

TB Infectiousness and the Impact of Treatment

(Implications for de-isolation policy)



Ryan Cooper, MD MPH
University of Alberta and Alberta Health Services
Edmonton, Canada
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Disclosure

- No financial Conflicts of Interest or relevant disclosures
- Will present some information from upcoming Canadian TB Standards, 8th Edition (2022) – Appendix B

Case: 34M from Northern Alberta

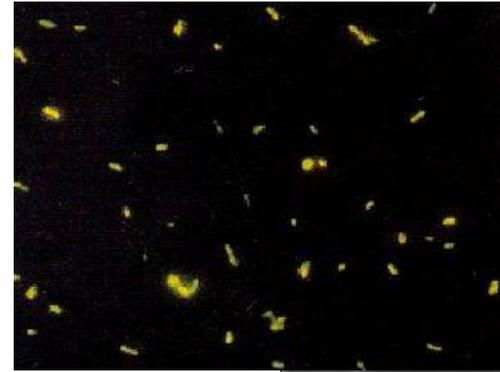
- Persistent cough for three months, intermittent fevers, weight loss
- Cough did not improve after treatment with Amoxil, then Azithromycin
- Chest Xray → admit to local hospital



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



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**

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
- Time to sputum culture conversion is even longer (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

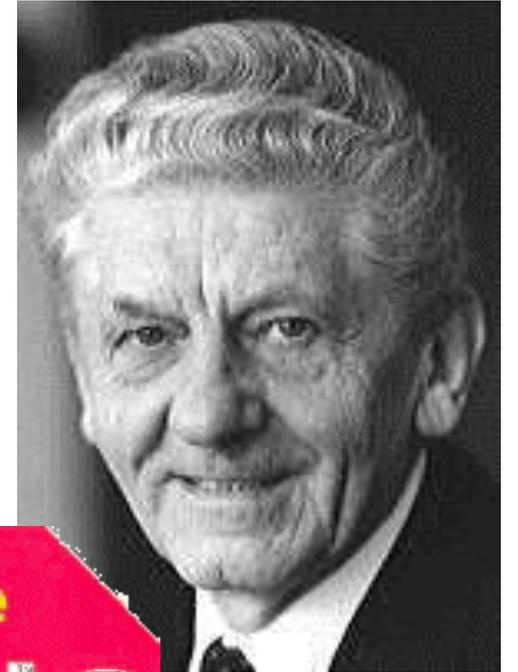
Questions from Case:

- 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 congregating 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

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 sanatorium
 - Co-primary outcome was TB rates in the 693 contacts of participants
 - 5 years of detailed follow-up, high retention in care

Madras RCT – TB in the 693 contacts

- No difference in TB incidence between household contacts of participants treated in sanatorium 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

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

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

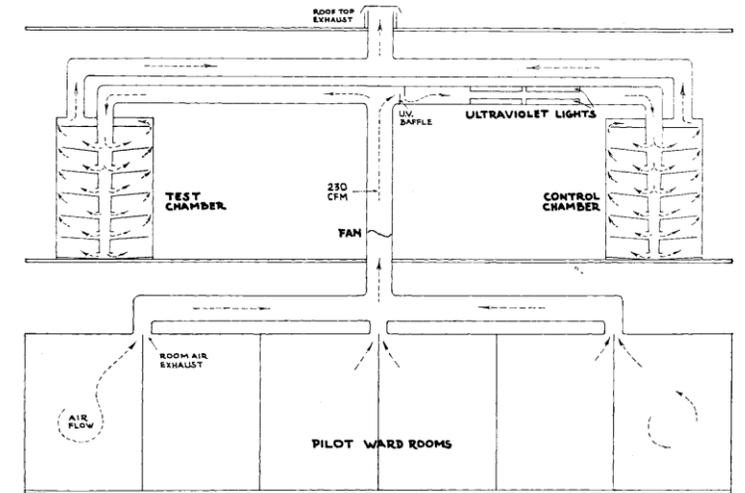
Riley RL Am Rev Resp Disease. 1974;110(6):810–812 – Baltimore Home treatment

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

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

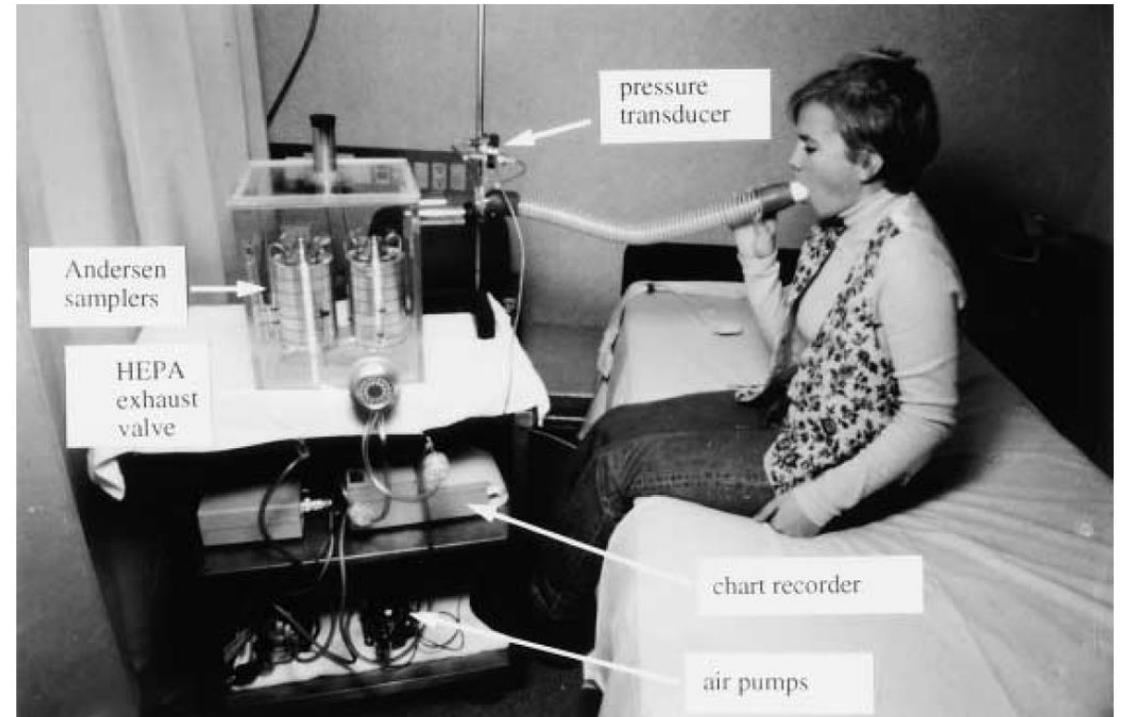
Dharmadhikari AS IJTBLD. 2014;18(9):1019–1025

Escombe AR PLoS Med. 2008;5(9):1387–1396

Escombe AR CID 2007; 44(10):1349–1357

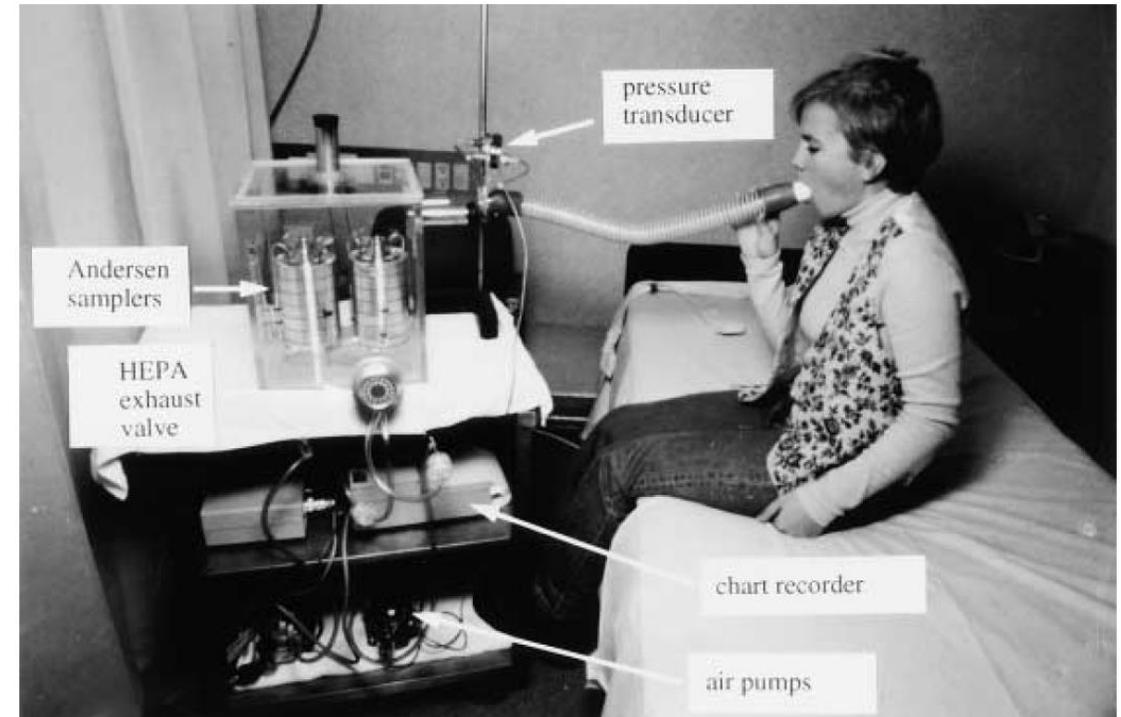
Cough Aerosol Sampling (CAS)

- 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



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

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

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)

Confirmed or suspected rifampin-resistant pulmonary TB:

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.

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

Thanks

Questions, comments:
rdcooper@ualberta.ca

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Extra Slides

Is sputum-smear the right endpoint?

- Most patients (70%) will remain sputum culture positive for weeks, even after achieving sputum smear conversion on treatment
 - Thus, under current guidelines, patients are still excreting culturable and possibly infectious bacilli for weeks after isolation precautions are lifted
 - Median time to culture conversion is ~42 days
- There are several lines of evidence that people with pulmonary TB may be non-infectious (or at least minimally infectious) very soon after initiation of effective treatment, and much sooner than smear- or culture-conversion is achieved....

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 control	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.

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

Case: At local hospital



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

Prior to recognition of TB

Evidence Review - Categories

1. Observation of people on treatment and subsequent rates of transmission to contacts – clinical data
2. Human-to- guinea pig exposure experiments
3. Direct measurements of viable bacilli in patient-produced aerosols
4. In vitro early bactericidal assays (won't discuss today)
5. Studies assessing the potential harms of prolonged isolation.

Evidence – In vitro EBA studies

- In vitro data to guide duration of infectiousness for drug-susceptible TB is best described in a review by Menzies 1997
 - With standard therapy, concentration of viable TB bacilli in sputum is expected to drop 3 logs within two weeks
 - This implies that for sputum smear-negative TB, less than 100 viable bacilli per mL of sputum would survive after two weeks of therapy, and patients could be judged non-infectious.
 - For heavily smear positive patients, two weeks of therapy would still leave more than 10,000 viable bacilli per mL, and patients would remain smear positive and infectious
- But the assumption that bacteriologic status predicts infectiousness once on therapy is challenged by clinical, guinea-pig, and CAS studies