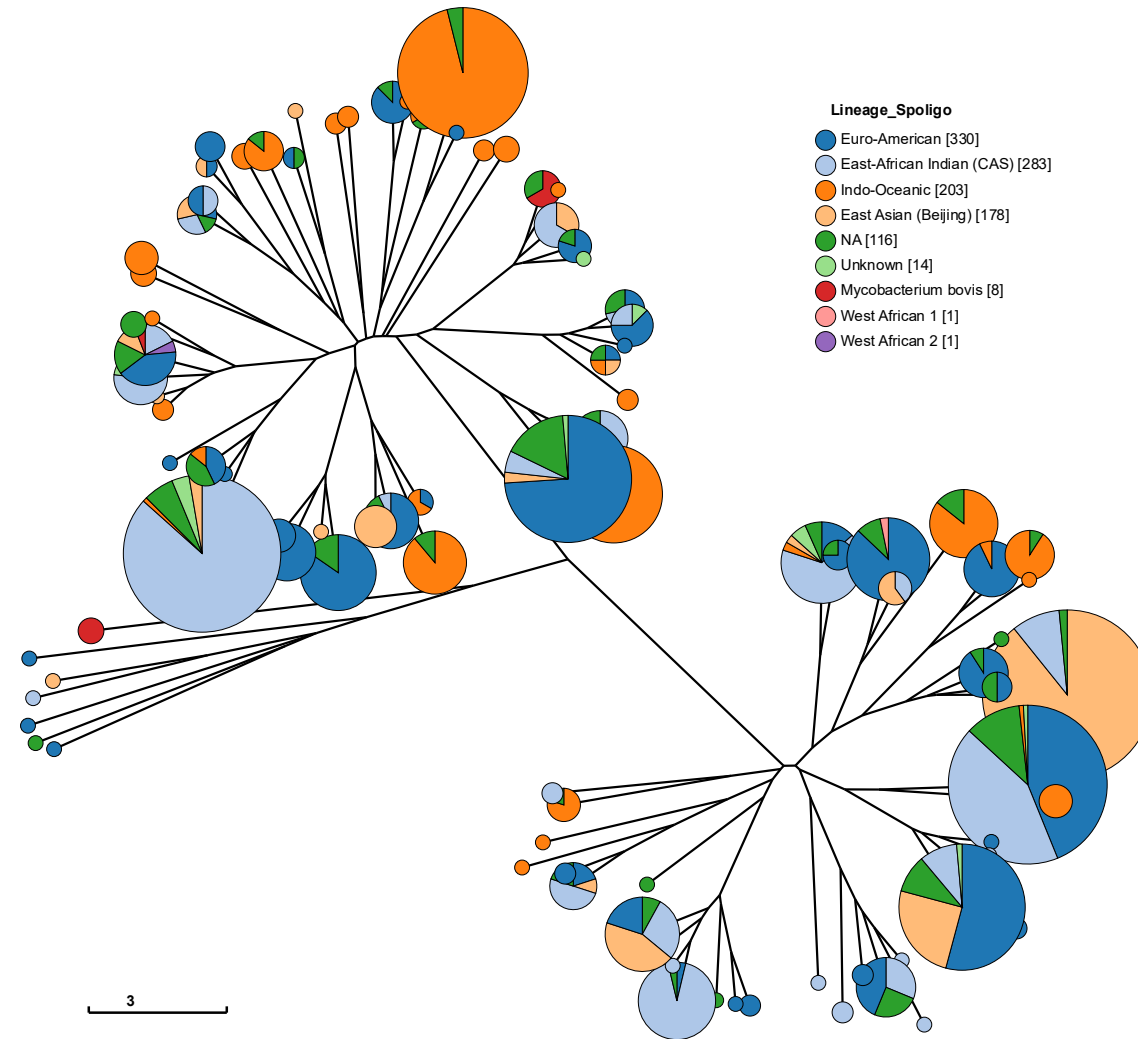
Improving TB clusters identification using WGS

- Identifying recent transmission is critical for TB control and outbreak response
- Traditional genotyping methods group isolates based on limited loci
 - Mycobacterial interspersed repetitive units-variable number of tandem repeat (MIRU-VNTR) typing is a genotyping method to determine MTBC relatedness that analyzes variation across 24 genomic loci
- Traditional genotyping methods have lower genetic resolution leading to larger cluster size
- WGS uses genome-wide genetic variation to identify closely-related strains with higher precision



Note: Graph is conceptual illustration and does not reflect actual genome positions

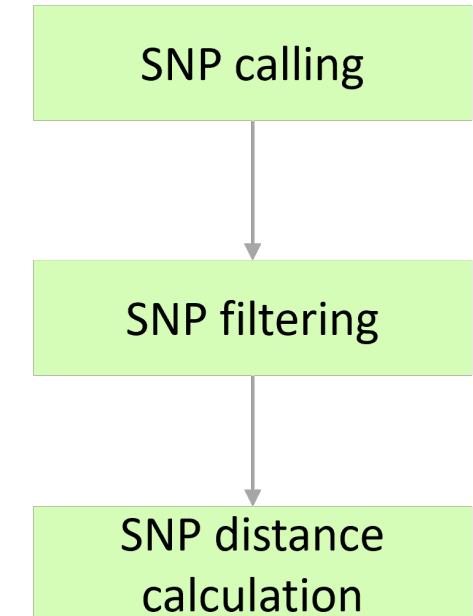
Identifying TB clusters by genotyping



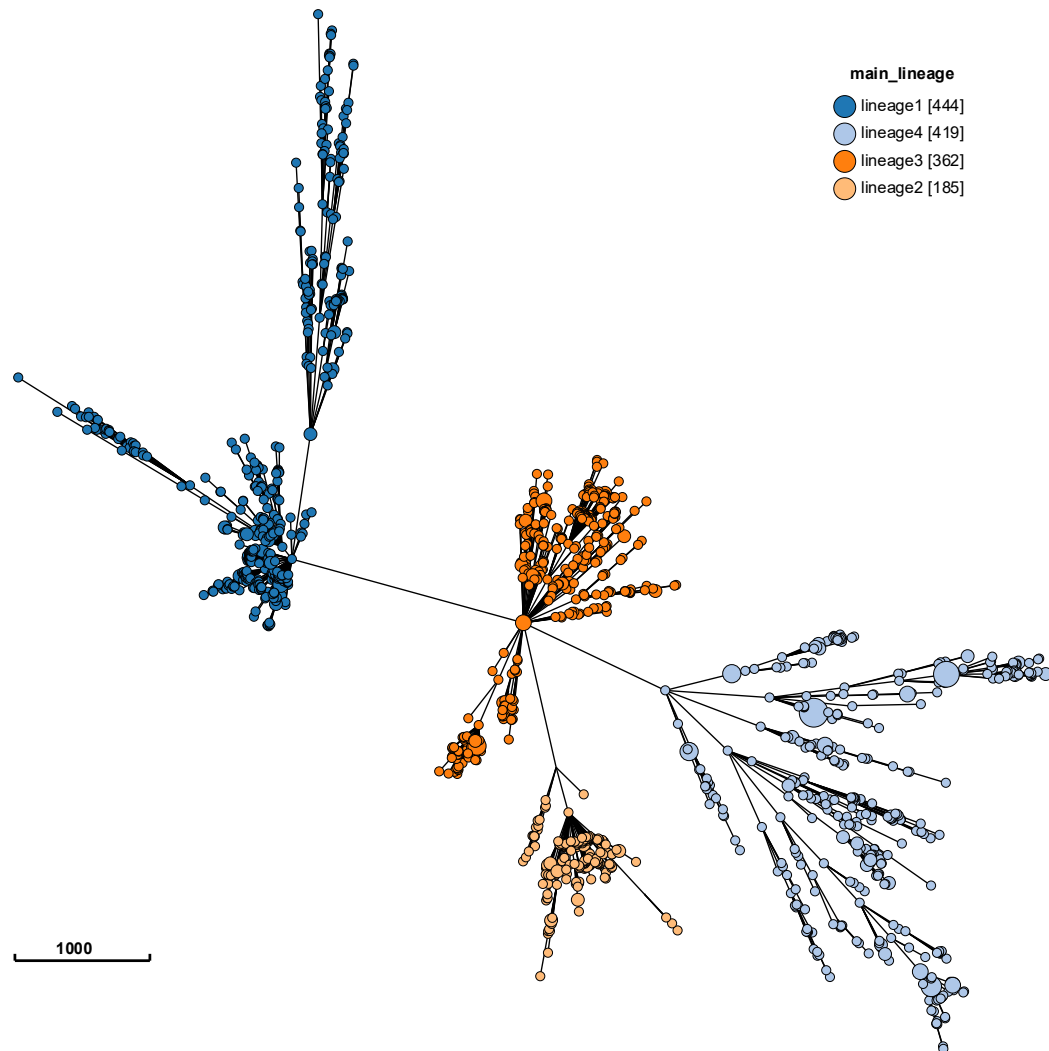
Identifying TB clusters using WGS

- Single nucleotide polymorphisms (SNPs) is a substitution of a single nucleotide at a specific position in the genome
- When we sequence a MTBC isolate, we compare its genome to a reference genome, identify positions where they differ, and each difference is a SNP
- Genome-wide SNPs help us measure how closely related strains are (transmission analysis), and detect mutations associated with drug resistance

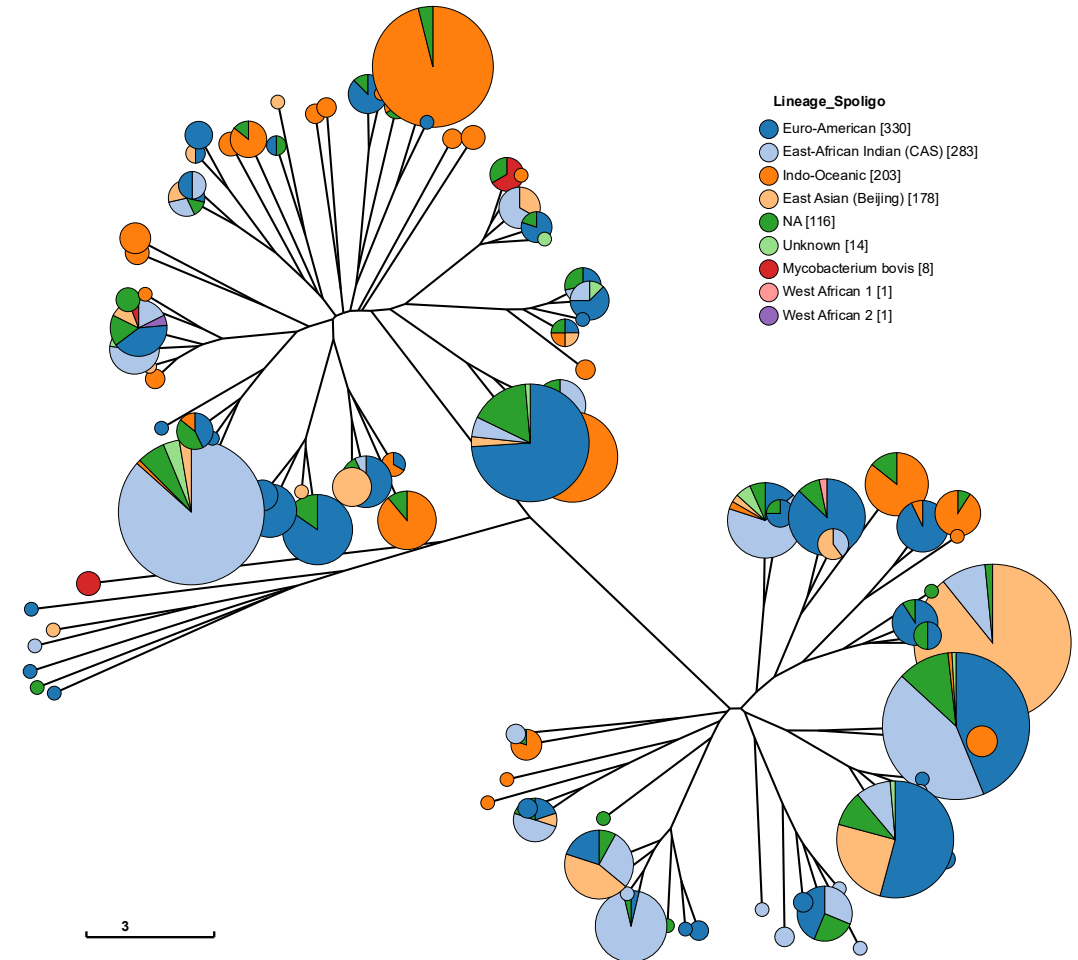
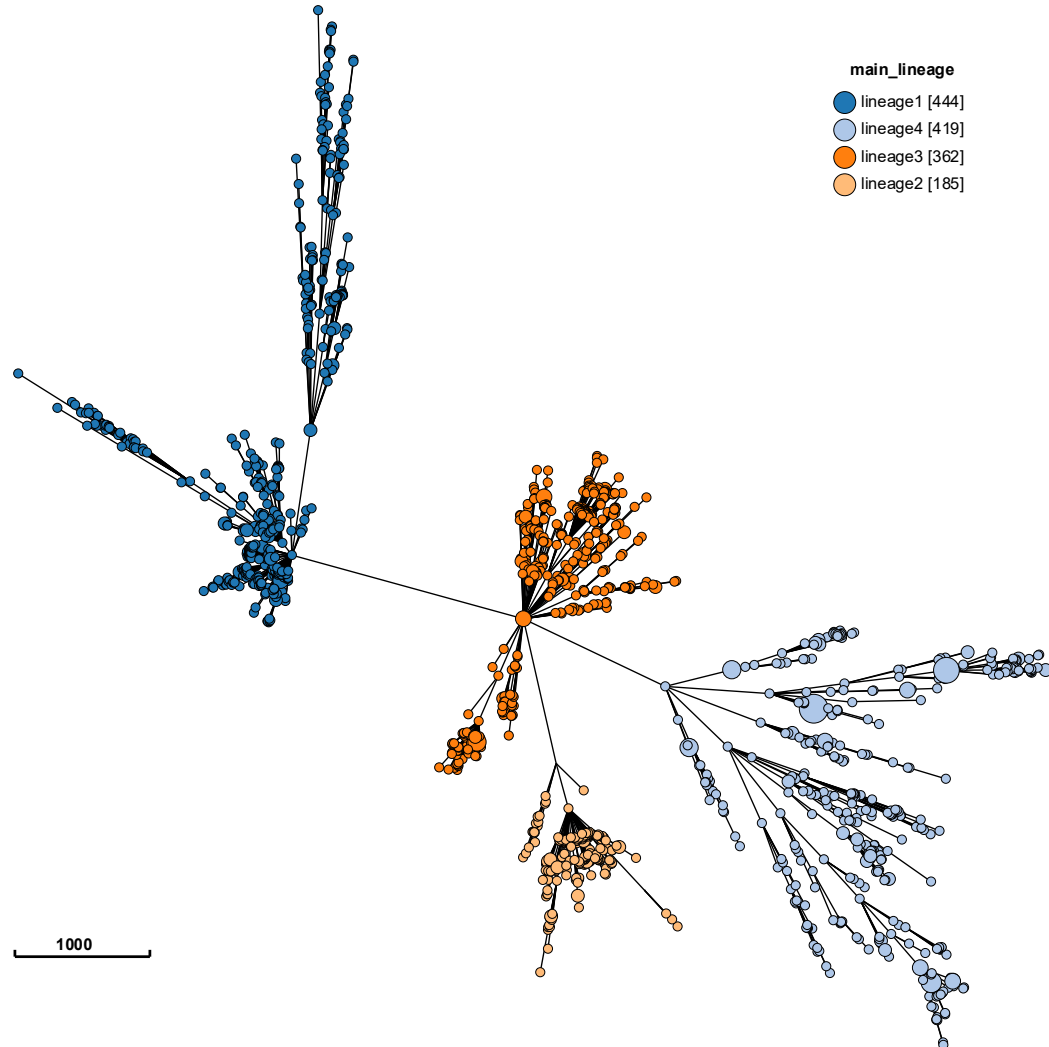
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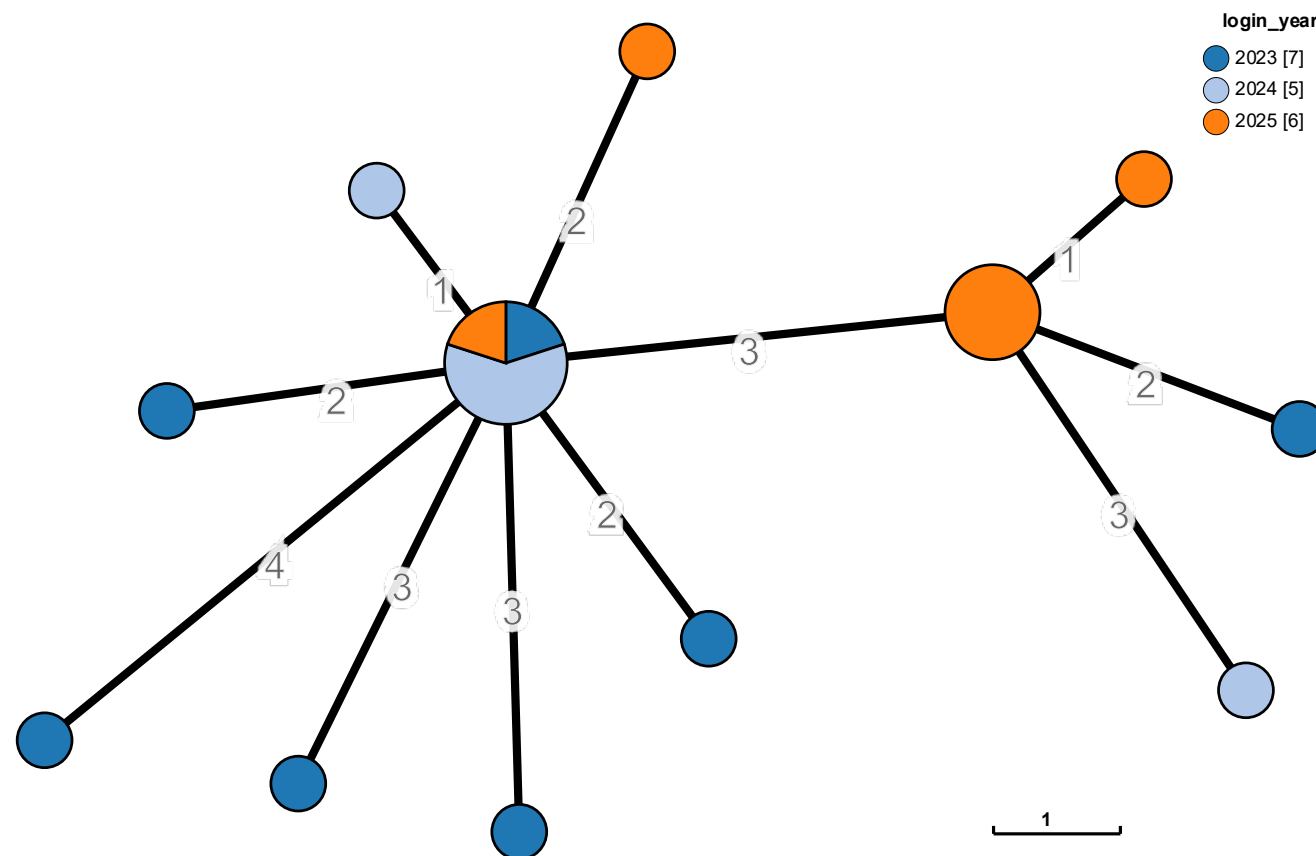
Identifying TB clusters using WGS



Identifying TB clusters using WGS

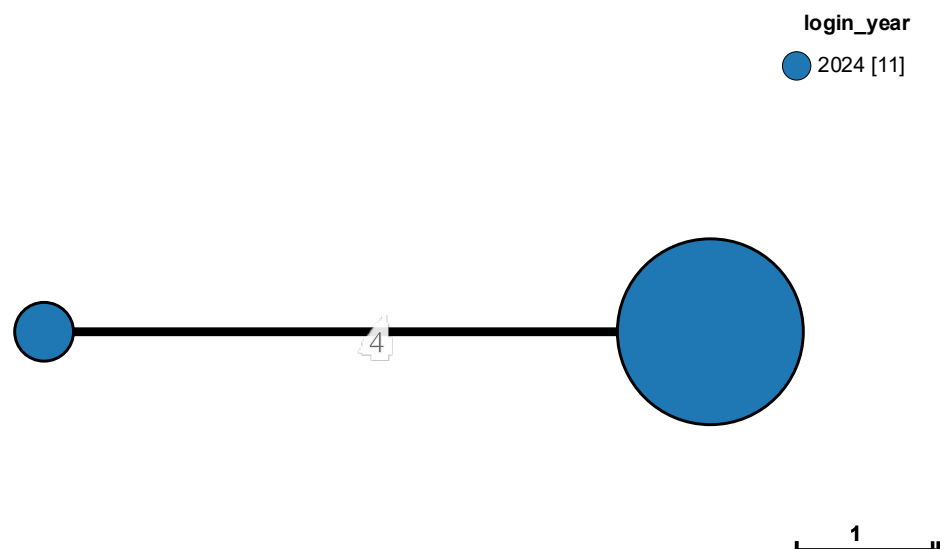


Identifying TB clusters using WGS – Case example 1



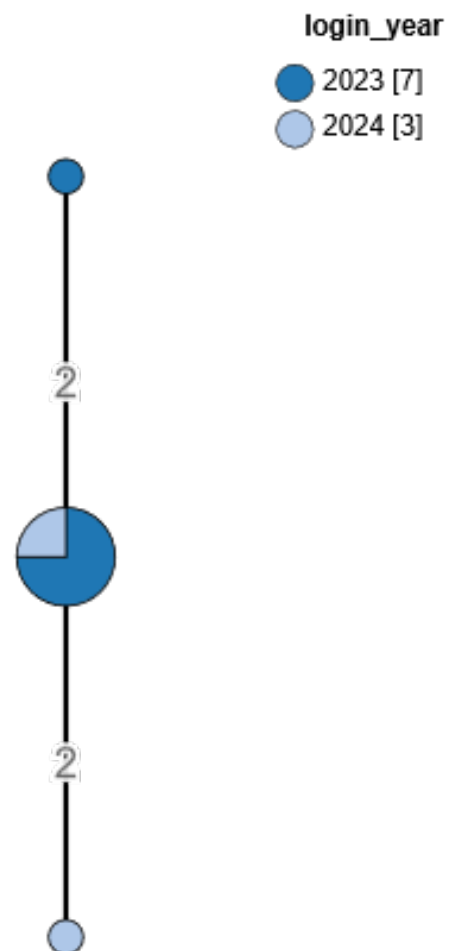
WGS cluster size: 18 cases; Genotyping cluster size: 73 cases

Identifying TB clusters using WGS – Case example 2



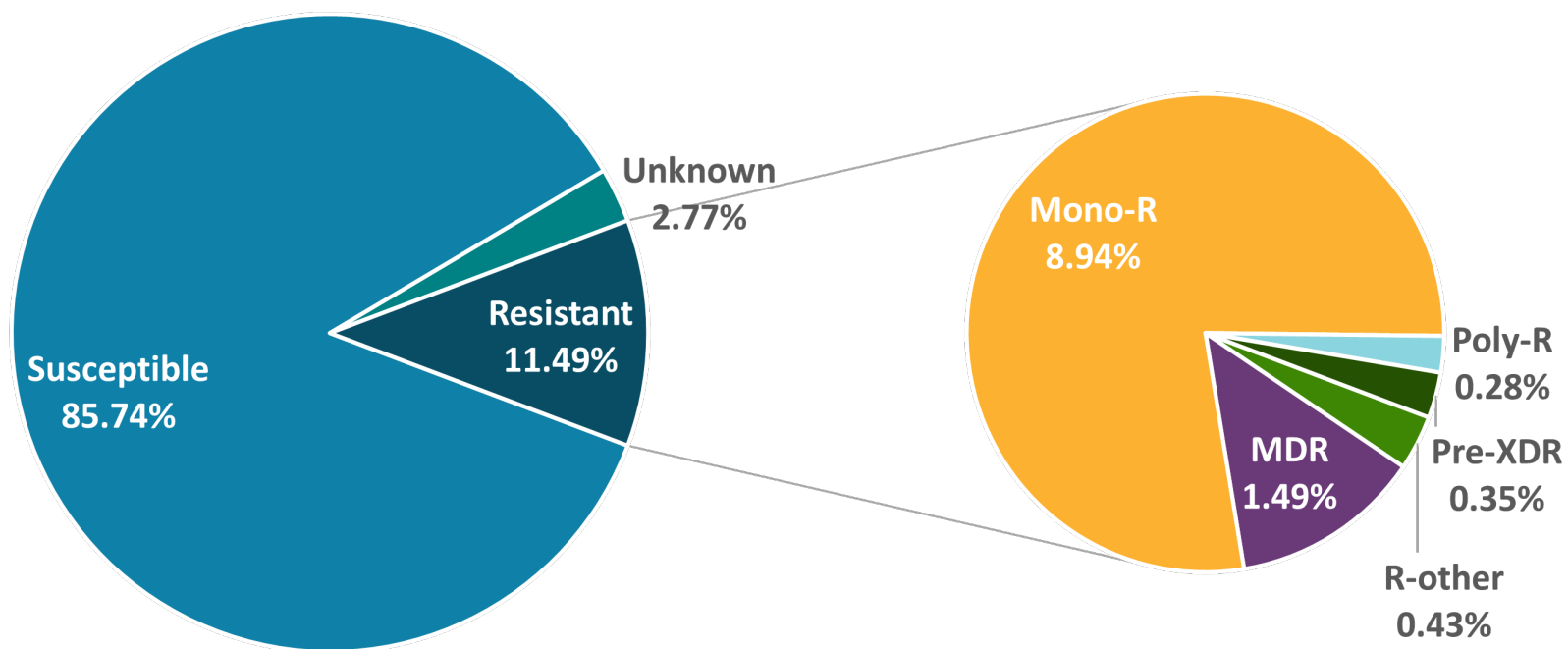
WGS cluster size: 11 cases; Genotyping cluster size : 73 cases

Identifying TB clusters using WGS – Case example 3



WGS cluster size: 10 cases; Genotyping cluster size : 14 cases

TB drug resistance (phenotypic drug susceptibility testing)



- Mono-R: resistant to one first-line drug
- Poly-R: resistant to more than one first-line drug, but not both Isoniazid and Rifampicin
- MDR-TB: resistant to at least Isoniazid and Rifampicin
- Pre-XDR: MDR plus resistance to fluoroquinolones
- R-other: resistant but do not meet criteria for the above categories

Drug resistance prediction using WGS data

- Identified variants are compared against curated TB resistance mutation database.
 - Presence of resistance-associated mutations: predicted resistant
 - Absence of known mutations: no genomic evidence of resistance; resistance remains possible if there are uncharacterized genetic or phenotypic mechanisms
- Genomic prediction vs phenotypic drug susceptibility testing (pDST)
 - Faster turnaround time supports earlier decision-making
 - Complements phenotypic testing
- High sensitivity for first-line drugs Isoniazid, Rifampicin, Ethambutol (pDST as the gold standard)

Comparison between WGS-based prediction and phenotypic DST

Drug	N	Concordant (n)	Concordance (%)	pDST Resistant (n)	Sensitivity (%)	Specificity (%)
Isoniazid	1380	1370	99.28	130	97.69	99.44
Rifampicin	1381	1370	99.20	28	100.00	99.19
Ethambutol	1381	1363	98.70	12	100.00	98.69
Pyrazinamide	1374	1351	98.33	40	45.00*	99.93

- Sensitivity = True Positives / (True Positives + False Negatives)
- Specificity = True Negatives / (True Negatives + False Positives)
- Discordant cases may include cases where:
 - New resistance mutations that is not in the current known database
 - Mutations cause low level resistance but not detected by pDST

*Average sensitivity of 45-65% is observed for pyrazinamide in various TB WGS pipelines

Drug resistant cases by immigration status (pDST)

- The majority of drug-resistant strains were identified among non-Canadian born individuals
- Overall drug resistance differed significantly between Canadian-born and non-Canadian-born
- Only one drug-resistant strain (MDR) was observed among Canadian-born individuals

Characteristic	Born in Canada N = 85 [†]	Born outside Canada N = 1,244 [†]	Unknown N = 81 [†]
Drug_Res			
MDR	1 (1.2%)	20 (1.7%)	0 (0%)
Mono-R	0 (0%)	121 (10%)	5 (6.4%)
Poly-R	0 (0%)	4 (0.3%)	0 (0%)
Pre-XDR	0 (0%)	5 (0.4%)	0 (0%)
R-other	0 (0%)	3 (0.2%)	3 (3.8%)
S	82 (99%)	1,057 (87%)	70 (90%)
Unknown	2	34	3
[†] n (%)			

*significant at p<0.05

Drug resistant cases by lineage (pDST)

- Overall drug resistance differed across lineages (*), with Lineage1 has the highest drug resistance (16%), while Lineage3 has the lowest (9%).

Characteristic	lineage1 N = 444 ¹	lineage2 N = 185 ¹	lineage3 N = 362 ¹	lineage4 N = 419 ¹
Drug_Res				
MDR	4 (0.9%)	4 (2.2%)	5 (1.4%)	8 (1.9%)
Mono-R	59 (14%)	11 (6.0%)	26 (7.4%)	30 (7.2%)
Poly-R	3 (0.7%)	0 (0%)	0 (0%)	1 (0.2%)
Pre-XDR	0 (0%)	4 (2.2%)	0 (0%)	1 (0.2%)
R-other	0 (0%)	2 (1.1%)	2 (0.6%)	2 (0.5%)
S	357 (84%)	162 (89%)	318 (91%)	372 (90%)
Unknown	21	2	11	5
¹ n (%)				

*significant at p<0.05

Drug resistant cases by sex (pDST)

- Slightly higher overall drug resistance observed in females (13%) compared to males (11%). Overall drug resistance did not differ significantly between females and males.

Characteristic	F N = 619 ¹	M N = 790 ¹	Other/unknown N = 1 ¹
Drug_Res			
MDR	11 (1.8%)	10 (1.3%)	0 (0%)
Mono-R	60 (9.9%)	66 (8.6%)	0 (0%)
Poly-R	0 (0%)	4 (0.5%)	0 (0%)
Pre-XDR	5 (0.8%)	0 (0%)	0 (0%)
R-other	3 (0.5%)	3 (0.4%)	0 (0%)
S	527 (87%)	681 (89%)	1 (100%)
Unknown	13	26	0
¹ n (%)			

*significant at p<0.05

Drug resistant cases by age group (pDST)

Characteristic	Ages: less than 25 N = 260 [†]	Ages: 25-34 N = 321 [†]	Ages: 35-44 N = 201 [†]	Ages: 45-54 N = 140 [†]	Ages: 55-64 N = 145 [†]	Ages: 65-74 N = 142 [†]	Ages: 75 and over N = 201 [†]
Drug_Res							
MDR	5 (2.0%)	4 (1.3%)	5 (2.5%)	2 (1.5%)	0 (0%)	2 (1.4%)	3 (1.5%)
Mono-R	22 (8.8%)	31 (10%)	23 (12%)	11 (8.0%)	14 (10%)	14 (10%)	11 (5.6%)
Poly-R	0 (0%)	2 (0.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (1.0%)
Pre-XDR	4 (1.6%)	1 (0.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
R-other	1 (0.4%)	2 (0.6%)	1 (0.5%)	0 (0%)	0 (0%)	0 (0%)	2 (1.0%)
S	219 (87%)	270 (87%)	168 (85%)	124 (91%)	126 (90%)	122 (88%)	180 (91%)
Unknown	9	11	4	3	5	4	3
[†] n (%)							

The 35-44 age group showed the highest overall resistance proportion (~15%), while 45-54 and ≥75 age groups had the lowest (~9%). Overall drug resistance did not differ significantly across age groups.

*significant at p<0.05

Key Genomic Epidemiology Insights (2023–2025)

- TB incidence in Ontario peaked in 2024 in the past 5 years.
- The majority of TB cases occurred among non-Canadian born individuals.
- Drug resistance (pDST) remains stable (~11%), predominantly in non-Canadian born populations.
- Lineage distribution varies geographically across Ontario. Lineage 1 showed the highest drug resistance burden.
- WGS provides more precise identification of recent transmission compared to traditional genotyping, reducing overestimation of clustering.
- WGS drug resistance predictions showed high sensitivity and specificity for Isoniazid, Rifampicin, and Ethambutol (pDST as gold standard)

Conclusions

- Role of genomic epidemiology in TB surveillance
 - Enables high-resolution detection of transmission clusters
 - Supports drug resistance profiling
- TB genomic epidemiology trends in Ontario (2023–2025)
 - TB incidence peaked in 2024, with a slight decline observed in 2025. Continued public health surveillance remains essential for TB control and elimination.
 - TB burden and drug resistance remain disproportionately higher among individuals born outside Canada.
 - WGS identified several recent transmission clusters during 2023–2025, indicating ongoing local transmission events. WGS combined with epidemiologic data will strengthen TB control efforts in Ontario.
- The research-use pipeline provides a flexible environment to explore new tools, parameters, and methods for analysis that may enhance the clinical workflow.

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