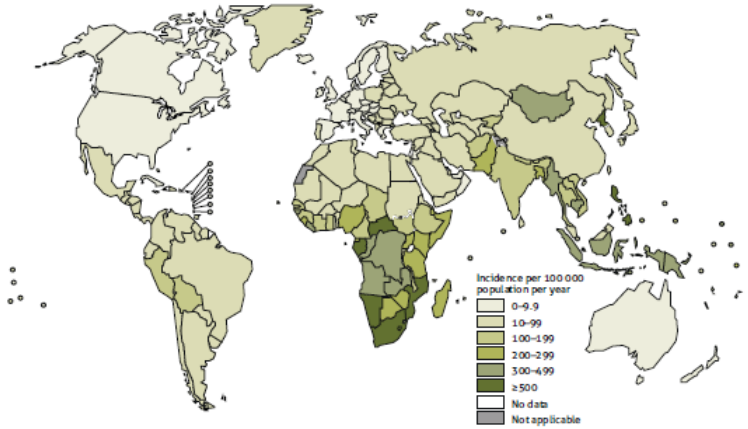

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NTCA Guidelines for Respiratory Isolation and Restrictions to Reduce Transmission of Pulmonary Tuberculosis in Community Settings

Maunank Shah MD PhD
Professor of Medicine, Johns Hopkins University
Medical Director, Baltimore City Health Department TB program

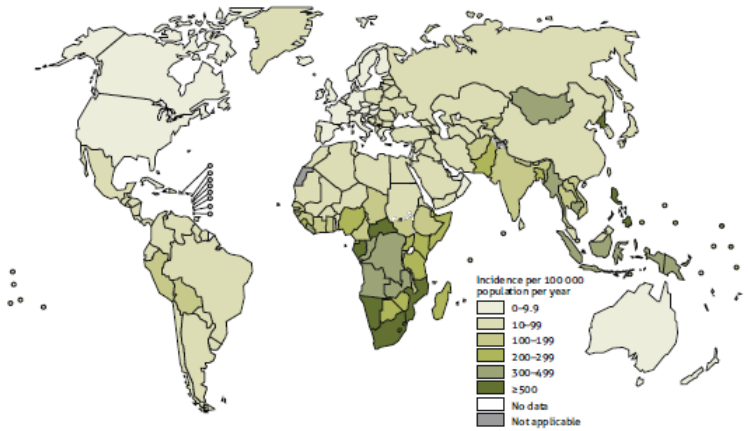
Roadmap and Take Home Points

- A little background and history:
  - Prior to NTCA guidelines, there were no national level guidelines on community isolation for people with TB

- What makes public health guidelines unique?
  - Responsibilities to the community/public health AND responsibilities to the patient
  - Rights-based limitations to public health power

- Guidelines : Balanced group of clinicians, nurses, epidemiologists, TB survivors
  - Evidence: Sputum examination does not correlate reliably with infectiousness after treatment initiation.
  - Evidence: Treatment rapidly renders a person non-infectious
  - Evidence: Low certainty that isolation reduces TB incidence, mortality
  - Evidence: Moderate certainty that isolation worsens mental health, stigma, finances

- Guideline recommendations: Isolation can be considered balancing community and patient well-being. Most people have low likelihood of infectiousness after at least five days of treatment.



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Accessing the guidelines and commentary: CID

Guidelines and Commentary: Clinical Infectious Diseases Available as Advance Articles

NTCA Guidelines:
https://academic.oup.com/cid/article-lookup/doi/10.1093/cid/ciae199

https://tinyurl.com/NTCAisolation

Table 1: Summary of the Recommendations

Table 1. Recommendations for Community-Based Respiratory Isolation and Restriction for Persons With Tuberculosis

Recommendation 1: Goals of RIR	1.1. The decision to recommend TB RIR should consider the potential benefits and harm for both the community and the PWTB.
Recommendation 2: Defining RIR (Table 2)	2.1. RIR in community settings should be conceptualized as a spectrum of tailored restrictions that are individualized for specific circumstances (Table 2).
Recommendation 3: Determining infectiousness and transmission risk (Figure 1)	3.1. Prior to effective[a] ATT initiation, PWTB with higher respiratory bacterial burden (ie, sputum smear and/or NAAT positivity, cavitation on chest imaging) may be considered as relatively more infectious than those with lower bacterial burden, with individual variability. 3.2. PWTB on less than 5 days of effective ATT should be considered relatively more infectious than those on longer durations of effective[a] therapy. 3.3. PWTB on effective[a] ATT for at least 5 days should be considered noninfectious or as having a low likelihood of infectiousness, regardless of sputum bacteriologic status during ongoing ATT (ie, smear microscopy or culture status), with certain exceptions.[b] 3.4. Overall risk of transmission to others should consider both a PWTB's infectiousness, as well as other factors including the environment of potential exposures, durations of exposure, and biological susceptibility of contacts.
Recommendation 4: Determining RIR (Table 3)	4.1. RIR is not recommended for persons with noninfectious forms of TB (ie, localized extrapulmonary TB without pulmonary involvement, as confirmed by sputum bacteriologic studies and/or chest imaging). 4.2. People with pulmonary TB on effective[a] ATT and a low likelihood of infectiousness should not have restrictions in most circumstances (ie, RIR should be removed, if present),[b] with individual exceptions for situations involving higher-risk community settings and populations (eg, children <5, immunosuppressed individuals). 4.3. Community-based RIR may be considered for PWTB who have higher infectious potential in which there is judged to be higher risk of transmission to the community.
Recommendation 5: Determining level of RIR (Table 3)	5.1. When community-based RIR is indicated for a PWTB, a moderate or midlevel range of RIR (Table 2) should be considered appropriate in most circumstances, with individual exceptions. 5.2. Specific RIR levels (eg, low, moderate, or extensive; Table 2) and duration for PWTB should be reassessed routinely (at least weekly) and may be modified based on individual considerations or changing circumstances. 5.3. When RIR is implemented, support should be provided to patients to mitigate anticipated and experienced harms.

Invited Commentary: Drs Caitlin Reed and Neela Goswami

JOURNAL ARTICLE ACCEPTED MANUSCRIPT

Duration of Effective Tuberculosis Treatment, not Acid-Fast Bacilli (AFB) Smear Status, as the Determinant for Deisolation in Community Settings FREE

Neela Goswami, MD, MPH, Caitlin Reed, MD, MPH

Clinical Infectious Diseases, ciae198, https://doi.org/10.1093/cid/ciae198

Published: 18 April 2024 **Article history**

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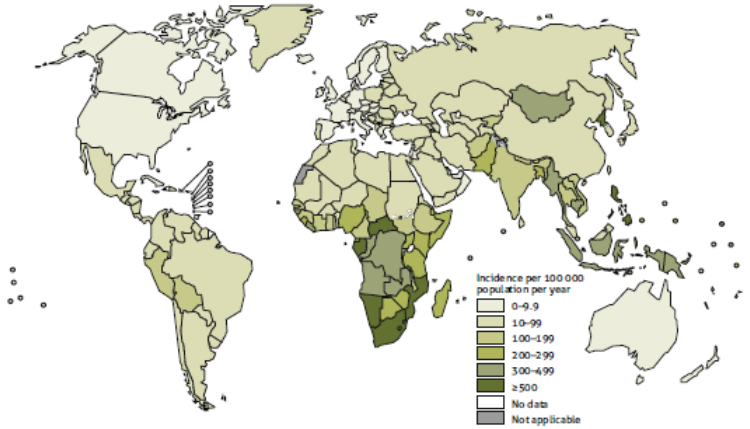
Issue Section: INVITED COMMENTARY

Invited Commentary:
https://academic.oup.com/cid/article-lookup/doi/10.1093/cid/ciae198

https://tinyurl.com/IsolationCommentary

IDSA Endorsement:

- *Endorsed by the Infectious Diseases Society of America, May 2024.*



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Background…

Why were new guidelines needed?

- Lack of national guidelines:
  - There are no existing national level recommendations or guidelines for respiratory isolation (for PWTB) in community settings
- Concern that current practices are not rooted in available scientific evidence
  - Long standing data that treatment rapidly reduces infectiousness and that smear-microscopy does not predict infectiousness
- Patient Centered Care: *Are patient concerns being heard?*
  - Heightened attention to public health interventions that affect individual liberties
- NTCA is unique in its inclusion of public health practitioners, nurses, clinicians, epidemiologists, program managers, and survivors/advocates

Todrys et al. Failing Siracusa: government's obligations to find the least restrictive options for tuberculosis control. Public Health Action 2013

Who makes public health policies unique?

- Public health policy for community based isolation has ethical and legal considerations
  - Closing the public health ethics gap: “public health decision makers haven’t always been transparent…failing to explain the reasoning behind their decisions about interventions such as mask mandates, quarantine and isolation policies, …”

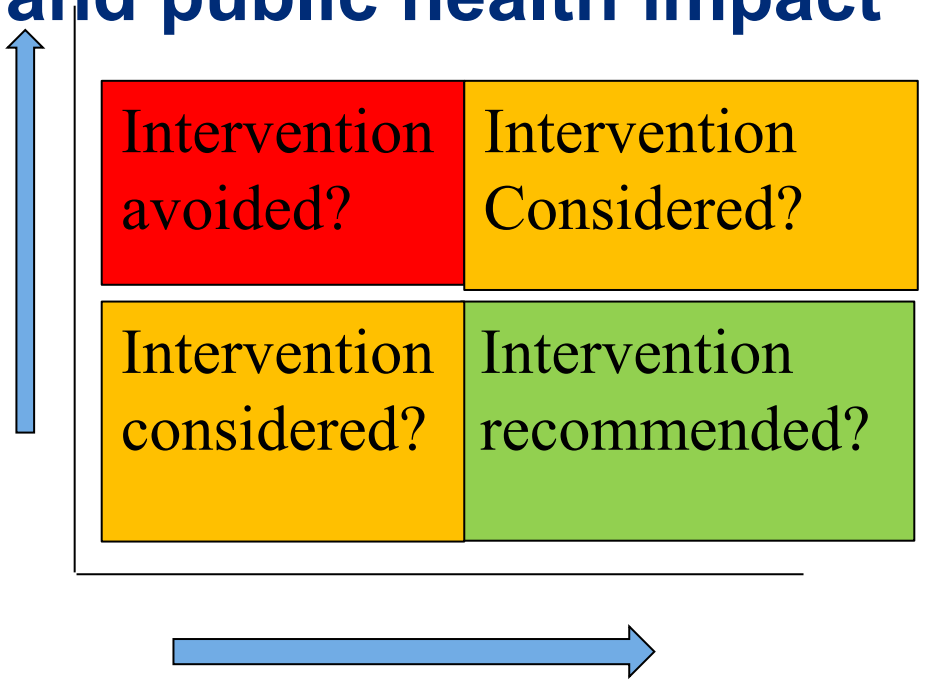
- Burdens and sacrifices on the part of some persons (PWTB) to protect the health of the public

- Public health guidelines are unique because the values and preferences may differ based on the lens

Boon et al. Challenges in applying GRADE approach in public health guidelines: a concept article from GRADE public health group, JCE 2021
Parasidis et al. Closing the public health ethics gap, NEJM Sept 2022

Evidence to recommendations: weighing relative individual and public health impact

Impact on patient Autonomy, rights, health, economics



Public Health Benefit from isolation

Guideline Development Group

Discussed Values and Preferences in constructing the guidelines

"A third function of the Constitution is to limit the ability of the government to violate individual rights, freedoms, and liberties, even when attempting to protect the public's health. Tensions arise when government actions to protect the public's health infringe on individual interests and autonomy. ***Resolving the tension between population-based regulations and individual rights requires trade-offs."***

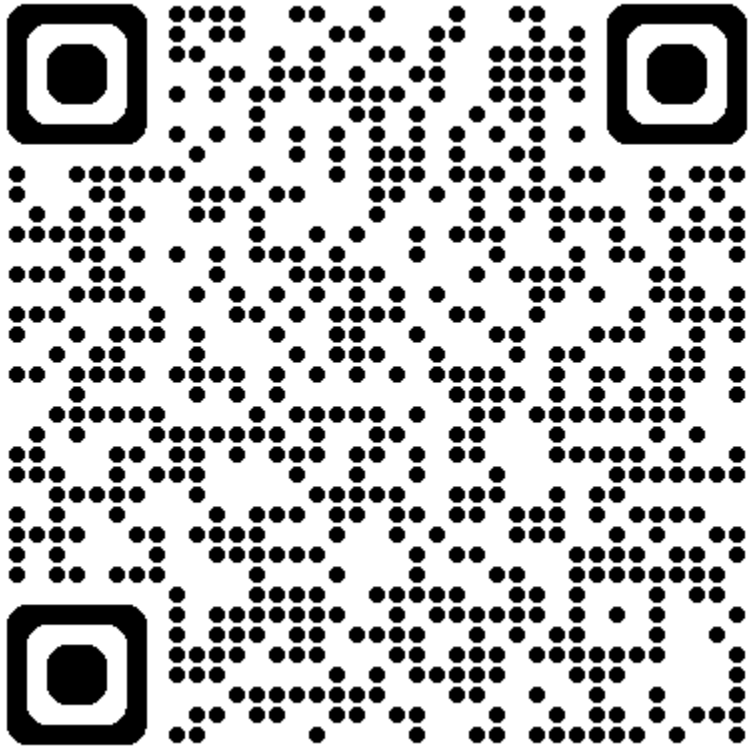
2009: TB Control Laws and Policies—a Handbook for Public Health and Legal Practitioners

Conflicts between values: incorporating an ethical framework

Domain	Term	Explanation
Approaches to uncertainty Support policymakers in interpreting limited scientific data	**Abstention**	Make no recommendation, but be mindful of what will happen in the absence of guidance
	Prioritization	Default to prioritizing a single value or good
	Evidence grading	Transparently describe the limitations of scientific data
	Practical wisdom	Critically examine and interpret limited data using expertise gained through relevant training and personal experience
Ethical values Support policymakers in deciding which effects of a policy decision would be desirable and should be promoted, or undesirable and should be avoided/ minimized	**Wellbeing**	**Individual** Health – Individual health and safety outcomes Livelihood – Access to work, school, housing, food, and basic resources Social relations – Access to a stable and supportive social network Esteem – Self-esteem and dignity **Community** Public health – Community and population health and safety outcomes Economic productivity – Community level economic stability; GDP Social cohesion – Strength and stability of shared community bonds Community identity – Sense of national, regional, or group identity and esteem
	Justice	**Recognitional:** Be aware of differences in identity and experience **Distributive:** Seek a fair distribution of benefits and burdens **Procedural:** Ensure due process
	Liberty	Freedom from obstructive interference, without exclusion from beneficial or empowering resources Incorporate opportunities for choice Offer compensatory resources
Justificatory conditions Support policymakers in determining whether a compromise between values is acceptable and fair	**Necessity**	Infringement on one value to promote another must be necessary or unavoidable
	Proportionality	Infringement on one value must be balanced by at least qualitatively proportional promotion of another
	Least infringement	Refine the conditions of a proposed compromise to minimize infringement on any value
	Lines in the sand	Identify the boundaries of a pluralistic framework by defining compromises that would be unacceptable because they violate fundamental rights or obligations

Kates et al. **Integrating ethics in public health guideline development: a case-study of the NTCA guidelines on respiratory isolation for persons with TB in community settings,** in preparation JID

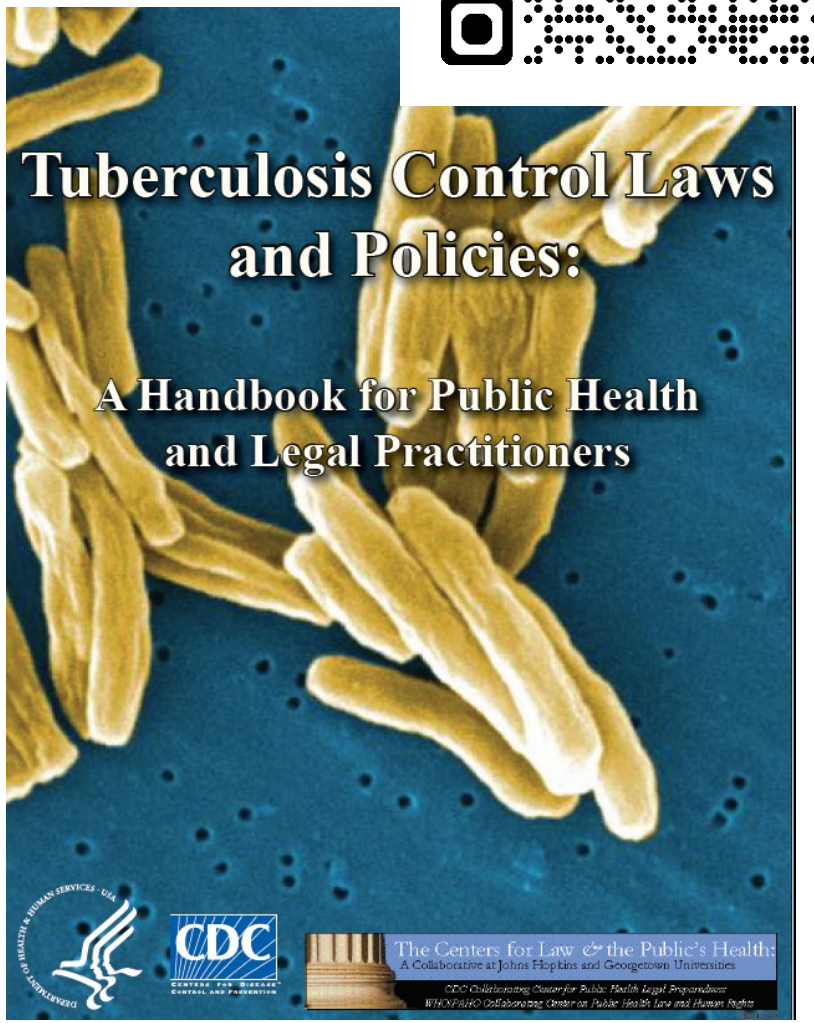
Integrating ethics in public health guideline development: a case- study of the NTCA guidelines on respiratory isolation for persons with TB in community settings



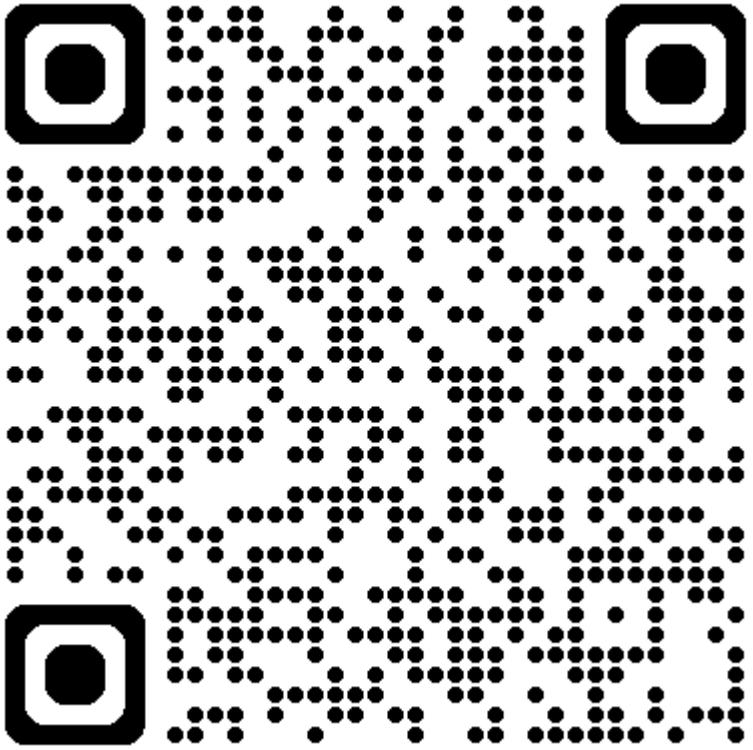
- https://doi.org/10.1093/intdis/jiae478

Is current practice consistent with ethical and legal principles governing public health authority?

- 2009: TB Control Laws and Policies—a Handbook for Public Health and Legal Practitioners
- Review the basic legal framework for control of communicable diseases
- Limitations of government powers:
  - Concerning powers to control TB and other communicable diseases, public health authorities must balance the magnitude of the public health risk against the rights of the individuals or groups." [17]
  - "prohibit government from depriving individuals of "life, liberty, or property without **due process of law**
  - "least restrictive means" should be used that achieves the purposes of the restrictions



Rights-Based Legal Considerations for TB Isolation Practices in Community Settings in the Post-Pandemic Era



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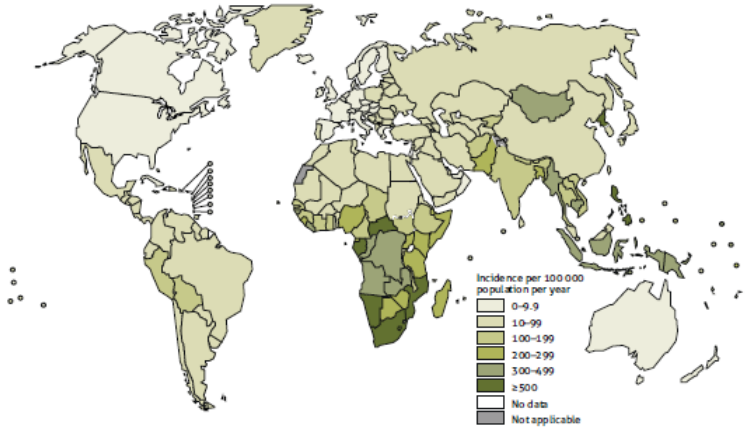

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Recommendation 1 and 2:
1.Goals of respiratory isolation
2.Defining respiratory isolation

Recommendation 1: Goals of respiratory isolation and restrictions

1.1: The decision to recommend TB respiratory isolation and restriction (RIR) should **consider the potential benefits and harm** for both the **community and the PWTB.**

- Formalizes the ethical and legal principle that decisions about RIR must consider both:
  - Individual Well Being: Duties as a health care professional to maximize health of the patient (“Do no harm”)
  - Community Well Being: Responsibilities as a public health professional to minimize transmission and negative health outcomes for others

Recommendation 2: Defining RIR

- 2.1 Respiratory isolation restrictions in community settings should be conceptualized as a **spectrum of tailored restrictions** that are individualized for specific circumstances

  - **Extensive Restrictions**:
    - Individuals limit movement to agreed upon location (e.g., home)
    - Exceptions are discussed with health department
    - Avoid visitors (previously unexposed)
  - **Moderate Restrictions**:
    - Spend *majority* of time at agreed upon location
    - Most activities in settings with good or natural ventilation (e.g., outdoors) allowable with discussion with health department
      - Avoid prolonged (e.g., multiple hours), or repeated close-contact, particularly those previously unexposed, particularly in indoor settings
      - Other risk mitigation strategies may be considered (i.e., surgical masks, KN95, N95)
  - **No restrictions**

General Schematic of Decision-making

Responsibility to the community/public health

Community Benefits (based on averting transmission)

1.*Is the PWTB infectious?*

- *Pre-treatment bacterial burden*
- *Duration of treatment*

2.*If infectious, is there significant risk of transmission in the community?*

3.*Will isolation meaningfully prevent transmission and improve population outcomes*

Responsibility to patients

Impact on patient:

1.Mental Health

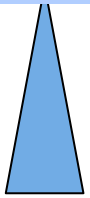
2.Financial/Employment

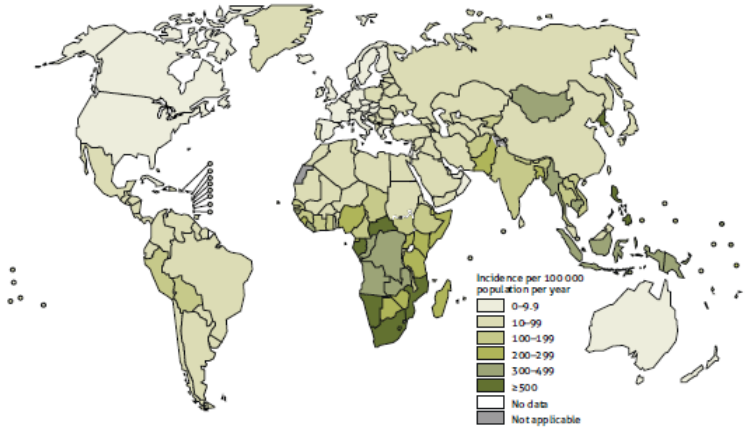
3.Food

4.Housing

5.Social/Stigma

1.1: The decision to recommend TB respiratory isolation and restriction (RIR) should **consider the potential benefits and harm** for both the **community and the PWTB.**





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Recommendation 3: Determining infectiousness and transmission risk

Assessing infectiousness and the impact of effective treatment to guide isolation recommendations for people with pulmonary tuberculosis

The duration of effective treatment is the primary determinant of infectiousness, not smear microscopy

https://doi.org/10.1093/infdis/jiae482

Prior to treatment, are bacteriologic tests associated with infectiousness?

- Sputum smear-microscopy:
  - Positive sputum smear is associated with bacterial burden (for clinical purposes; requires 5000-10000 AFB/ml)
  - Cohort studies suggest a higher proportion of contacts [uncertain duration] exposed to person with smear-positive TB have TB infection compared to smear-negative
  - Molecular fingerprinting studies suggest that persons with smear-negative PTB account for 13-17% of TB transmission.
- Sputum NAAT: semiquantitative results are available in the form of cycle thresholds (Ct)
  - Cycle thresholds correlate with bacterial burden (for clinical purposes)
  - Cohort studies suggest that Ct are associated with likelihood of IGRA conversion among contacts

Shaw, Wynn-Williams 1953, Van Geuns, Behr Lancet ID 1999, Tostman CID 2008, Asadi eClinical Medicine 2022

Prior to treatment, are bacteriologic tests associated with infectiousness?

- Cough Aerosols: positive cultures from cough aerosols may be better predictors of infectiousness than sputum smear-microscopy
  - High variability in cough aerosol positivity between individuals (20-40%)
  - Higher colony forming units in CASS are associated with higher rates of TB infection among contacts

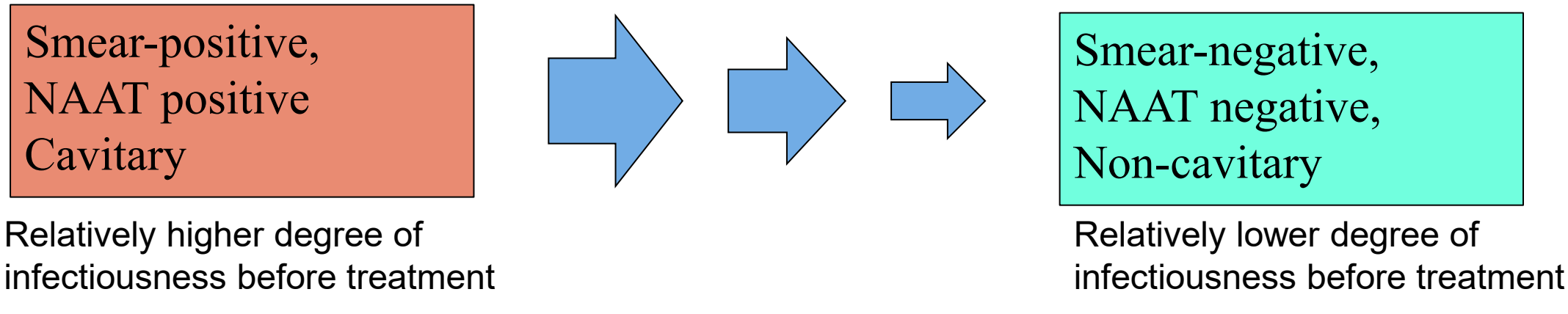
- Face Mask Sampling (FMS):
  - Cohort studies suggest that levels of M. tuberculosis in FMS are associated with incident TB infection among contacts, measured by IGRA
  - FMS has poor correlation with sputum smear-microscopy

- *Suggests that our sputum may not be the optimal measure of infectiousness*

Acuna-Villaorduna OFID 2019, Fennelly 2004; Fennelly 2012; Jones-Lopez 2013

SUMMARY: BEFORE TREATMENT, higher bacterial burden is likely associated with infectiousness

- 3.1 *Prior to effective treatment initiation, PWTB with higher respiratory bacterial burden (i.e., sputum smear and/or NAAT positivity, cavitation on chest imaging) may be considered as relatively more infectious than those with lower bacterial burden, with individual variability.*
  - Strong recommendation, Moderate certainty of evidence



SUMMARY: AFTER TREATMENT INITIATION, infectiousness declines rapidly (regardless of smear/culture)

- "Effective" treatment within available studies refers to usage of multi-drug regimen to which the *M. tuberculosis* isolate is susceptible

- **No single test or biomarker that can measure infectiousness**

  - Laboratory bacteriologic studies (measuring viability)

  - Human-to-guinea pig experiments
    - No human-to-human randomized trials to measure the impact of treatment on infectiousness

  - Clinical studies

LAB STUDIES: Viability declines within 48hours of treatment

- Laboratory bacteriologic studies:
  - Early bactericidal activity studies (*recognizing that viability may not correspond to infectiousness)*
    - Relative to bacterial burden prior to treatment, declines > 90% within the first two days (10-fold) and >99% (100 fold) at later time points (i.e., 14 days)
    - "If no other factor other than elimination of viable *M. tuberculosis* were to account for infectivity, majority of patients who receive treatment for as few as 2 days of RHZE could be assumed to have an infective potential that averages 10% of that at the time of diagnosis*"
    - **Suggests the persons with TB are at their highest infectious potential prior to treatment initiation, and that the bacterial burden declines rapidly**

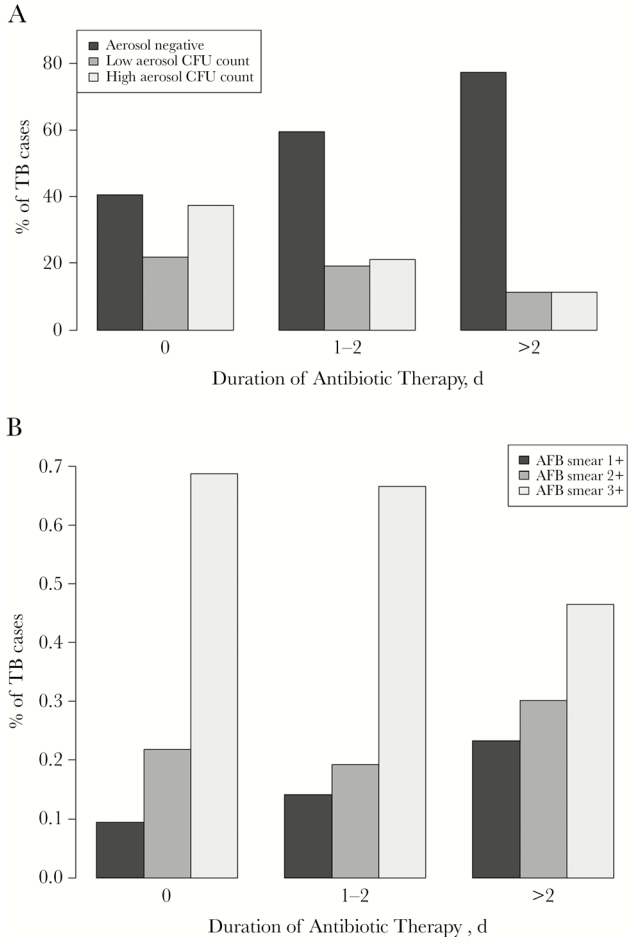
*Controlling Tuberculosis in the United States: Recommendations from the American Thoracic Society, CDC, and the Infectious Diseases Society of America

LAB STUDIES: Viability declines within 48hours of treatment

- Laboratory bacteriologic studies
  - Treatment effect in Cough Aerosol Studies
  - Culture positive in 60% of those with no treatment
  - Culture positive in only 20% receiving > 2 days of treatment
  - Not apparent with sputum smear

  - *“Antituberculous therapy seems to rapidly decrease bacterial viability in aerosol samples”*

  - *We posit that effective therapy could decrease tuberculosis infectiousness in 2 ways: (1) by decreasing bacterial burden and (2) by impairing the innate ability of the mycobacteria to survive in aerosol samples.”*



Acuna-Villaorduna 2019 OFID, https://doi.org/10.1093/ofid/ofz184

Transmission Experiments: *transmission stops almost immediately after treatment initiation*

- Human to guinea pig (HTG) transmission studies
  - Guinea pigs (GP) exposed to individuals with drug-susceptible TB receiving streptomycin/INH/PAS
  - Comparing those initiating treatment to not on treatment, 98% reduction in GPs infected
    - "decrease in infectiousness preceeded elimination of organisms from sputum…"
  - Another cohort on treatment, with 3 mo of continuous exposure to GP, only 1/90 GP infected
  - More recent, expose GP after 72 hours of BPaL resulted in no GP being infected

- Decline in infectiousness appears to be an almost immediate effect in HTG studies

Riley et al 1957, Escombe CID 2007, Dharmadhikari IJTLD 2014

WHY: *Treatment damages the bacterium even if you can still see it/grow it*

- Studies of gene-expression suggest alterations, despite viability in mycobacterial culture:
  - *changes in M. tuberculosis transcriptional profiles within days of treatment initiation, which may indicate lower pathogenicity and infectiousness*
  - *mRNA abundance (gene expression) declined by 98% within 4 days*
  - *rRNA synthesis (RS) is suppressed within hours of exposure to sterilizing drugs sch as BDQ and PZA in vitro (while colony forming units did not decrease substantially until 8-12 days)*

- **Suggest that ability to generate infectious aerosols capable of infecting others may decline prior to absence of growth in culture, or visibility on microscopy.**

  – Nonetheless, many studies to evaluate treatment effect focus on viability in culture

Clinical Research: No difference between isolation/separation and treatment

- Clinical Research (trials and observational data, each with limitations)
  - Madras RCT: similar rates of household contact transmission regardless of PWTB's sputum smear status when comparing those initiating treatment at home vs those separated
    - Over 5 years, 11 vs 10.5% developed TB disease
    - 22% versus 23% with TB infection (transmission)
    - Suggests rapid effect without increased incremental risk despite ongoing exposure
  - Multiple Cohort Studies:
    - No or few conversions (TST) after treatment initiation, irrespective of sputum smear status.

Sputum Smear and Culture do not appear to reliably predict infectiousness during effective therapy

- Observation on microscopy may not correspond to viability (culture)
- Detection in laboratory culture (viability, culture positivity) may not correspond to infectiousness (transcriptomic, gene-expression studies)
- Recent analysis:
  - Mean time to smear-conversion 34 days +/- 26 days (SD)
  - Mean time to culture conversion 38 days +/- 32 (SD)

- **There was no evidence of an association between smear-status or culture-status and infectiousness in available experimental or epidemiological studies of individuals on effective treatment.**

Fortun et al. AAC 2007

Determination of infectiousness: disconnect between scientific evidence and current practice

Editorial Response: An Unholy Trinity—Three Negative Sputum Smears and Release from Tuberculosis Isolation

"In an understandable effort to minimize the likelihood of similar mishaps elsewhere, the CDC guidelines established several criteria for removal of patients from isolation: three consecutive negative smears of specimens"

"This represents a drastic break from the previous practices in the tuberculosis field, which had identified 2 weeks of chemotherapy as a presumptive surrogate for noninfectiousness"

"If one accepts the premises of the CDC guidelines…clinicians would be compelled to keep smear-positive TB patients in isolation for ~6-7 weeks"

"Finally, health care workers should realize that the great majority of patients with TB are rendered non-infectious by modern chemotherapy"

"The requirements for 3 negative sputum smears represents an exaggerated response to some unusual circumstances that rarely apply."

Iseman CID 1997

TREATMENT is the likely the best marker of infectiousness

- Summary of evidence by other guideline groups and public health agencies:
  - "*Aforementioned studies do not provide convincing evidence that patients undergoing effective treatment can infect their contacts, regardless of smear or culture status*"
    - Reducing TB Transmission: consensus document from the WHO Regional office for Europe
  - "*The preponderance of data suggests that appropriate treatment rapidly renders people with tuberculosis (TB) non-infectious, perhaps within a few days of treatment initiation, even for initially smear-positive cases*."
  - *"These studies also suggest that sputum smear and culture status are less predictive of infectiousness once patients are established on effective therapy."*
    - Canadian Tuberculosis Standards 8th edition
  - *"treatment will sufficiently damage mycobacteria to affect transmissibility of organisms much earlier than the damage required to prevent growth in liquid culture in the laboratory"*
    - Guidelines for tuberculosis control in NZ, 2019

How much treatment is needed to reduce *M. tuberculosis* transmissibility?

- **The effect of treatment appears to be rapid and steady**

- **Infectiousness is anticipated to decline within a few days of treatment in most individuals, even in persons with smear-positive TB**

- **There may be individual variability: factors for consideration**
  - Initial bacterial load/disease site (may have longer duration of detectable bacteria in culture)
  - Immune status (area of uncertainty)
  - Bactericidal potential of the treatment regimen (may affect rate of decline in viability, recognizing viability may not be sole determinant of infectiousness)
  - Sterilizing potential of the treatment regimen (may affect gene expression, infectiousness)

Summary: MOST individuals are non-infectious after at least five days of therapy, and likely declines further with additional treatment

- ***3.2: PWTB on less than five days of effective treatment should be considered relatively more infectious than those on longer durations of effective therapy***
  - Strong recommendation, Moderate certainty of evidence

- ***3.3: PWTB on effective[1] treatment for at least five days should be considered non-infectious or low likelihood of infectiousness, regardless of sputum bacteriologic status during treatment (i.e., smear-microscopy, NAAT or culture status), with certain exceptions[2]***
  - Conditional recommendation, Moderate certainty of evidence

--No single test or treatment duration universally predicts non-infectiousness.

--Available evidence suggests **most** PWTB are unlikely to transmit to others within the first few (24-72hours) days after treatment initiation.

--Other factors to consider may include pre-treatment bacterial load, adequacy and adherence to treatment regimen, and/or adherence and clinical response to treatment.

Recommendation: Consider both infectiousness and community transmission risk

- ***3.4: Overall risk of transmission should consider BOTH a PWTB's infectiousness, AS WELL AS other factors including environment of potential exposures, duration of exposures, and biological susceptibility of contacts***

Transmission depends on more than infectiousness of a person with pulmonary TB

- Different environments and activities are anticipated to have different transmission risk, independent of infectiousness of PWTB
- Studies suggest that the risk of transmission is lower with outdoor activities and those with natural ventilation, compared to shared ventilation indoors
- There is no minimum duration of exposure that is required for infection, but studies suggest that longer durations have greater risk than shorter
  - 120 contact hours per month has been used to stratify risk in prior contact investigation guidelines
  - 8 hours of close exposure in closed space has been used (derived from limited evidence related to air travel)
- ***Individual circumstances and community context is important for assessing the expected benefits from isolation decisions***.

Guidelines for the investigation of contacts of persons with infectious tuberculosis. Recommendations from the National Tuberculosis Controllers Association and CDC. MMWR Recomm Rep **2005**; 54(Rr-15): 1-47

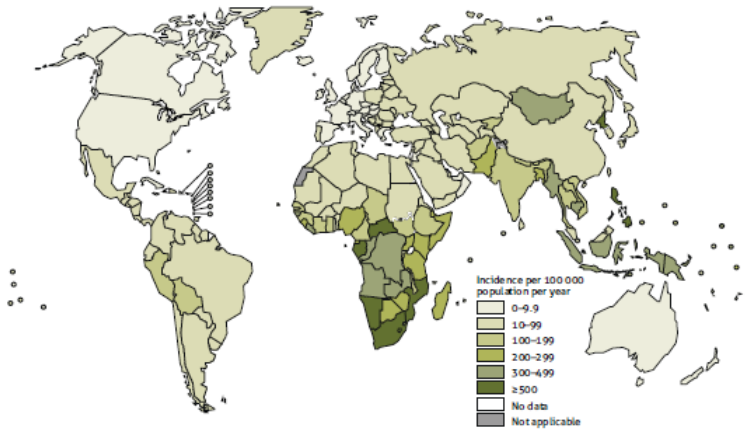
ARPE Contact Investigation Data

Counts for Smear-positive Cases

Cases and Contacts	2017	2018	2019	2020	2021
Cases for investigation	3364	3398	3481	2879	3320
Cases, no contacts	247	187	193	206	270
Number of contacts	51447	53783	51419	35915	27202
Evaluated	41489	42302	38942	28095	20738
TB disease	416	352	345	317	381
Latent TB infection	6428	6044	5587	4229	4438
	15%	14%	14%	15%	21%

Counts for Smear-negative Cases

Cases and Contacts	2016	2017	2018	2019	2020
Cases for investigation	1,932	1,827	1,903	1,784	1333
Cases, no contacts	401	312	258	257	205
Number contacts	13,914	14,100	13,589	12,679	8795
Evaluated	11,460	11,627	10,703	9,905	6893
TB disease	60	72	72	63	66
Latent TB infection	1,493	1,319	1,427	1,146	896
	13%	11%	13%	11.5%	13%



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Should individuals with pulmonary TB in the community be isolated?

Recommendation 4: Determining whether community based RIR is indicated

General Schematic of Decision-making

Treatment is the best 'marker' of infectiousness

Net transmission depends on more than just being infectious

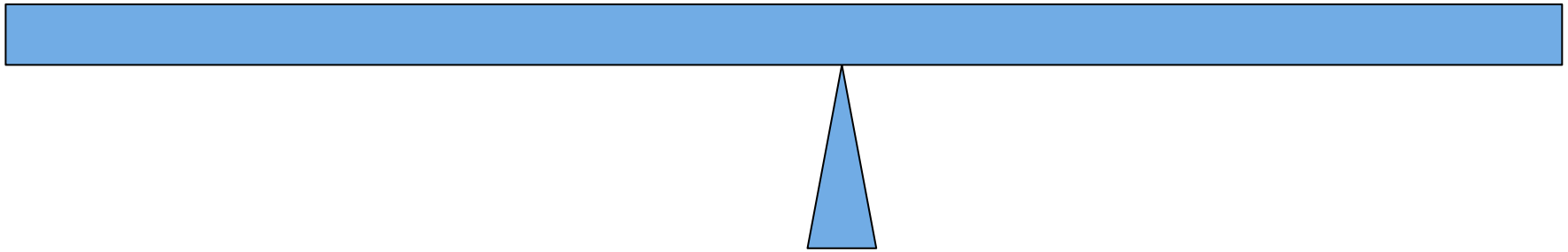
????

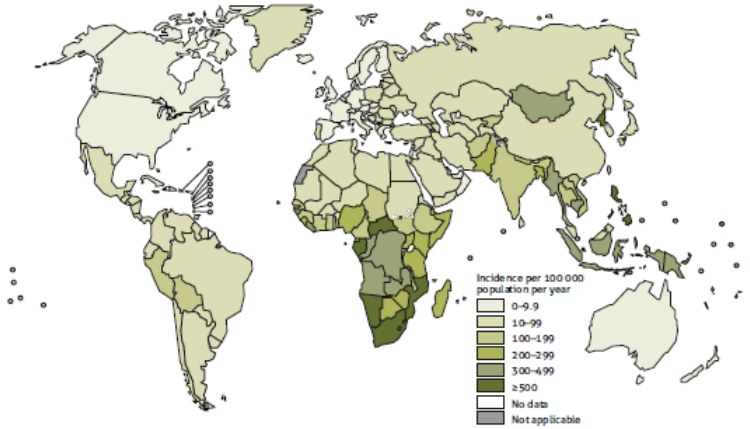
Community Benefits (based on averting transmission)

1. *Is the PWTB infectious?*
   - *Pre-treatment bacterial burden*
   - *Duration of treatment*
2. *If infectious, is there significant risk of transmission in the community?*
3. *Will isolation meaningfully prevent transmission and improve population outcomes*

Impact on patient:

1. Mental Health
2. Financial/Employment
3. Food
4. Housing
5. Social/Stigma





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Evidence summary of benefits and harms:

Should individuals with pulmonary TB in the community be isolated

Summary of "Benefits" (population outcomes) of isolation of persons with pulmonary TB

- One RCT ('Madras trial') assigned PWTB to treatment in sanatorium (i.e., isolation) versus at home (i.e., not isolated)
  - No difference in incident TB infection among contacts
  - No difference in incident TB disease among contacts
  - No difference in mortality among PWTB or contacts
- Modeling studies: possible reduction in TB transmission
  - *indirect, modeled interventions included other prevention measures, and many assumptions*
- *Healthcare settings*: Studies typically included other infection control measures*
  - *LTBI: range from 1% increase to 20.5% decrease*
  - *"Packages of IPC measures appeared to reduce MTB transmission, but evidence for effectiveness … was indirect and low quality."*
- **Guideline panel acknowledged that measuring these outcomes is challenging, and absence of data may not reflect absence of benefit (Very low certainty of evidence regarding magnitude of benefits)**

*Karat et al. CID 2021.

General Schematic of Decision-making

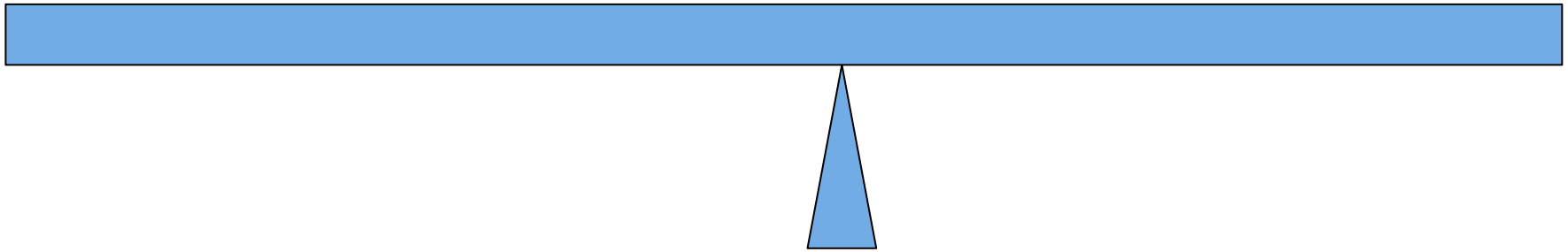
Treatment is the best 'marker' of infectiousness

Net transmission depends on more than just being infectious

Very Low Certainty of evidence

Community Benefits (based on averting transmission)

1. *Is the PWTB infectious?*
   - *Pre-treatment bacterial burden*
   - *Duration of treatment*
2. *If infectious, is there significant risk of transmission in the community?*
3. *Will isolation meaningfully prevent transmission and improve population outcomes*



Summary of “Harms” (patient outcomes) of isolation of persons with pulmonary TB

- *Hospital duration:* increased hospital duration
  - *Limited data on community-based isolation*
- *Costs:*
  - increased health system costs (primarily with hospitalization)
  - Patient related costs related to loss of income, food insecurity, increased transporation costs, housing insecurity, and negative impact on educational progress
- *Mental Health/Stigma:* Several qualitative studies
  - *Negative effects, particularly in populations with health disparities including migrants/immigrants, indigenous persons, incarcerated persons*

- **Guideline panel acknowledged that while these effects may vary by setting and individual circumstance, there was consistent evidence of negative impact for PWTB (Moderate certainty of evidence for harms or undesirable outcomes)**

General Schematic of Decision-making

Treatment is the best 'marker' of infectiousness

Net transmission depends on more than just being infectious

Very Low Certainty of Evidence

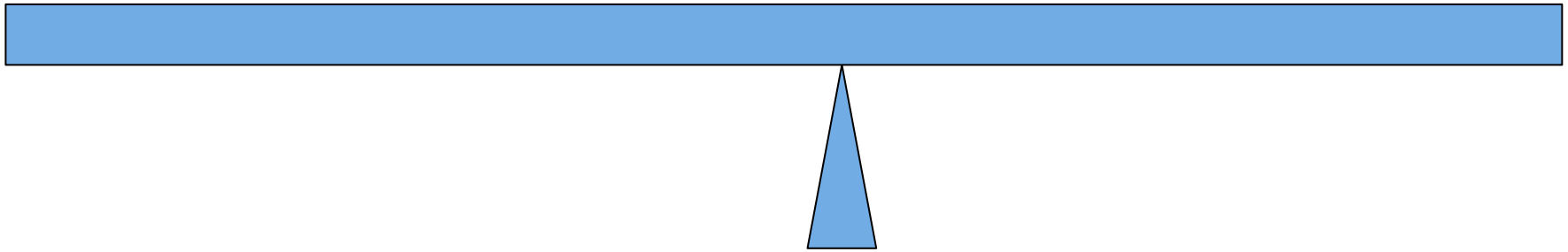
Community Benefits (based on averting transmission)

1. *Is the PWTB infectious?*
   - *Pre-treatment bacterial burden*
   - *Duration of treatment*
2. *If infectious, is there significant risk of transmission in the community?*
3. *Will isolation meaningfully prevent transmission and improve population outcomes*

Moderate Certainty of Evidence

Impact on patient:

1. Mental Health
2. Financial/Employment
3. Food
4. Housing
5. Social/Stigma



No restrictions for persons with localized extrapulmonary TB

- ***4.1: RIR is not recommended for persons with non-infectious forms of TB (i.e., localized extrapulmonary TB without pulmonary involvement, as confirmed by sputum bacteriologic studies and/ or chest imaging).***

- Foundational principle that persons not considered infectious should not have isolation or restrictions of liberties

Consider restrictions/isolation when infectious AND community risk factors for transmission

- ***4.3: Community-based RIR may be considered for PWTB that have higher infectious potential in which there is judged to be higher risk of transmission to the community***
  - ***Conditional recommendation, Low Certainty of Evidence***

- Infectious potential is based on assessment of pre-treatment bacterial burden and duration of effective treatment

- Community assessment includes considerations of the environment, duration, proximity and frequency of new exposures within school, employment and other activities

- Based on considerations of weighing values and preferences related to community and individual well being and harm.

- **“Desirable consequences of RIR probably outweigh undesirable consequences in most situations”**

The benefits of isolation decline after a person has been on treatment for > 5 days, and many people can be de-isolated

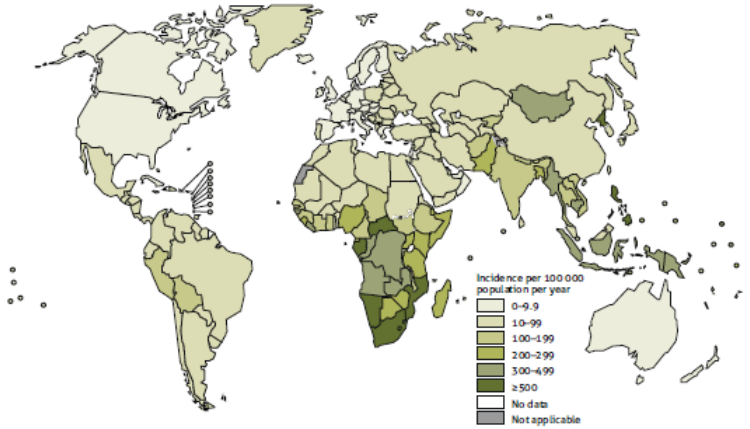
- ***4.2: People with pulmonary TB on effective treatment and low likelihood of infectiousness should not have restrictions in most circumstances (i.e., RIR should be removed, if present), with individual exceptions for situations involving higher risk community settings and populations (e.g., children < 5, immunosuppressed individuals)***
  - ***Conditional recommendation, Low Certainty of Evidence***

- **Undesirable consequences outweigh desirable consequences in most situations at longer durations of the intervention.**

- Longer durations of treatment may lead to greater certainty of diminishing infectiousness

Integrated schematic and decision-aid: TABLE 3

Recommendation 3: Determining infectiousness			Recommendation 4: Determining RIR	Recommendation 5: Level of RIR	Notes
Treatment Status	Pre-treatment Respiratory bacterial burden[1]	Assessment of individual infectiousness*	Is RIR indicated? [4]	What level of RIR to choose? (Rec. 2, Table 2)	Specific Recommendations should balance community and patient risks and benefits (Rec 1)
Pre-treatment	High	Highest (Rec. 3.1)	Yes (Rec 4.3)	Extensive	Support should be provided to mitigate harm to PWTB (Rec 5.3).
	Low	Moderate (Rec 3.1)	Yes (Rec 4.3)	Extensive or Moderate (Rec 5.1)	
Treatment <= 5 days	High	Moderate (Rec 3.2)	Yes (Rec 4.3)	Moderate (Rec 5.1)	
	Low	Moderate/Low (Rec 3.2)	Yes (Rec 4.3)	Moderate (Rec 5.1)	
Treatment > 5 days	High	Low (Rec 3.3) [2]	Not indicated in most situations (Rec 4.2)[3]	None	Individual exceptions to continue RIR may be considered (Rec 5.2) [3]
	Low	Lowest (Rec 3.3)		None	



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Recommendation 5: Determining level of respiratory isolation and restrictions

Moderate restrictions are appropriate in most situations

- ***5.1: When considering restrictions for PWTB, a moderate or mid-level range of RIR should be considered appropriate in most circumstances, with individual exceptions***

- Determination of RIR is based on weighing benefits and harms to the community and the individual
- Principle of “least restrictive means” to achieve the desired public health goals
- Moderate restrictions allows for some outdoor activities where there is lower transmission risk.
- Extensive restrictions may be considered in circumstances with higher infectious potential (e.g., prior to treatment initiation) and high community transmission risks or consequences (e.g., concern for transmission of drug-resistant TB)

Reassess routinely

- ***5.2: Specific RIR levels (e.g., low, moderate, or extensive) and duration for PWTB should be reassessed routinely (at least weekly) and may be modified based on individual considerations or changing circumstances.***

- The highest risk of transmission to others is anticipated to be prior to treatment initiation

- Assess community benefits and individual impact.
  - Longer durations of treatment may lead to greater certainty in the assessment of infectiousness

  - Longer durations of RIR are anticipated to lead to increased harms to PWTB

Support patients to mitigate harms of public health interventions

- ***5.2: When RIR is implemented, support should be provided to patients to mitigate anticipated and experienced harms***

- Implementation of RIR of PWTB involves sacrifices and potential harms to PWTB for public health benefit
- Assess and support concerns for financial security, as resources allow
- Assess and support concerns for food security, as resources allow
- Assess and support concerns for housing security, as resources allow

EXAMPLE: Pre-treatment Smear positive, not on Treatment

Recommendation 3: Determining infectiousness			Recommendation 4: Determining RIR	Recommendation 5: Level of RIR	Notes
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Treatment <= 5 days	High	Moderate (Rec 3.2)	Yes (Rec 4.3)	Moderate (Rec 5.1)	
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Treatment > 5 days	High	Low (Rec 3.3) [2]	Not indicated in most situations (Rec 4.2)[3]	None	Individual exceptions to continue RIR may be considered (Rec 5.2) [3]
	Low	Lowest (Rec 3.3)		None	

EXAMPLE: Pre-treatment Smear positive, initiating Treatment (< 5 days)

Recommendation 3: Determining infectiousness			Recommendation 4: Determining RIR	Recommendation 5: Level of RIR	Notes
Treatment Status	Pre-treatment Respiratory bacterial burden[1]	Assessment of individual infectiousness*	Is RIR indicated? [4]	What level of RIR to choose? (Rec. 2, Table 2)	Specific Recommendations should balance community and patient risks and benefits (Rec 1)
Pre-treatment	High	Highest (Rec. 3.1)	Yes (Rec 4.3)	Extensive	Support should be provided to mitigate harm to PWTB (Rec 5.3).
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	Low	Moderate/Low (Rec [illegible])	Yes (Rec 4.3)	Moderate (Rec 5.1)	
Treatment > 5 days	High	Low (Rec 3.3) [2]	Not indicated in most situations (Rec 4.2)[3]	None	Individual exceptions to continue RIR may be considered (Rec 5.2) [3]
	Low	Lowest (Rec 3.3)		None	

EXAMPLE: Pre-treatment Smear positive, Treatment for >5 days—consider additional factors (treatment response, community risk, patient impact)

Recommendation 3: Determining infectiousness			Recommendation 4: Determining RIR	Recommendation 5: Level of RIR	Notes
Treatment Status	Pre-treatment Respiratory bacterial burden[1]	Assessment of individual infectiousness*	Is RIR indicated? [4]	What level of RIR to choose? (Rec. 2, Table 2)	Specific Recommendations should balance community and patient risks and benefits (Rec 1)
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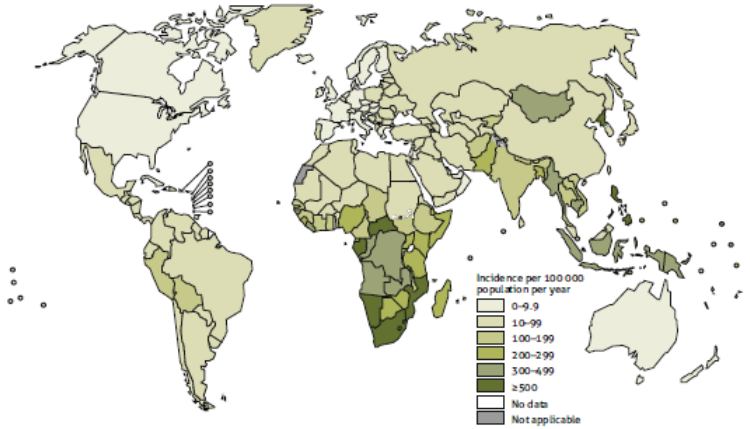

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Implementation

Our local experiences with implementation

- Beginning to build tools to aid with decision making
- Development of documentation framework

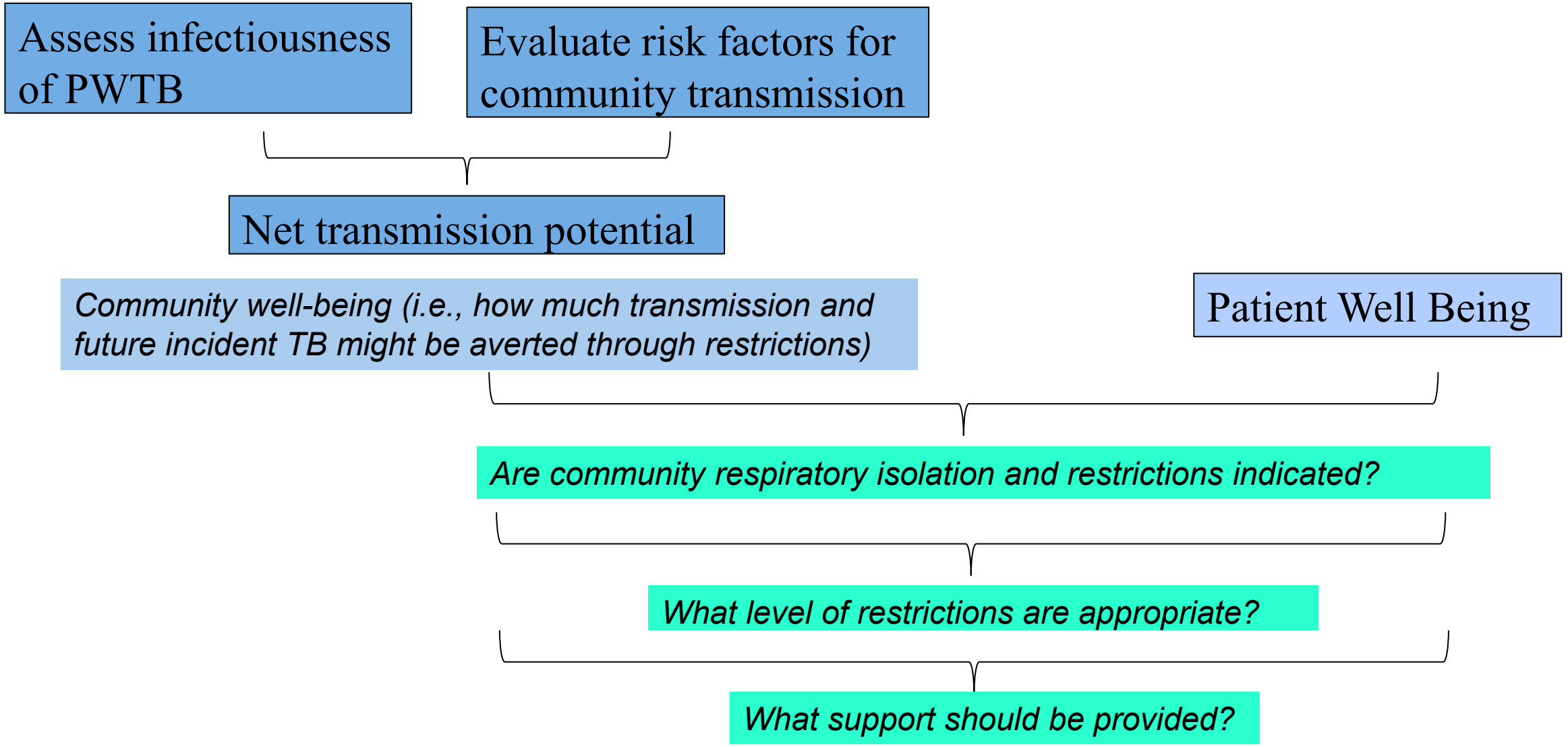
Resources: Implementation Aid for Isolation Duration Determination

Table 4 and 5

- Determine pre-treatment bacterial burden
- Evaluate treatment
- Assess Community Risk
- Patient Harms

Step	Assessment	Notes and Recommendations
1.Assess how long PWTB has been under community-based RIR	1.Has PWTB been under community-based RIR for more than five days?	1. Decisions should be reassessed at least weekly, as well as with change in assessment of infectiousness, and changing circumstances related to patient and community benefits and harms (See Rec. 5.2) 2.Consider additional expert consultation or review when RIR duration has extended longer than fourteen days, while ensuring adequate support for PWTB. (See Rec 5.3)
2.Assess PWTB infectiousness	1.Assess duration of verified (i.e., DOT or vDOT) treatment 2.Was ATT considered effective? 3. Infectiousness is expected to progressively decline with ongoing ATT; alternatively prolonged duration of RIR is expected to result in harm for PWTB*.	1.Effective ATT is defined as a multi-drug regimen to which the organism is susceptible or anticipated to be susceptible. If full DST is unavailable, decisions may be made based on available information (e.g., rifamycin susceptibility), and clinical assessment of probability of drug-resistance. 2.Most individuals completing at least five days of effective ATT have low infectious potential (See Rec. 3.2-3.3), and RIR may be discontinued (See Rec 4.2). A) While ATT rapidly reduces a PWTB's infectiousness there may be individual variability. Available bacteriologic tests do not reliably predict infectious potential during ATT. B) In some instances of high initial bacterial burden (e.g., pre-treatment, sputum AFB smear-positive, cavitation), longer treatment durations (e.g., 5-14 days) are expected to further reduce a PWTB's infectious potential (See Figure 1, Chart A). C) Clinicians may use individualized judgement in assessing infectiousness based on pre-ATT bacterial burden (i.e., initial sputum AFB smear status and cavitation); clinical response to ATT; drug-susceptibility, adherence, and duration of ATT. D) Available data does not support repeated sputum smear-microscopy and NAAT testing solely to assess ongoing infectiousness during ATT. Some clinicians may consider repeat sputum bacteriologic labs to monitor ATT response. However, changes to sputum smear, culture and NAAT test results on ATT may not correlate with a PWTB's infectious potential.
3.Assess community risk of TB transmission	1.Is there high risk of community TB transmission?	See Step 1, Assessment 4, Table 4
4.Assess potential patient harms	1.Is patient experiencing harms related to RIR?	There is a lack of validated tools to reliably measure or capture patient harm resulting from RIR. Consider assessment of stigma, financial security, housing, food security, and mental health. Appropriate supportive services should be used to minimize the harm of RIR, such as provision of nutritious, culturally appropriate food, phone or video contact with friends and remote access to school and employment where possible. See Appendix 1 in published version.
5.Determine if RIR should be continued	1.Is there ongoing high likelihood of infectiousness and risk of community transmission? 2.Are there vulnerable populations to consider, drug resistance, or other special community circumstances?	1.RIR should be discontinued for most PWTB with low infectious potential (See Rec 4.1-2) after five days of effective treatment. 2.RIR may be extended based on comprehensive assessment of the PWTB's infectiousness (see above), community risks and consequences of TB transmission, and individual harms. Some considerations that may warrant extended RIR despite PWTB's low infectious potential: A) Anticipated exposures to vulnerable populations including children < 5 (e.g., daycares, schools), and immunosuppressed individuals (e.g., healthcare settings); B) Anticipated return to congregate living facilities (e.g., homeless shelters) or densely populated environments with poor ventilation1 C) Known or suspected TB drug resistance where the consequences of transmission should be weighed with the harms of prolonged RIR 3) Decisions to extend RIR should balance individual harms of prolonged restrictions, with anticipated community benefits. Instances where duration has extended beyond 14 days warrant additional review and expert consultation. (See Rec 1)

Implementing NTCA guidelines



Determine whether community based RIR is indicated: *assess benefits and harms*

HOUSING	1. Do you have a consistent and safe place to live while receiving TB treatment? ☐ Yes ☐ No 2. Are you worried that you will be asked to move due to TB treatment or isolation ☐ Yes ☐ No 3. Do you have children under the age of 5 at home? ☐Yes ☐No 4. Are there any individuals in the home that are immunocompromised? ☐Yes ☐No
FOOD	1. In the past year were you ever hungry but did not eat because there wasn't enough money for food? ☐Yes ☐ No 2. Are you concerned about access to food? ☐Yes ☐ No
JOBS	1. Do you have a job? ☐ Yes ☐ No (If yes, complete additional questions below) 1a. Do you think you may lose your job if you need to take time off from work due to TB treatment or isolation)? ☐ Yes ☐ No 1b. Do you work outside your home? ☐ Yes ☐ No 1c. Are you able to work remotely? ☐ Yes ☐ No
MENTAL HEALTH	1. Do you use drugs or drink at least 4 drinks of any kind in a single day? ☐ Yes ☐ No 2. Have you experienced any of the following problems within the past 2 weeks? • Feeling down ☐ Yes ☐ No • Feeling depressed ☐ Yes ☐ No • Feeling worried or frightened? ☐ Yes ☐ No • Any thoughts of harming yourself? ☐ Yes ☐ No
FINANCES	1.) In the past year- have you had trouble paying for Rent /Mortgage? ☐Yes ☐ No • Medical care? ☐Yes ☐No • Other bills? ☐Yes ☐N 2.) Have you borrowed any money this year? ☐Yes ☐No
SOCIAL	1.) Are you afraid to tell your family/friends about your diagnosis of TB? ☐Yes ☐No 2.) Are there activities you are worried you will not be able to do because of TB? ☐Yes ☐No Comments_____
GENERAL	Do you anticipate any challenges to being isolated? ☐Yes ☐No Comments:

Case Examples

Patient (all with GXP+, rpoB neg)	Pre-treatment	Treatment	Community risk	Harms	Isolation Duration
24 yo smear-negative, no cavity, not coughing PTB	Low	HRZE	No vulnerable contacts, 4 roommates,Worked outside [LOW]	Financial, Housing	5 days (moderate restriction)

Case Examples

Patient (all with GXP+, rpoB neg)	Pre-treatment	Treatment	Community risk	Harms	Isolation Duration
24 yo smear-negative, no cavity, not coughing PTB	Low	HRZE	No vulnerable contacts, 4 roommates,Worked outside [LOW]	Financial, Housing	5 days (moderate restriction)
47 yo Laotian M, HIV-neg, smear-positive, Cavity (6cm) PTB, uncontrolled DM	High	HRZE (high dose Rif) (Discuss HPMZ)	6 roommates Dishwasher [Moderate]	Financial, Job loss, housing, food	-4 days in hospital -10 days (moderate) -Clinical improvement + DOT/vDOT continuing to mask

Case Examples

Patient (all with GXP+, rpoB neg)	Pre-treatment	Treatment	Community risk	Harms	Isolation Duration
24 yo smear-negative, no cavity, not coughing PTB	Low	HRZE	No vulnerable contacts, 4 roommates,Worked outside [LOW]	Financial, Housing	5 days (moderate restriction)
47 yo HIV-neg, smear-positive, Cavity (6cm) PTB	High	HRZE (high dose Rif) (Discuss HPMZ)	6 roommates Dishwasher [Moderate]	Financial, Job loss, housing, food	-4 days in hospital -10 days (moderate) -Clinical improvement + DOT/vDOT -continuing to mask
32 yo smear neg, cavitary, incidentally found PTB (MVA)	Moderate	HRZE	1 household contact, 4 children (do not live together) Unemployed, unstable housing [Moderate]	Mental health	Hospital isolation x 8 days; home isolation x 2 days

Early lessons:

- How often to obtain sputum?
  - Continuing weekly collection for individuals that are smear positive, than monthly (Purpose is for assessing microbiological response and documenting culture conversion, not isolation)
- Setting: These guidelines apply to community (non congregate settings)
- Assessment of impact of TB and isolation on patient (harms) is an important component of public health decision making process
- Extending beyond five days in situations where there are moderate/high community risks and high initial pre-treatment bacterial burden
  - OR when treatment effectiveness is uncertain

Summary

- Public health interventions are unique in their need to balance Community Well Being AND Patient Well Being

- NTCA guidelines were developed to address gaps:
  - There was no existing CDC or other federal guidance
  - Existing practices were not uniformly developed or based on available scientific evidence

- Sputum microscopy and culture do not reliably predict infectiousness in PWTB who is on effective therapy

- Treatment rapidly and steadily reduces infectiousness

Summary (my annotated take-home points)

- Recommendation 1: Decisions on restrictions and isolation should consider the overall community and individual benefits and harms
- Recommendation 2: Respiratory isolation and restrictions should be conceptualized as a spectrum of tailored interventions
- Recommendation 3: Treatment rapidly reduces infectiousness among PWTB, irrespective of bacteriologic studies (i.e., smear) collected during treatment
- Recommendation 4: Most PWTB can be removed from community based RIR after 5 days of effective treatment, with some exceptions for higher risk scenarios (e.g., very high pre-treatment bacterial burden, and anticipated exposure to vulnerable populations).
- Recommendation 5: Moderate restrictions are appropriate when community based RIR is indicated. PWTB should be offered support to mitigate harms of RIR.

Additional information….a series of manuscripts in JID and CID

- Review article on Determinants of Infectiousness (JID)
- Systematic review of the impact of isolation on population and patient outcomes (CID)
- Building an ethics-informed framework for public health guidelines (JID)
  - Presentation: Oxford Global Health and Bioethics International Conference
- Legal considerations for tuberculosis restrictions (JID)
- History of TB isolation practices (JID)

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Guidelines and Commentary: Clinical Infectious Diseases Available as Advance Articles

NTCA Guidelines:
https://academic.oup.com/cid/article-lookup/doi/10.1093/cid/ciae199

Caitlin Reed Invited Commentary:
https://academic.oup.com/cid/article-lookup/doi/10.1093/cid/ciae198

Additional manuscripts

https://doi.org/10.1093/infdis/jiae482

Determinants of Infectiousness

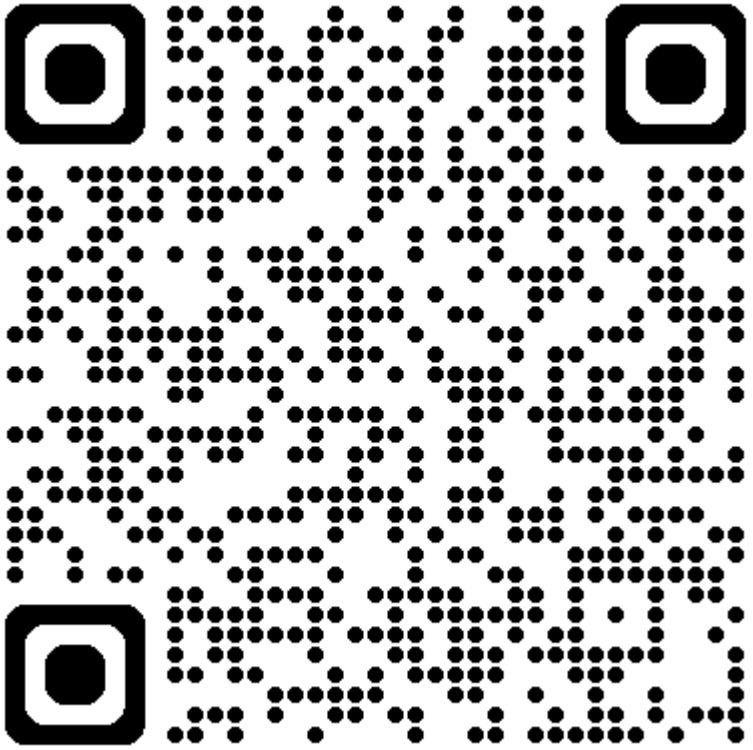
https://doi.org/10.1093/infdis/jiae477

Historical Perspective

Integrating ethics in public health guideline development: a case-study of the NTCA guidelines on respiratory isolation for persons with TB in community settings

- https://doi.org/10.1093/infdis/jiae478

Rights-Based Legal Considerations for TB Isolation Practices in Community Settings in the Post-Pandemic Era



- https://doi.org/10.1093/infdis/jiae479