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TB Infectiousness and the Impact of Treatment

(Implications for de-isolation policy)

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Disclosure

- No financial Conflicts of Interest or relevant disclosures
- Recommendations from Canadian TB Standards, 8th Edition (2022) – Appendix B

Objectives

1. Describe the levels of evidence informing de-isolation of people on treatment for TB
2. Outline the new de-isolation guidelines from the Canadian TB Standards, 8th edition

Case

Although a real case, details slightly altered and representative photos/images are from other cases

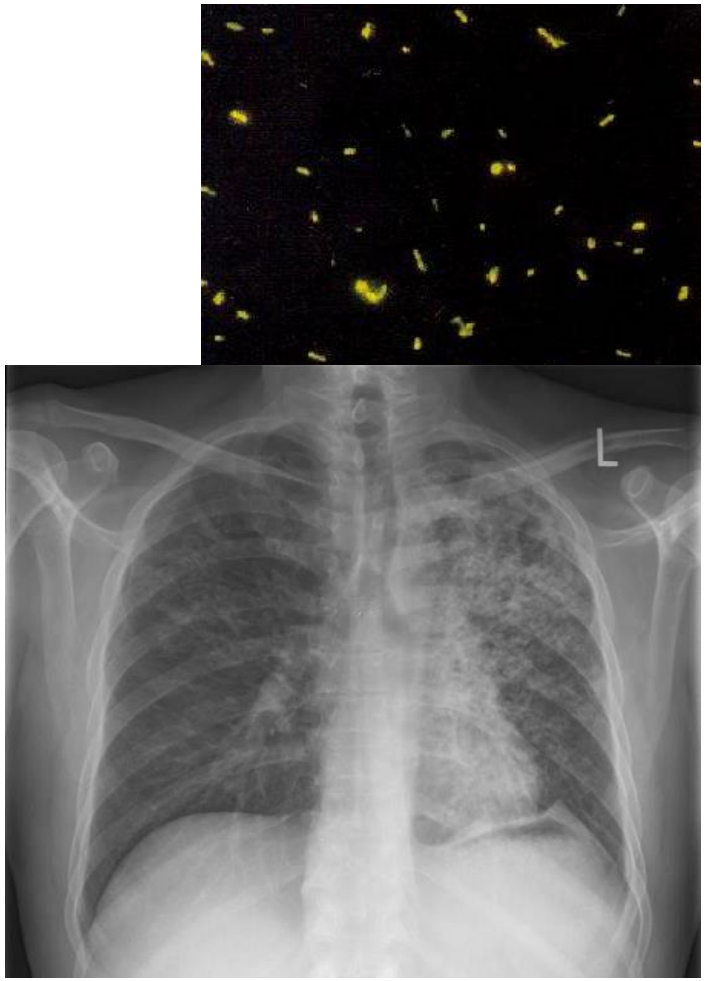
Case: 34M from Northern Alberta

- Persistent cough for three months, intermittent fevers, weight loss
- Cough did not improve after treatment with Amoxil, then Azithromycin
- Chest Xray → admit to local hospital

CXRAY: R. Long Can Resp Journal 2015 22(6)

Case: Diagnosis

- Sputum 4+ AFB on direct stain, PCR positive for MTBC (no rifampin - resistance detected)*
- Transported to Edmonton for treatment start
  - Single bed isolation rooms, each under negative pressure with anteroom, and each with high rates of air-exchange and with exhaust HEPA filtered



CXRAY: R. Long Can Resp Journal 2015 22(6)
Images – CDC Public Health Images

*using Xpert MTB/RIF qPCR

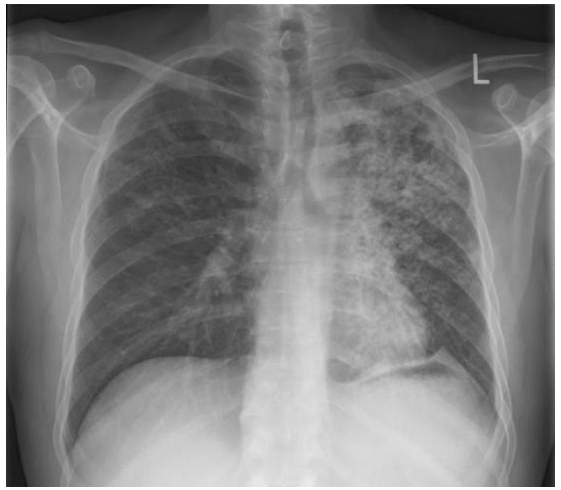
Case: Two weeks into treatment

- Excellent clinical response to INH+RIF+PZA+EMB:
  - Fevers noted on admission resolved within 8 days
  - Cough improving, but not gone
  - Starting to ”feel better”
  - Phenotypic DST results pending
  - Tolerating treatment

- Sputum still 4+ for AFB on direct smear

Case: Four weeks into treatment

- Still smear-positive (now 1-2+)
- Confirmed fully drug-susceptible
- Nearly asymptomatic and really wants to go home and go back to work
  - ”at least get me out of this isolation room”
- Deemed ineligible for home isolation
  - Crowded household, dynamic membership, can’t control visitors, most household not yet assessed for PT, household consent not yet received
- Bed manager …”These COVID patients need an isolation room…”, ”your guy looks ready to go home to me”



Current Practice:
TB Standards 7th Edition 2013

People with Smear-positive PTB should be kept under airborne precautions until there is clinical evidence of improvement, adherence to **at least 2 weeks** of effective multidrug therapy based on the known antibiotic sensitivity of the patient's organism, **and three consecutive negative AFB sputum smears**

Menzies CRJ 2013; Consistent with US Guidelines MMWR 2005

But… sputum smear conversion takes a long time

- In systematic review of 8 clinical studies: Sputum smear conversion took median 27 days (mean 37 days)
- In Alberta: <10% smear convert by day 14 and <25% by day 21
- Sputum *culture* conversion takes even longer:
  - Time to sputum culture conversion median ~42 days

Time to sputum conversion: When 3 consecutive sputum samples are smear-negative

Calderwood PLOS Medicine 2021 SR
R. Long ICHE 2003
Hales Annals ATS 2013

Questions from Case:

- How soon after starting anti-TB treatment for pulmonary TB can we consider a person no longer infectious?

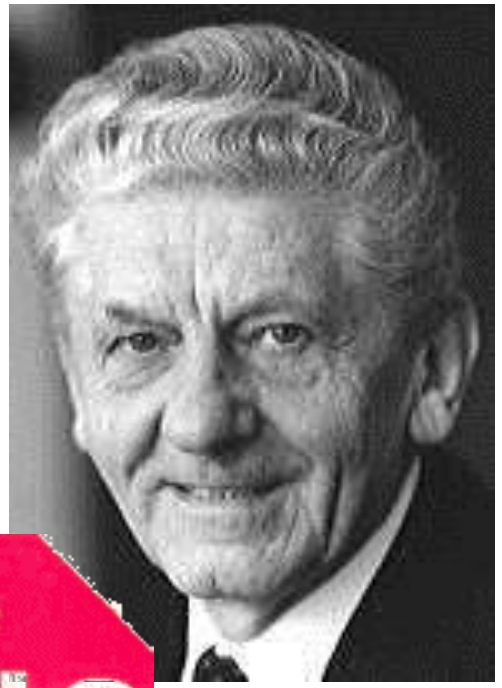
- Does sputum smear status predict infectiousness once on TB treatment? Do we really have to wait for this?

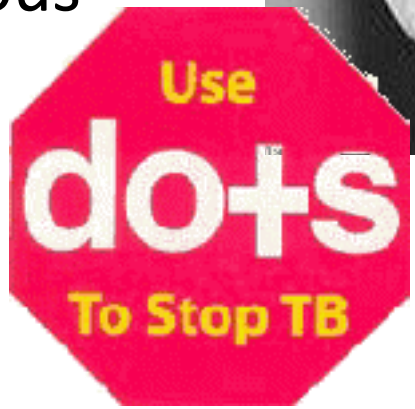
- What are implications for policy? When can we “De-isolate”? When can people go home, back to work, to congregate setting, or remove from isolation room if still in hospital?

Historical Perspective

Treatment is Prevention

- Treatment of TB disease quickly reduces infectivity and is thus a fundamental component of TB public health management
- Just how quickly patients become non-infectious after initiating effective therapy is unknown





Van Cutsem G CID 2016;62(Suppl 3:S238–S243
Yuen CM Lancet 2015;386(10010):2334-2343
Petersen *Int J Infect Dis.* 2017;56:34-38

The ”Two-Week” rule

- Prior to the 1990s, the “two-week rule” commonly guided de-isolation
  - Based on clinical experience, original guinea-pig data, clinical trial data
- But in 1993, in response to high-profile nosocomial MDR-TB outbreaks, the CDC recommended prolonging isolation until sputum smear conversion achieved
  - This pragmatic step helped to avoid premature de-isolation of people not on effective therapy

Iseman CID 1997;25(3)
MMWR Morb Mortal Wkly Rep 1993 Jun 11;42(22):427, 433-4
Pearson ML Ann Intern Med 1992 117(3):191-6

TB infectious once treatment started: Evidence Review

Calderwood PLOS Medicine 2021 Systematic review Animal Studies
Karat AS CID 2021;72(1):155–172 – Systematic Review Clinical studies
Migliori GB ERJ 2019;53(6) – WHO non-systematic review
Menzies D. ICHE 1997;18(8):582–586 – Non-systematic Review
Cooper RD CRJ 2022

Clinical RCT level data - One study

- Madras Study: 1957 in Chennai by WHO, BMRC, ICMR
  - N=193 participants with PTB treated with 12 months INH and PAS
  - Randomized to receive this treatment in home setting or while isolated in TB sanitorium
  - Co-primary outcome was TB rates in the 693 contacts of participants
  - 5 years of detailed follow-up, high retention in care

Karat AS CID 2021;72(1):155–172 – Systematic Review
TB Center Madras, 1959, Bull WHO 21:51-144

Madras RCT – TB in the 693 contacts

- No difference in TB incidence between household contacts of participants treated in sanitorium and those “de-isolated” at-home
  - Rates of TST conversion, test positivity also similar between groups
  - Lots of TB in the community, some hospital visitation (cross-over), may have obscured important differences

- Sub-analysis of Chennai data: duration of persistent smear and culture positivity on treatment didn’t predict transmission to contacts

Kamat SR Bull WHO 1966;76(2):109–124 – Chennai Trial 5-year FU Contacts
Devadatta S Bull of the WHO 1970;42(3):337–351 – Additional transmission analysis
Rouillon A Tubercle 1976;57(4):275–299.

Observational Data – One Comparative study

- Arkansas Study, 1967- 1971
  - Contact tracing from 155 people admitted to hospital with PTB
  - Some people were de-isolated and sent home despite persistent sputum smear and culture positivity (86 patients) while others were kept in isolation until sputum culture negativity was achieved (69 patients)
  - Transmission, as judged by TST positivity of contacts (N=500), did not differ by sputum bacteriologic status at time of de-isolation
  - But de-isolation occurred about 4 weeks after treatment start

Gunnels JJ Rev Res Dis 1974;110(6):810–812

Observational Data – Two Non-comparative

- Baltimore, 1972-1973
  - 27 people with PTB and their 156 contacts closely followed with serial TST
  - Some treated at home, some isolated in hospital
  - Based on timing of TST conversion, it was judged that no transmission occurred post-treatment initiation from people who weren't isolated

- Cincinnati, 1969-1971
  - 21 people with smear-positive pulmonary tuberculosis and their 107 contacts
  - All were initially treated in hospital, then discharged home after 2-weeks, off isolation, despite nearly all remaining smear-positive
  - Of the 70 initially TST negative household contacts, no skin-test conversions occurred
  - Frequent use of gap prophylaxis

Brooks SM Rev Resp Dis 1973;108(4): 799–804 - Cincinnati
Riley RL Am Rev Resp Disease. 1974;110(6):810–812 – Baltimore Home treatment

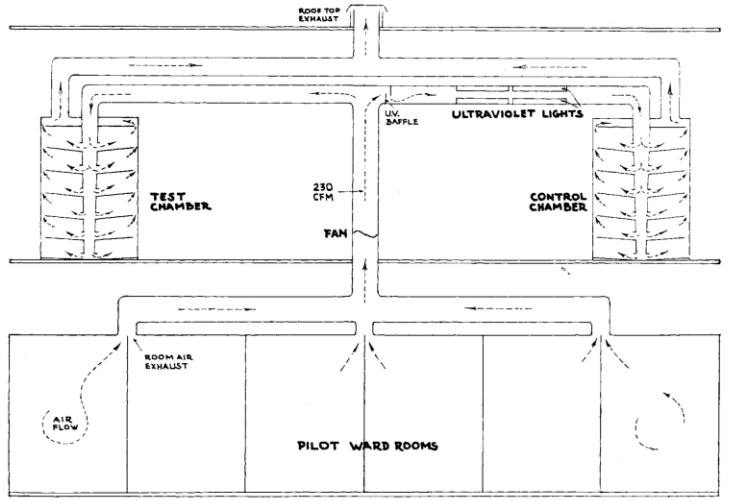
Observational Data – Case Reports

- One case report of transmission occurring in the hours after first dose of anti-TB treatment
- No reports of confirmed TB transmission occurring after person with pulmonary TB had received two weeks of treatment, as far as I am aware

Haley C ICHE 1989; 10(5):204 – Texas Case
Migliori GB ERJ 2019;53(6)

Human-to-Guinea Pig (Four studies)

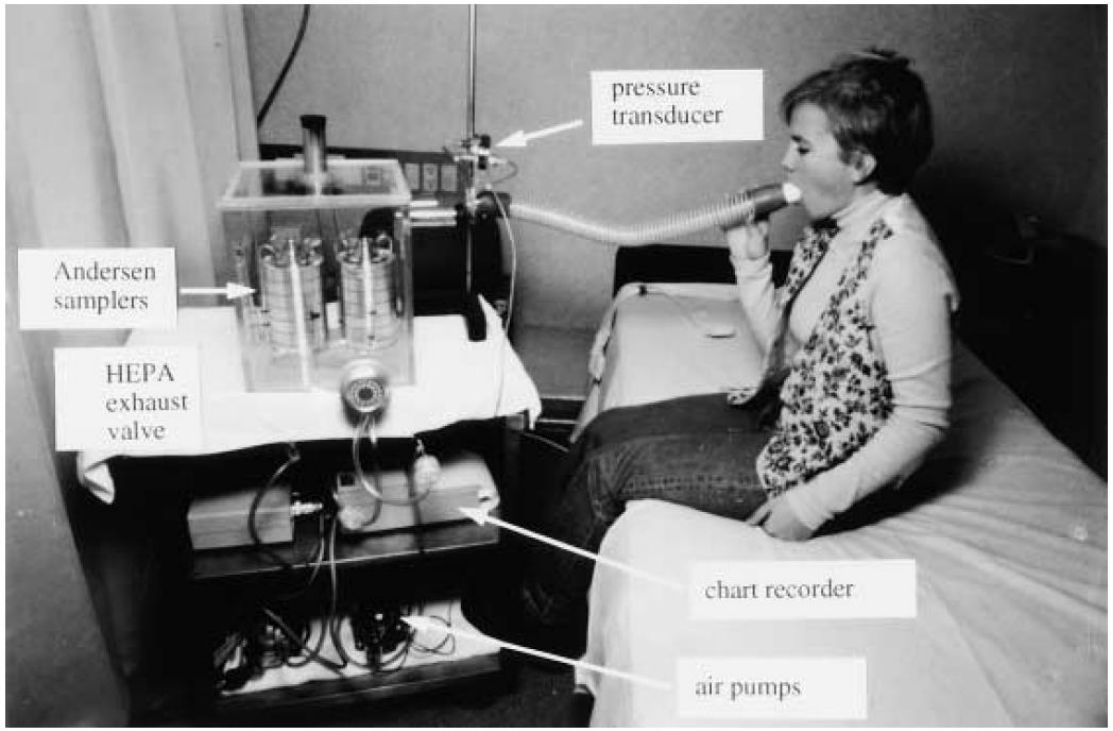
- Transmission to guinea-pigs *nearly* stops within a day or two of initiation of effective treatment
  - Regardless of sputum bacteriologic status on treatment
  - Demonstrated in MDR-TB and DS-TB
  - However – none of the studies were designed to find the precise time after treatment start people become completely non-infectious



Riley RL. Am Rev Tub. 1957;76(6):931–941
Dharmadhikari AS IJTBLD. 2014;18(9):1019–1025
Escombe AR *PLoS Med.* 2008;5(9):1387–1396
Escombe AR CID 2007; 44(10):1349–1357

Cough Aerosol Sampling (CAS)

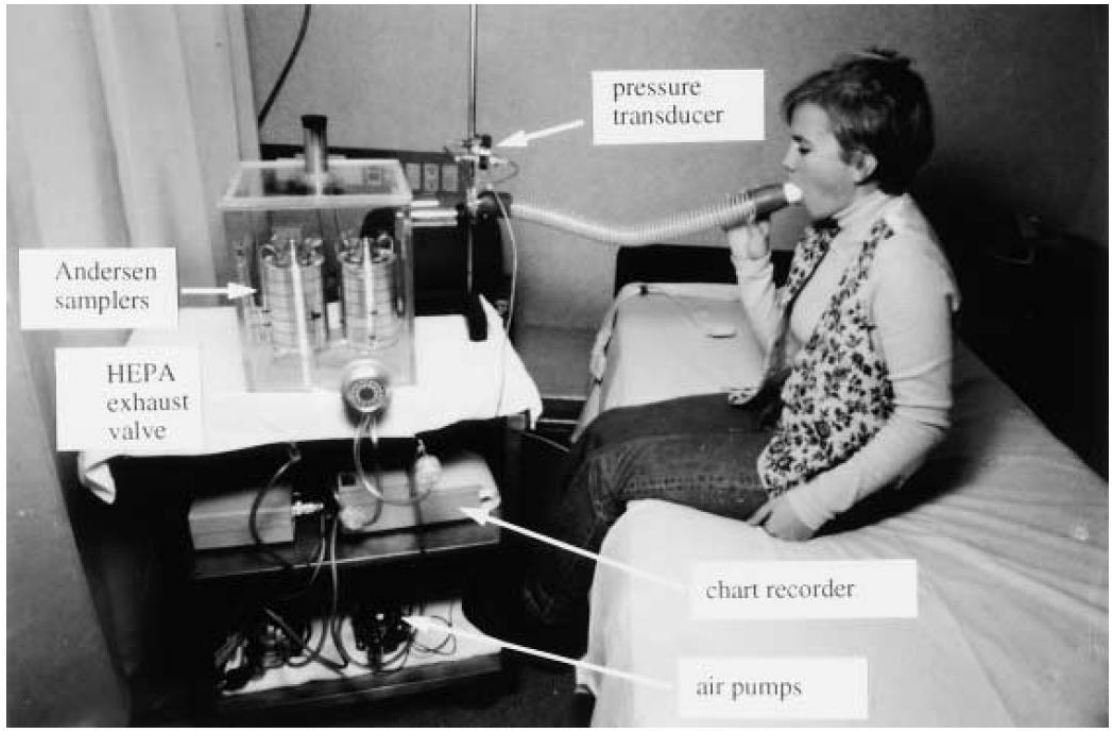
- Specialized cough aerosol sampling devices allow measurement of the number of “infectious aerosols”
- Cohort studies have shown that CAS predicts infectiousness to contacts better than conventional sputum smear and culture



Fennelly KP AJRCCM 2004 and 2012;186(5):450–457

Cough Aerosol Sampling (CAS)

- Two CAS studies show that once on treatment, production of cough aerosols with culturable bacilli declines rapidly within days (even as traditional sputum smears remain positive)
- More study to measure impact of treatment more precisely over the first weeks would be helpful



Fennelly KP AJRCCM 2004 and 2012;186(5):450–457
Jones-López EC CID 2016;63(1):10–20
Jones-López EC AJRCCM 2013;187(9):1007–1015
Acuña-Villaorduña C OFID 2019;6(6):1–9
Theron G Nature Medicine. 2020;26(9):1435–1443

Evidence Review: Take-Home

- Few clinical studies
  - None recent
  - Perhaps more reviews articles than primary studies
- GP and CAS don’t yet directly assess how long until all patients non-infectious - but promising tool
- I find data very convincing that sputum smear is inadequate marker of infectiousness post-treatment

What about the other side of the equation….

Potential Harms of Prolonged Isolation

- Isolation for TB has been associated with significant anxiety, fear, and mood dysfunction
- Patients under isolation often have less visitors than other patients
- Recent qualitative studies in patients with MDR-TB and their family indicate a strong preference for early de-isolation over prolonged hospitalization
- Providers may feel obligated to “intensify therapy” to facilitate smear conversion (even if this may not improve cure rates, even if more attendant AEs)
- Providers may perform more frequent sputum sampling to detect smear conversion ASAP, increasing costs

Gammon J. *Journal of Clinical Nursing.* 1999;8(1):13–21

Basham CA *Ann Epidemiol.* 2021;63:7-14.

Sprague E *Can Respir J.* 2016. 2016;2016:5352625

Moffatt J *Qualitative Health Research.* 2013;23(12):1591–1599

Horter S, *BMC Health Services Research.* 2014;14:1–8..

Implications for Policy

Canada TB Standards Guidelines Process

What we hoped to achieve with policy

- Balance the real, tangible harms of prolonged isolation to person with TB with our responsibility to prevent any avoidable TB transmission

- Achieve agreement on when the risk of TB transmission on treatment becomes negligible – the point where ongoing isolation is no longer justifiable

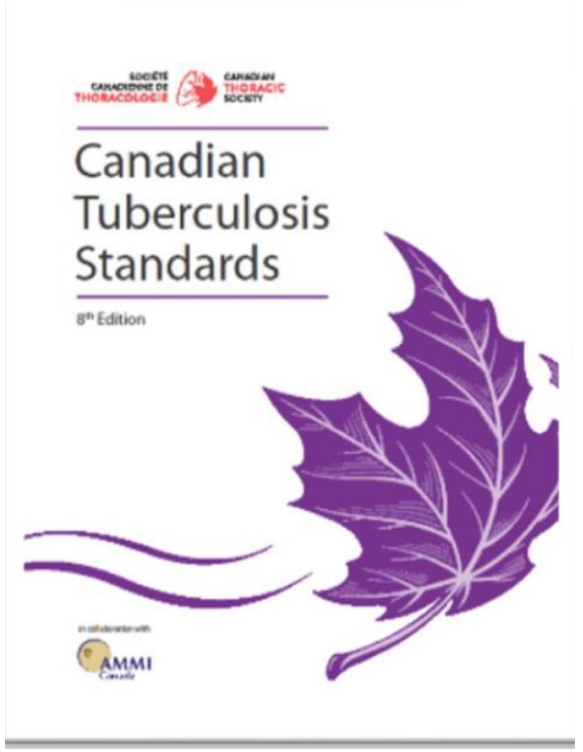
What we initially thought would work

- Let’s go back to the two-week rule with provisos
  - Perhaps extend isolation longer for those residing in very high-risk settings
  - Genotypic DST means we know if treatment is effective immediately and MDR-TB recognition is not delayed

What actually happened

- Had to acknowledge evidence is imperfect
  - Just because we can't find a published case of TB transmission after two weeks of effective TB treatment doesn't mean it can't or won't ever happen
- Changing longstanding policy usually requires robust evidence
  - Even if the original policy of prolonged isolation wasn't based on direct evidence either
- Policymakers were cautious:
  - Increase in number of medically immune compromised people
  - Want policy to be directive, generalizable to all cases, and usable by non-experts
  - With increasing availability of WGS, any transmission from TB patients on effective therapy will be detected/proved

Recommendations: Canadian Standards 8th (March 2022)



All judged as conditional recommendations, poor evidence

Recommendations: Canadian Standards (1)

Smear-negative, rifampin-susceptible pulmonary TB:

Airborne precautions can be discontinued (and person de-isolated) once there is clinical evidence of improvement and a minimum of two weeks of effective therapy

No change from previous edition

Recommendations: Canadian Standards (2)

Smear-positive, rifampin-susceptible pulmonary TB:

Airborne precautions can be discontinued once there is clinical evidence of improvement, a minimum of two weeks of effective therapy has been completed, and there are three consecutive negative acid-fast bacilli sputum smears

Airborne precautions may also be discontinued if there is clinical evidence of improvement after completing a four weeks of effective therapy, even if the sputum smears are persistently positive

Similar to previous but now maximum duration of isolation established

Recommendations: Canadian Standards (3)

<u>Confirmed or suspected rifampin-resistant pulmonary TB:</u>

Airborne precautions may be discontinued once there is clinical improvement, second-line drug susceptibility results are available, and a minimum of four weeks of effective therapy has been completed. In addition, for those initially smear positive, three consecutive sputum smears must be negative.

Significant change – no longer need to confirm culture conversion

Recommendations: Canadian Standards (4)

Caveats and footnotes:

- Emphasis on home-isolation wherever possible, and ASAP
- Reminder to ensure person taking treatment and is adequately supported in their adherence plan
- Effective therapy specifically defined and linked to both treatment response and drug-susceptibility test results
- Genotypic antibiotic susceptibility testing considered adequate

Back to the Questions

Questions from Case:

- It’s not known exactly when someone on effective TB treatment is no longer infectious, but the preponderance of data suggests it occurs quickly, almost certainly within two weeks

- Sputum smear status once patient is responding to effective therapy doesn’t appear to predict infectiousness

- Creating and implementing de-isolation policy requires changing a long-established standard, which is difficult absent definitive data – but it’s still important given burden shouldered by people with TB. We ended up with incrementalism

Discussion Questions:

- What guides de-isolation in Ontario currently?
- How often is home-isolation used? Who doesn’t get home isolation?
- What is availability of AIIR infrastructure?
- How quickly can RIF resistance be detected?

Thanks

Questions, comments:
rdcooper@ualberta.ca

Acknowledgements:

- Drs. Dina Fisher and Richard Long
- Drs. Elizabeth Rea
- Drs. James Johnston, Richard Menzies, Lynn Johnston

Bonus

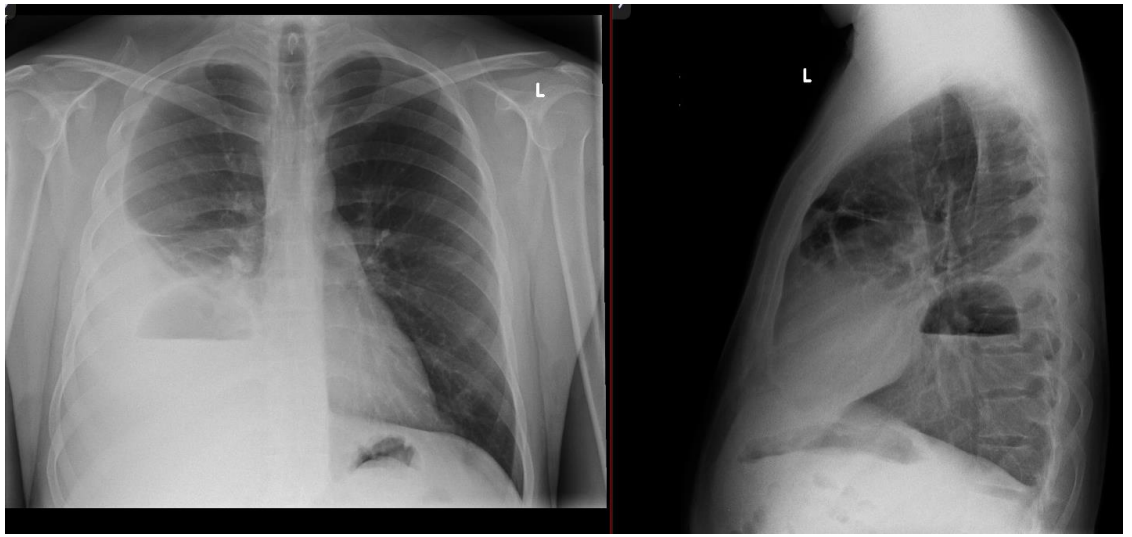
Discontinuation of Airborne Precautions in hospital patients with possible pulmonary TB

Case: 23M from Northern Alberta

- Chest discomfort and mild dry cough for three months
- Cough did not improve after treatment with Amoxil
- Chest Xray → Admit to local hospital
- Transferred down to Edmonton for further investigations

January

April



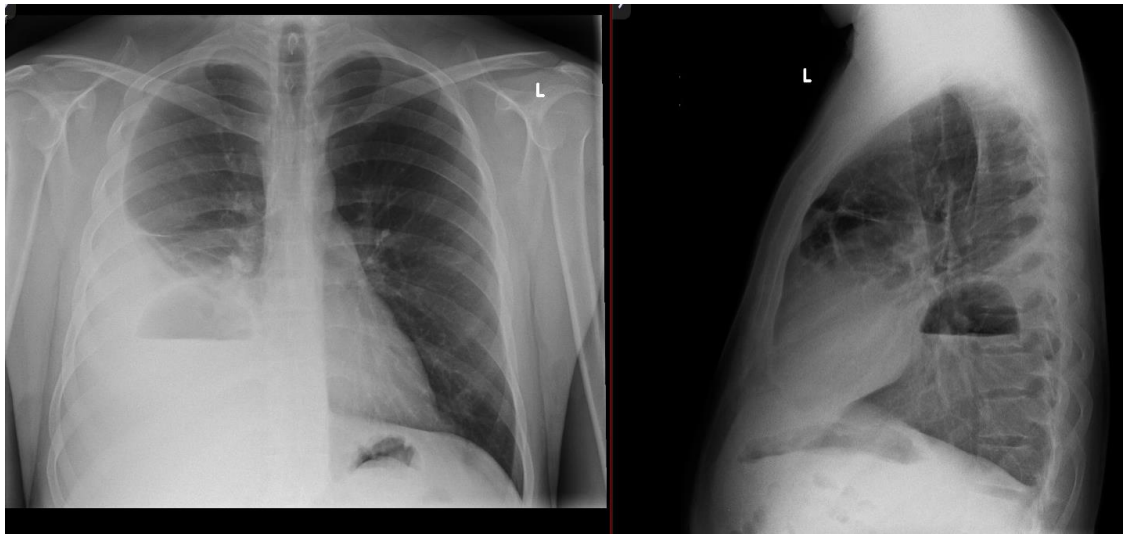
Case: 23M from Northern Alberta

- Broad differential raised by admitting service which included pulmonary TB
- Placed in isolation under airborne precautions
- First sputum samples is smear-negative for AFB

When can airborne precautions be safely removed?

January

April



Discontinuation of Airborne Precautions in hospital patient with possible pulmonary TB

CDC 2005

↓

Three sputum smear-negative
Collected 8-24 hours apart
Alternative diagnosis

CTS 8th Edition 2022

↓

Three sputum smear-negative
Alternative diagnosis
Infection control practitioner approves

US NTBC 2016

↓

Two sputum samples negative on PCR (Xpert)
TB not most likely diagnosis

CTS 8th Ed CRJ 2022
MMWR 2005
National TB Controller Consensus Statemene 2016

Evidence for using PCR to guide removal of AII

- Several retrospective studies, conducted in low-prevalence settings have evaluated sputum TB PCR to guide removal from hospitalAII
- These have found that first sputum sample submitted for TB PCR was able to detect nearly all cases of TB, performing as well as three sputum smears
- Further - PCR shortened time spent in isolation and were cost saving compared to 3 sputum smears
- Most used Xpert-MTB/RIF, others “in-house” assays

Lippincott CID 2014 –UNC N=207
Chaisson JAMA-IM 2018 –UCSF N=621
Seth - ID Week AB793 2018 –Boston Univ N=171
Campos AMJCCM 2008 – Univ Miami N=433
Dowdy PLOS 2013

New Diagnostic for Active TB:

- In Summer 2021 Alberta replaced the old Xpert MTB/RIF PCR test with the new “Ultra” Xpert MTB/RIF PCR cartridge

- Same Cartridge technology but now:
  - Multiple gene targets, larger volume cartridge
  - Ultra can detect 16 bugs per drop of sputum instead of 130
  - Sensitivity on sputum: AFB Stain ~50%, Xpert ~80%, Ultra Xpert ~90%,

Lancet ID 2017 – Xpert Ultra
Zifodaya Cochrane Review 2021

Alberta Pilot

- Calgary Zone Hospitals recently introduced pilot protocol:
  - ICP can remove from airborne precautions if alternative diagnosis and if one respiratory sample of adequate volume is Xpert-Ultra negative for TB

October 2021

Discussion Questions:

- What is current practice in Ontario for removing airborne precautions in those with possible TB?
- Who makes/approves the decision to remove isolation?
- Is there a significant need to speed up the process of removing isolation in these patients?
- How easily can sputum samples be collected?

Extra Slides

What is out there?

- A recent SR for the 2019 WHO TB infection Control Guidelines failed to find definitive clinical data on the precise amount of time it takes to become non-infectious
- Perhaps unsurprisingly, guidelines in various low-incidence countries on when to stop isolation vary

Christof C 2019 WHO TB IP&C Guidelines
Fielding, K 2018 LSTMH TB Center
Petersen *Int J Infect Dis.* 2017;56:34-38

Guidelines from Low-incidence Countries (1/2)

USA	MMWR Hospital Infection Control Guidelines	2005	Smear-positive	Minimum two weeks and three sputum samples are smear-negative
			Smear-negative	Minimum two weeks of treatment
			MDR-TB	Until sputum culture conversion on treatment documented
Europe	ERS/ECDC Statement #20:	2017	Smear-positive	Until sputum smear conversion on treatment achieved
Europe	Reducing tuberculosis transmission: a consensus document from WHO-E	2019	All patients	Sputum smear status should not be used to guide de-isolation. However, specific guidance on duration of infectious cannot be made.
WHO	WHO guidelines on tuberculosis infection prevention and control:	2019	All patients	No specific duration of isolation or parameter provided. Guidelines state that “deisolation should be based on the likely infectivity of the individual case and the availability of other supportive systems (in particular, decentralised models of care)”

Guidelines from Low-incidence Countries (2/2)

UK	NICE Tuberculosis: management and infection contro	2020	Drug-susceptible, pulmonary TB, regardless of smear-status	Consider de-isolation after two weeks of therapy if rifampin-resistance is not suspected and treatment response well-documented.
New Zealand	Guidelines for Tuberculosis Control in New Zealand	2019	Drug-susceptible cases	"A pragmatic approach may be to isolate cases of pulmonary TB until the full susceptibility results are back from the laboratory. This would mean that most patients are in airborne isolation for up to two weeks, by which time infectivity of even heavily smear-positive patients will have fallen to negligible levels." "Default de-isolation occurs at two weeks" in hospitalized patients.
Australia	Infection control guidelines	2016	Drug-susceptible cases	"Should remain isolated until: reduction in or absence of cough; reduced smear burden or smear negativity; assured treatment by direct observation; and an appropriate discharge plan.