
Halton
Healthcare

Mycobacterium Tuberculosis: Use of TB PCR

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Halton Healthcare

Declaration of Conflict

- None

Outline

- Local epidemiology

- Overview of the clinical applications of molecular tests for *Mycobacterium tuberculosis*
  - Diagnosis
  - Infection Control

- Halton Healthcare experience

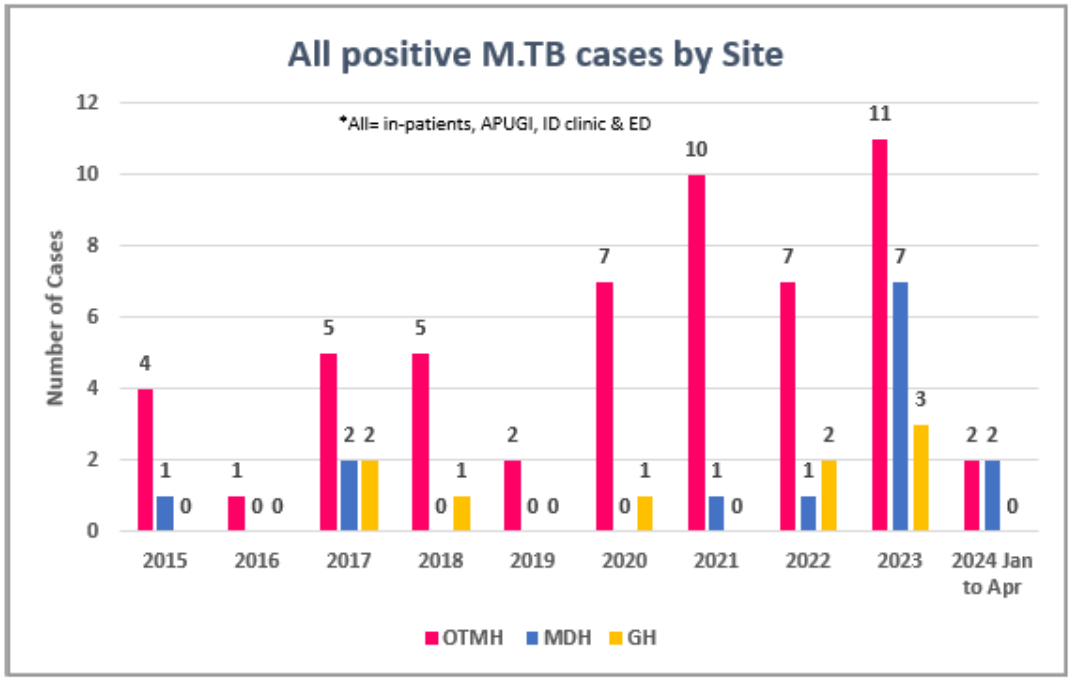
Halton Healthcare and Halton Region: Changing Demographics and TB Epidemiology

- Significant population growth (375K in 2001, 600k in 2021)
- 36% now visible minorities, many are from high incidence TB countries

2023 Tuberculosis Cases

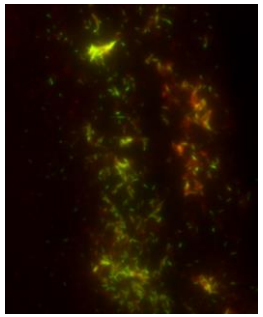
Type of Tuberculosis	2022	2023
Pulmonary	13	24
Miliary	1	1
Extra Pulmonary	5	6

Halton Region



Halton Healthcare

Conventional Testing



Drug Susceptibility Testing

At least 3
sputum samples
Bronchoscopy

Smear microscopy

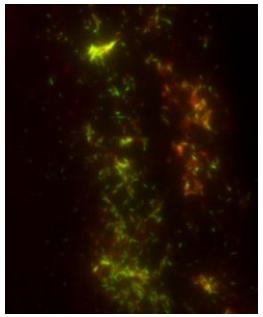
\+

Culture

PCR

Behr, M. A. et al. (2022) Canadian Journal of Respiratory, Critical Care, and Sleep Medicine
Public Health Ontario: Test information Index

Conventional Testing: Limitations



Drug Susceptibility Testing

Variable 1-4 days

Smear microscopy

+

Up to 8 weeks, average 2 weeks

Culture

Up to 12 days from culture report

PCR (up to 4 days)

Behr, M. A. et al. (2022) Canadian Journal of Respiratory, Critical Care, and Sleep Medicine
Public Health Ontario: Test information Index

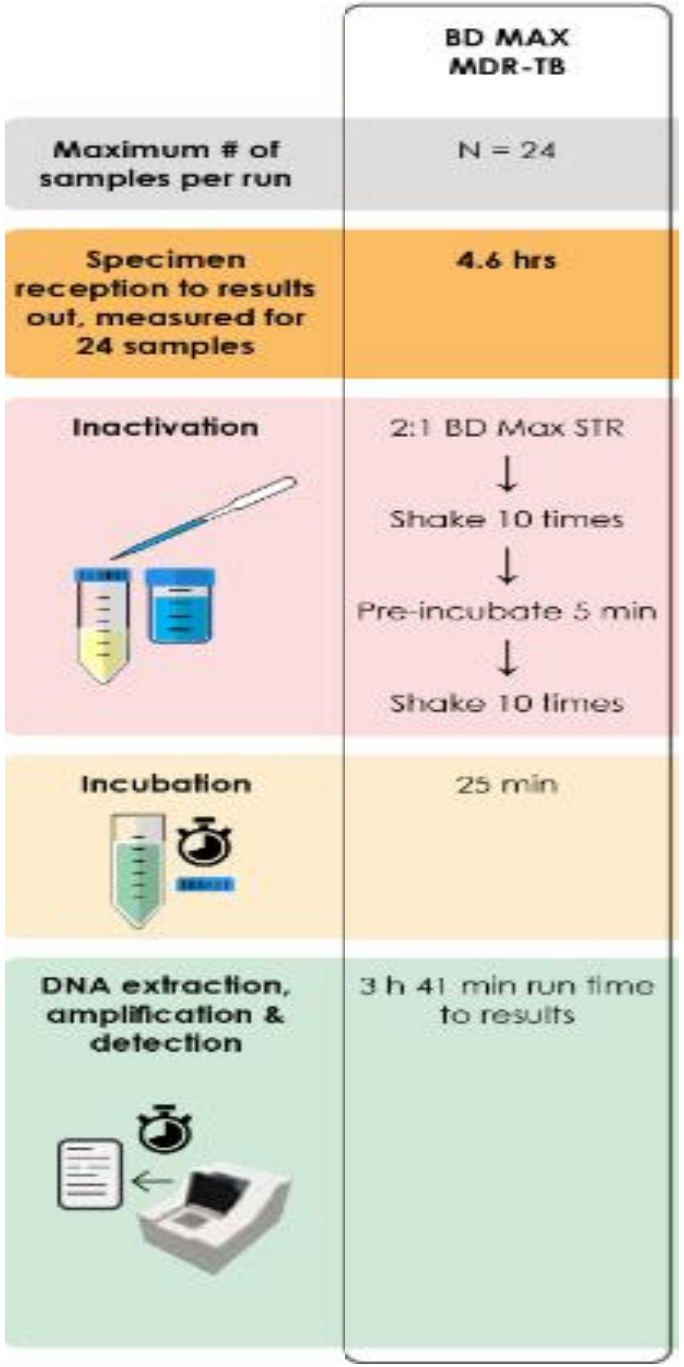
Conventional Testing: Limitations of Smear Microscopy

- Limited sensitivity:
  - Modest and variable ranging between 20-80%
  - High bacterial load required for detection (5-10,000 bacteria(AFB)/ml)
- Specificity hampered in low TB incidence settings:
  - Cannot distinguish between MTB and NTM

Behr, M. A. et al. (2022) Canadian Journal of Respiratory, Critical Care, and Sleep Medicine
Public Health Ontario: Test information Index

Nucleic Acid Amplification Tests for the Diagnosis of Tuberculosis

- A molecular test used to detect *M. tuberculosis* DNA from clinical specimens
- Polymerase chain reaction (PCR) is the most common form of NAAT
- There are multiple partially or fully automated systems
- At Halton Healthcare we are currently using the BD MAX MDR TB Assay
- Can detect
  - 1) MTB
  - 2) Mutations that confer resistance to rifampin and isoniazid



- Fully integrated and automated system
- Benchtop platform
- Can provide results for up to 24 samples per run
- Results obtained in <5 hours
- AT HH: one run each day Monday-Friday, if staffing allows on an as needed basis

WHO TB knowledge haring platform: https://tbksp.org/en/node/747

TB NAATs: Diagnostic Accuracy TB Detection

TABLE 1 Diagnostic accuracy of each index test: tuberculosis detection

Index test	Smear status	Datasets n (specimens n)	Sensitivity (95% CI)	Specificity (95% CI)
Abbott MTB	All	10 (4858)	96.2% (90.2–98.6)	97.1% (93.7–98.7)
	Positive	10 (765)	99.0% (97.7–100)	-
	Negative	10 (4056)	88.4% (74.0–95.3)	98.3% (96.3–99.2)
FluoroType MTB	All	5 (2660)	92.1% (87.6–93.3)	98.9% (64.0–99.9)
	Positive[#]	3 (174)	Range: 100% (92–100)	-
	Negative[#]	3 (1754)	Range: 30%–85%	Range: 62%–98%
FluoroType MTBDR[#]	All	2 (782)	Range: 91%–96%	Range: 100% (97–100)
	Positive	2 (288)	Range: 98%–100%	-
	Negative	2 (494)	Range: 69%–98%	Range: 100% (97–100)
BD Max MDR-TB[#]	All	1 (892)	93% (89.0–96.0)	97% (96.0–98.0)
	Positive	1 (176)	100% (98–100)	-
	Negative	3 (713)	81% (73–88%)	98% (96–99%)

- Overall sensitivity: 91-96%
  - Smear positive: 98-100%
  - Smear negative: 69-81%
- Overall specificity: 97-100%

✓Improved sensitivity over smear microscopy
✓No cross reactivity between NTM

Mikashmi et al, European Respiratory Journal (2021)

TB NAATs: Diagnostic Accuracy Resistance Detection

TABLE 2 Diagnostic accuracy of each index test: resistance detection

Index test	Datasets n (specimens n)	Sensitivity (95% CI)	Specificity (95% CI)
Abbott RIF/INH			
Rifampicin resistance	7 (1008)	94% (89–99)	100% (99–100)
Isoniazid resistance	7 (1013)	89% (86–92)	99% (98–100)
FluoroType MTBDR#			
Rifampicin resistance	2 (231)	Range: 97%–99%	Range: 100% (85–100)
Isoniazid resistance	2 (207)	Range: 70%–92%	Range: 100% (84–100)
BD Max MDR-TB#			
Rifampicin resistance	1 (232)	90% (55–100)	95% (91–97)
Isoniazid resistance	1 (232)	82% (63–92)	100% (98–100)

✓Able to detect drug resistance

Mikashmi et al, European Respiratory Journal (2021)

Advantages of NAATs for TB

- ✓ Rapid results within 24hours
- ✓ Immediate confirmation of TB and drug resistance
- ✓ Reduce time to (effective) treatment
- ✓ Reduce period of infectiousness
- ✓ Earlier initiation of contact tracing
- ✓ Isolation may be discontinued earlier in cases where TB is unlikely
- ✓ Better utilization of airborne isolation rooms and PPE

HH Assay Verification Experience

- Real time parallel testing with OPHL February 2021 to Nov 2023 (with COVID-19 related interruptions)
- Only false-negative TB results (2/26) were few or no AFB present specimens
- All "low-positives" were smear-negative
- No false-positive TB results with 25 NTM-positive specimens

		BDMAX RESULT			
PHL Microscopy	TB Culture	MTB DETECTED	MTB LOW POSITIVE	MTB NOT DETECTED	Grand Total
no acid fast bacilli	MTB COMPLEX	1	5	1	7
AFB seen few	MTB COMPLEX	1		1	2
acid fast bacilli: 1+	MTB COMPLEX	2			2
acid fast bacilli: 2+	MTB COMPLEX	1			1
acid fast bacilli: 3+	MTB COMPLEX	8			8
acid fast bacilli: 4+	MTB COMPLEX	6			6
Grand Total		19	5	2	26

Case #1

- 91M admitted Jan 4 2024 with fall and COVID-19 infection
- Originally from India, came to Canada 20 years ago
- Initial CXR showed L perihilar opacity (?volume loss) and L lower lobe opacity (possible infiltrate)
- Received dexamethasone and remdesivir for COVID-19 then a course of piperacillin tazobactam for pneumonia/aspiration
- Admitted to ICU in February with respiratory failure and was intubated
- Chest imaging showed multifocal consolidation without cavitation or significant effusions

Case #1

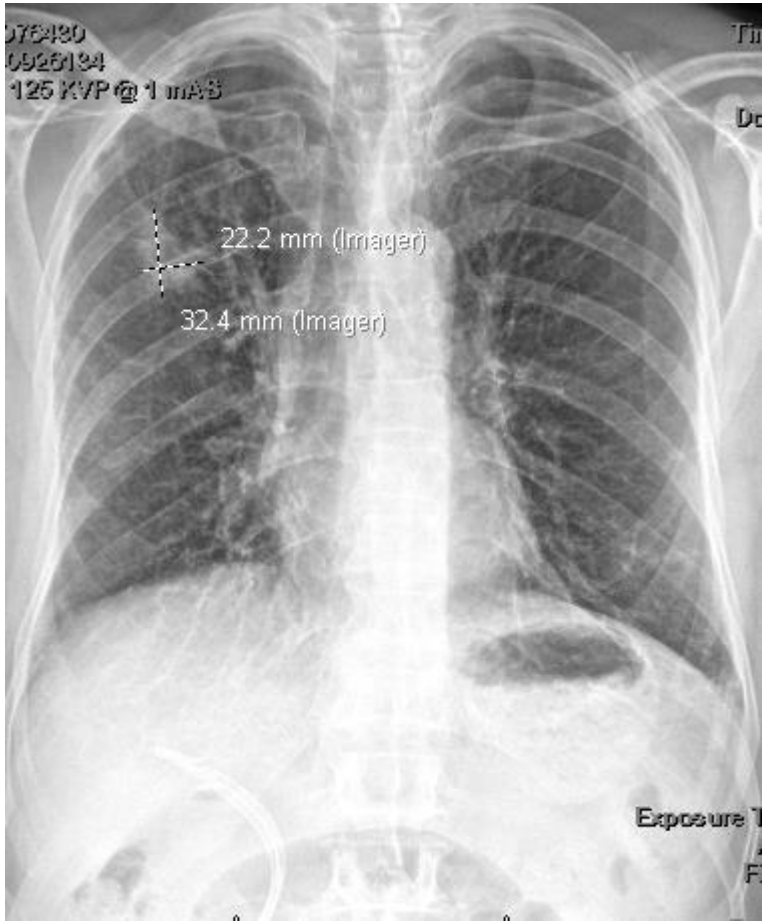
- Underwen
  - Feb 15:
    precaut
  - Feb 18:
  - March 4
  - March

airborne

Rapid diagnosis < 24 hours
Isolation and treatment initiated 2.5 weeks earlier
Earlier initiation of contact tracing

Case #2

- 68Y M admitted November 8 2023, with a one day history of cough and large volume hemoptysis
- PMHX: CAD, Diabetes, smoker
- Born in India and came to Canada in September 2023 to visit son.
- No preceding pulmonary, infectious or constitutional symptoms
- No history of TB or known exposures


125 KVP @ 1 mAS
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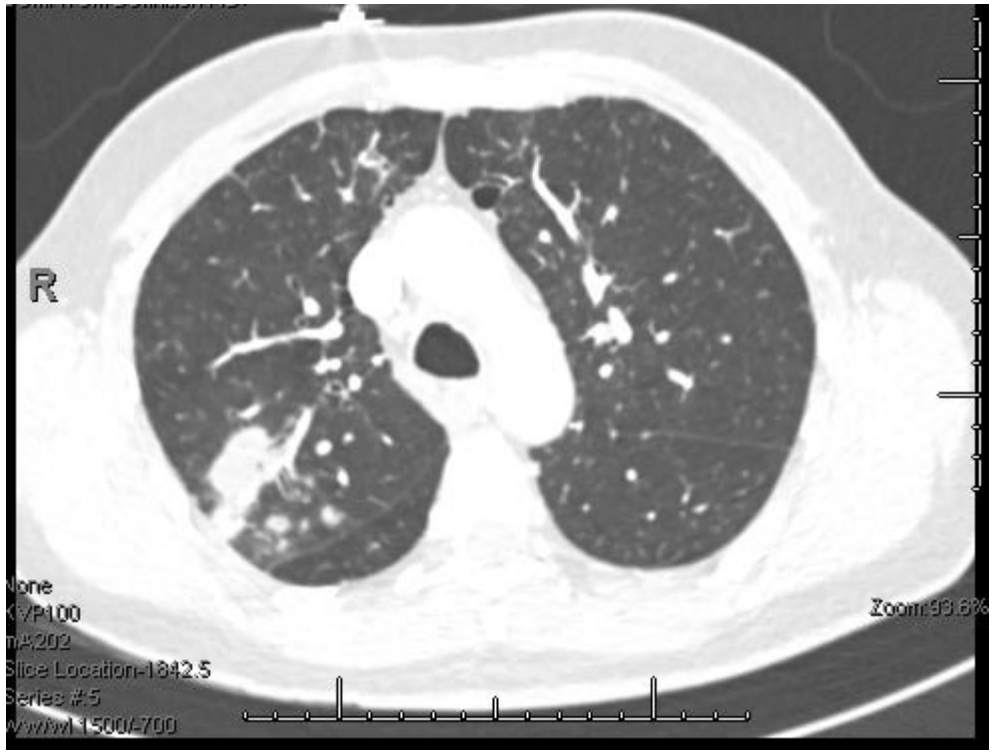
32.4 mm (Imager)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Case #2

- Placed in airborne precautions
- Treated up front with antibiotics for ? Post obstructive pneumonia in setting of malignancy
- Seen by Respirology
- Underwent diagnostic bronchoscopy on November 10
- One BAL and one post bronchoscopy sputum specimen sent for TB
- Initial cultures came back revealing *Klebsiella pneumonia*
- Hemoptysis settled in hospital
- Plan was to discharge him home on oral antibiotics and follow up results on an outpatient basis

Case #2: TB Results

- TB
- AFB
- MTB
- Susc

023

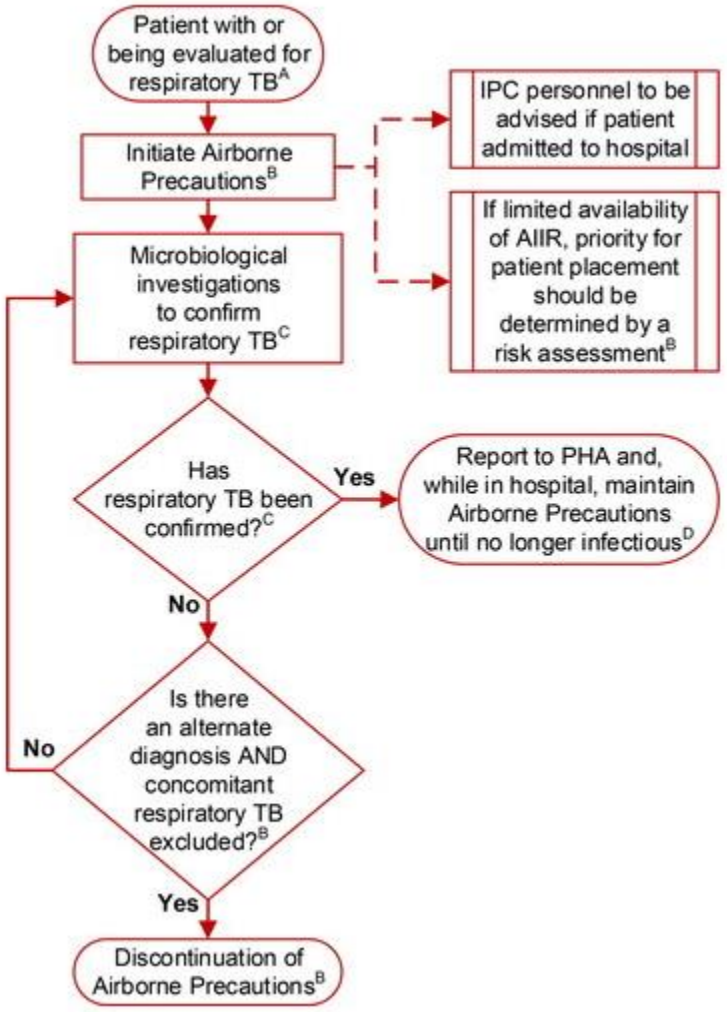
2023

✓Treatment initiated 3 weeks earlier

✓Decreased risk of transmission (in the community)

What if patient remained in hospital? Would you have taken him out of airborne precautions with 2 negative AFB (including one from BAL)?

Discontinuation of Airborne Precautions



Criteria for discontinuing airborne precautions in hospitalized adolescents and adults:

- **Three consecutive smear-negative sputum samples**
- **Alternative diagnosis**

Is there a role for NAATs ?

Johnston et al, *Canadian Journal of Respiratory, Critical Care, and Sleep Medicine* (2022)

Case # 3

- 87F presented to hospital on April 26 2024 with witnessed out of hospital PEA arrest with ROSC
- PMHX: hypertension
- She was born in India and moved to Canada in 2023
- Preceding cardiac arrest was feeling unwell for 4-5 days with initial non productive cough that resolved followed by chest congestion
- No hemoptysis, weight loss or fevers
- No personal history of TB or known contacts

Case # 3

- CT chest to rule out PE
    - "There is bilateral groundglass opacity and multifocal consolidation. Findings could relate to pulmonary edema. Other possibility could represent some hemorrhage or potentially aspiration"
- Patient placed in airborne precautions
- Multiple sputum specimens sent for smear microscopy and mycobacterial culture
- Started on empiric antibiotics for community acquired pneumonia

Case # 3

- Diagnosis:
  - Cardiac arrest likely secondary to hypoxic respiratory failure from pneumonia +/- aspiration.

- Risk of TB?
- Would this patient have been isolated at your hospital?
- When would you remove this patient from isolation?

Use of TB NAATs for Discontinuation of Precautions: Summary of Evidence

- Multiple retrospective studies conducted in low TB incidence countries have provided evidence to support the use of NAATS to reduce the use of airborne isolation rooms
- Results:
  - 1) TB [illegible] onary tuberculosis on first specimen collected
  - 2) Almost all false negative PCR cases were smear negative/low grade smears (lower risk of transmissibility)
  - 3) 2-specimen PCR was able to identify all TB cases

One negative PCR is as good as three negative AFB

Flee et al, CID (2015)
Lippincott et al, CID (2014)
Chaisson et al, JAMA Intern Med (2018)
Campos et al, Am J Respir Crit Care Med (2008)
Hamdi et al, J Clin Tuberc Other Mycobact Dis (2020)

Use of TB NAATs for Discontinuation of Precautions: Summary of Evidence

- Reduction in duration of airborne isolation (Range 10-47 hours)

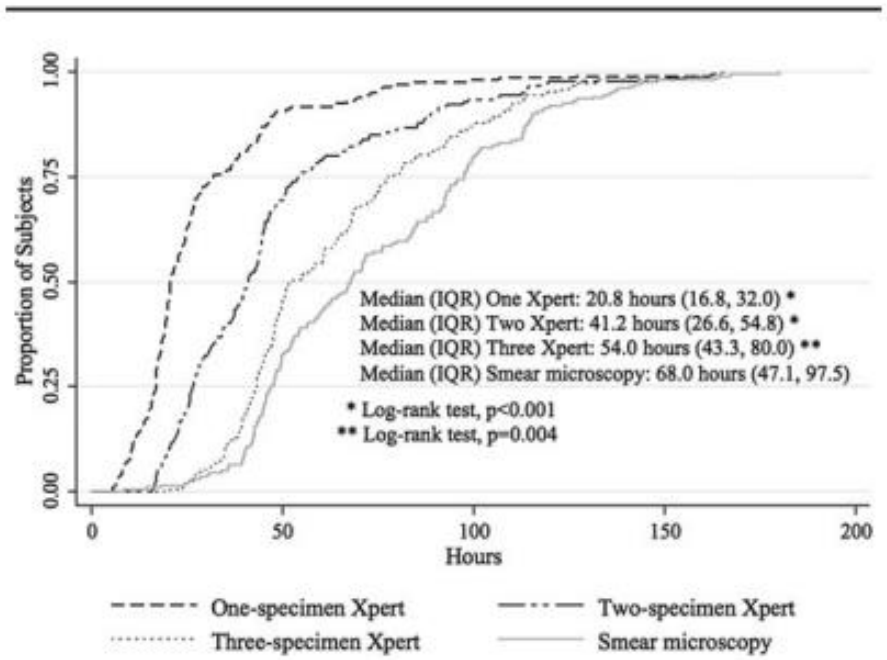


Table 3. Length of Stay in Respiratory Isolation and Time Intervals in the Isolation Process for Patients With Negative Results on Rapid Testing for Pulmonary Tuberculosis

	Median (IQR)		
Time Period	Preimplementation (n = 207)[a]	Postimplementation (n = 226)[a]	*P* Value
Isolation admission to isolation discharge, days[b]	2.9 (2.0-3.7)	2.5 (1.7-3.4)	.001

Average utilization and economic costs per patient.

Outcome	SmearStrategy	XpertStrategy	Difference	95% UncertaintyRange‡
Length of Stay *				
Isolation room	2.7	1.4	1.3	1.2, 1.3

Lippincott et al, CID (2014)
Chaisson et al, JAMA Intern Med (2018)
Millman et al, PLoS One (2013)

Use of TB NAATs for Discontinuation of Precautions: Summary of Evidence

- Cost saving

Total annual utilization and economic costs for all patients.

Outcome	SmearStrategy	XpertStrategy	Difference	95% UncertaintyRange‡
Length of Stay *				
Isolation room	632	328	304	281, 304
Standard room	749	1030	−281	−281, −257
Total	1,381	1,358	23	−23, 47
Costs †				
Isolation room	$2,453,022	$1,241,370	$1,211,652	$990,756, $1,216,800
Standard room	$1,704,690	$2,335,320	−$630,630	−$645,500, −$585,936
Diagnostictesting	$3,510	$51,012	−$47,502	−$163,655, −$15,444
Total	$4,161,222	$3,627,702	$533,520	$370,188, $1,069,380

Millman et al, PLoS One (2013)

Halton Healthcare TB Policy

Discontinuation of Airborne precautions on suspected pulmonary TB

a) Prior to discontinuation of Airborne Precautions, consult the IPAC team.

b) For suspected pulmonary TB cases:

- **i)** One negative TB PCR from a sputum specimen, in conjunction with all other clinically relevant and/or radiological information.
- **ii)** If TB is strongly suspected, two negative PCR and/or three negative AFB smears.
- **iii)** Bronchoscopy (BAL) specimens, one negative PCR in consultation with Infectious Disease Physician.
- **iv)** An alternative diagnosis is made and/or pulmonary TB has been ruled out.
- **v)** When the AFB smear is positive and the PCR assay is negative. This could be a non-tuberculosis Mycobacterium species (NTM).
- **vi)** Decisions to discontinue Airborne Precautions will be guided by infection control in consultation with infectious diseases.

Case # 3

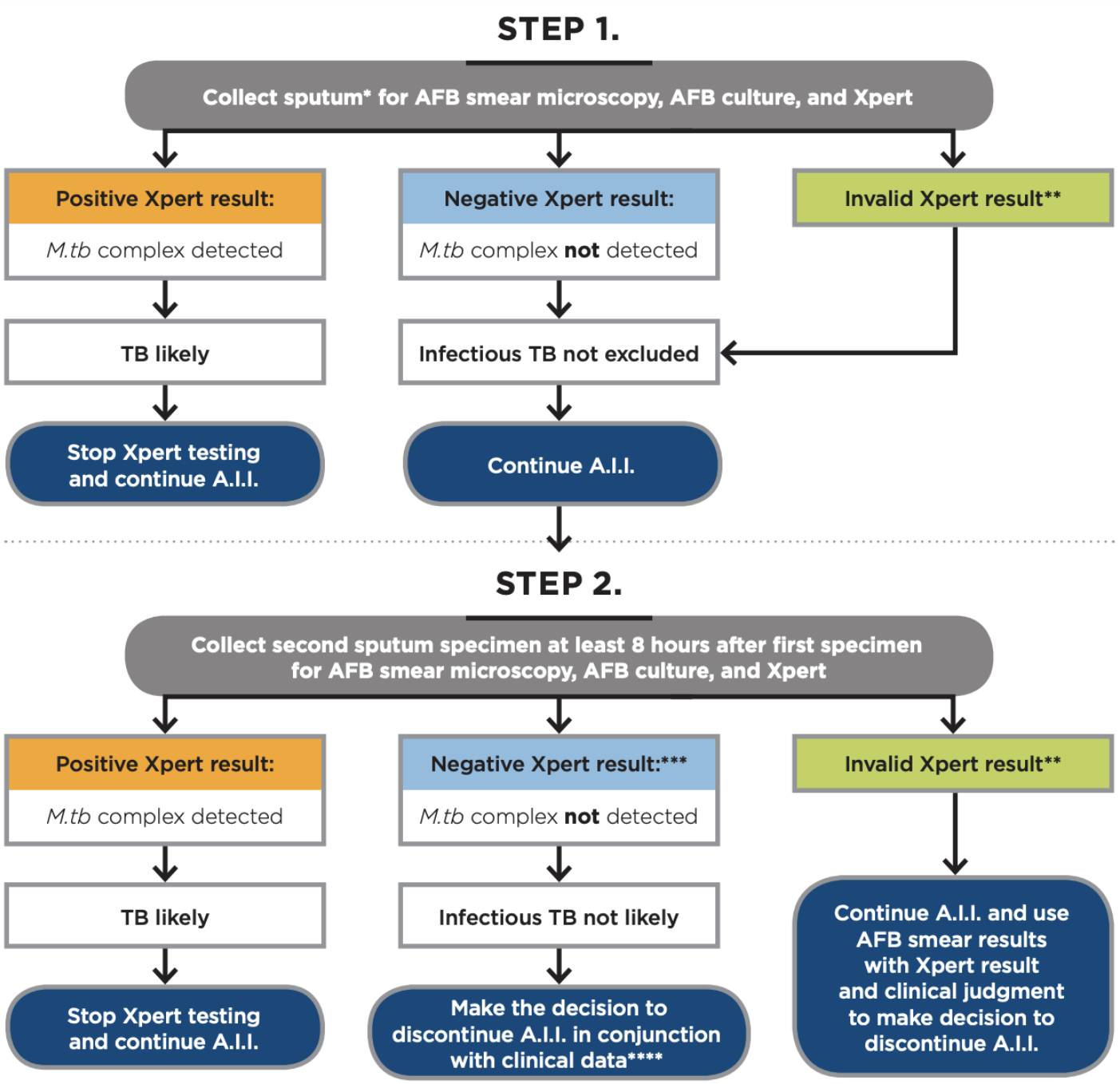
- Sputum for AFB/mycobacterial culture
  - April 26 x 1
  - April 27 x 2 (both with non sufficient quantity for TB PCR)
  - April 28 x 1
- April 29 @ 14:37: TB PCR negative x 2 from April 26 and 28 (isolation stopped)
- April 30 @ 13:18 : AFB negative x 4 reported
- Isolation duration difference: ~ 22.5 hours

TB NAATs: What Do Guideline Say?

Canadian TB Standards 8th Edition (2022)	TB Diagnosis	We strongly recommend that in all new smear-positive patients, at least one AFB positive respiratory sample should be tested with a Health Canada-approved or -validated laboratory-developed nucleic acid amplification test We conditionally recommend that in smear-negative patients suspected of having TB, a nucleic acid amplification test may be performed on one AFB negative sample upon request by the physician or public health
	De isolation	Not mentioned
ATS/IDSA/CDC Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children (2017)	TB Diagnosis	We suggest performing a diagnostic nucleic acid amplification test (NAAT) on the initial respiratory specimen from patients suspected of having pulmonary TB
CDC(2005)	De isolation	Not mentioned

TB NAATs: What Do Guideline Say?

US National Tuberculosis Controllers Association (2016)	De isolation	**Negative First and Second Xpert Results**: If the first Xpert result is negative (M. tuberculosis complex not detected), a second specimen collected at least eight hours after the first specimen should be tested if TB still is clinically suspected. If the second Xpert result is negative, infectious TB is not likely. Consider release from A.I.I. if infectious TB is no longer a significant clinical consideration.
EU Standards for Tuberculosis (2017)	TB Diagnosis	All patients thought to have pulmonary tuberculosis should have at least two sputum specimens submitted for microscopic examination and one for rapid testing for the identification of tuberculosis and drug resistance using an internationally recommended (rapid) molecular test.
	De isolation	Not mentioned



M.tb: *Mycobacterium tuberculosis* **A.I.I.:** Airborne infection isolation

National Tuberculosis Controllers Association, 2016

TB NAATs: What Do Guideline Say?

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Thank You
Questions?

Halton Healthcare