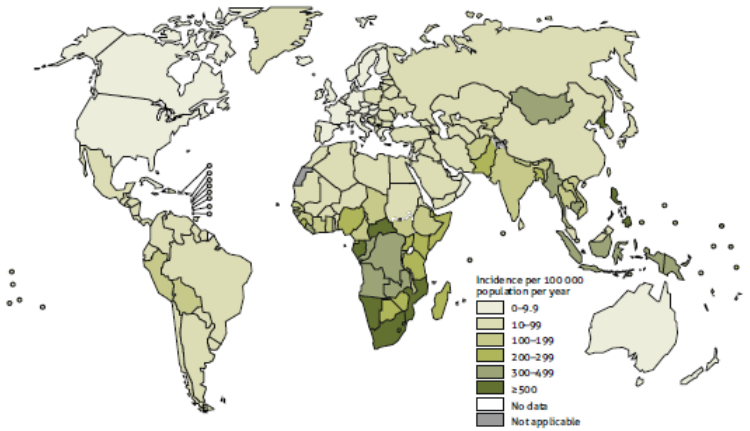

JOHNS HOPKINS MEDICINE

Case Studies: NTCA and MDH Guidelines for Respiratory Isolation and Restrictions in Community Settings

Maunank Shah MD PhD
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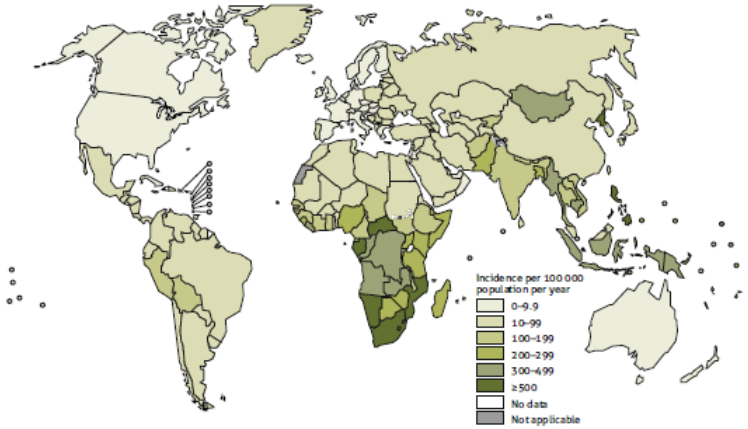
Medical Director, Baltimore City Health Department TB program

Case Studies:

- *Scenario 1: low bacterial burden, low/modest community risks, low harm*
- *Scenario 1a: low bacterial burden, moderate/high community risk, moderate harm*
- *Scenario 1b: low bacterial burden, moderate/high community risk, moderate harm*
- *Scenario 2: high bacterial burden; moderate community risks, low harm*
- *Scenario 3: moderate bacterial burden, moderate risks, high harm*
- *Scenario 4: high bacterial burden, high risks, high harm*

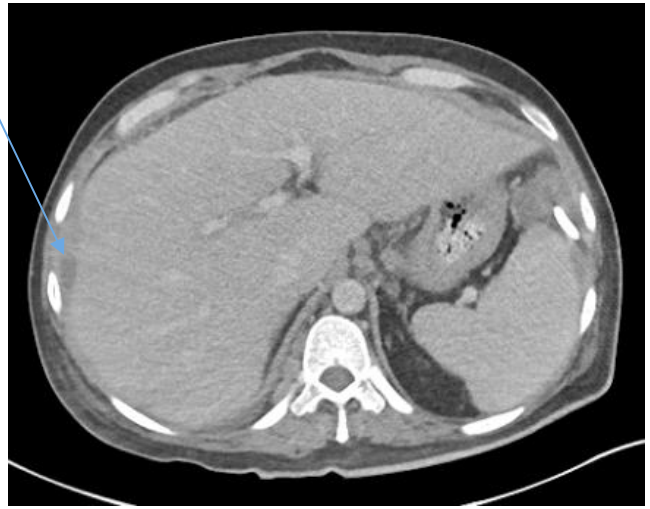


JOHNS HOPKINS
MEDICINE

Warm up case

Case

- 36 year old immigrated from India 2 years ago,
- Admitted with fevers and ETOH intoxication, and ETOH withdrawal
- Imaging:
  - Clear Chest Xray
  - 8mm lesion in Right Hepatic lobe
  - Multiple loculated complex fluid collections adjacent to liver and spleen
- Sputum:
  - AFB Smear negative
  - MTB NAAT negative
  - MTB culture *pending*
- Peri-Hepatic fluid:
  - AFB smear negative
  - Cepheid GeneXpert MTB/RIF: positive
  - Cultures: *pending*
- Exam: vital signs stable; **52kg, temporal wasting**
  - No apparent distress
  - Normal exam



Case: Interpreting molecular test results

- Lab performed the Xpert XDR assay
- **katG mutation is detected, predicting high level INH resistance**
- **No resistance to FQ is identified**
- *Note, cultures are still pending (day 3 of hospitalization) and no other tests have been positive*
- *Sputum is collected: smear negative, GXP negative*
- *CXR is normal*

What regimen would you use for treatment based on this molecular testing?

A. Rifampin, Isoniazid, Pyrazinamide, Ethambutol — 0%

B. Rifampin, Pyrazinamide, Ethambutol — 0%

C. Rifampin, Moxifloxacin, Pyrazinamide, Ethambutol — 0%

D. Bedaquiline, Pretomanid, Linezolid, Moxifloxacin — 0%

None of the above — 0%

Panel Discussion

US approach

- Rifampin (R), Pyrazinamide(Z), Ethambutol (E) x 6 months
- Rifampin, Moxifloxacin (M), Pyrazinamide, Ethambutol x 6 months
- RMZE x 2 months→ Rifampin + Moxi +/- Ethambutol x 4 months

PICO Question 20—Treatment of isoniazid-resistant TB:
Recommendation 20a: We suggest adding a later-generation fluoroquinolone to a 6-month regimen of daily rifampin, ethambutol, and pyrazinamide for patients with isoniazid-resistant TB (conditional recommendation, very low certainty in the evidence).
Recommendation 20b: In patients with isoniazid-resistant TB treated with a daily regimen of a later-generation fluoroquinolone, rifampin, ethambutol, and pyrazinamide, we suggest that the duration of pyrazinamide can be shortened to 2 months in selected situations (i.e., noncavitary and lower-burden disease or toxicity from pyrazinamide) (conditional recommendation, very low certainty in the evidence).

https://www.atsjournals.org/doi/full/10.1164/rccm.201909-1874ST#_i191

Does this patient need to be placed in respiratory isolation?

A. Yes

0%

B. No

0%

C. Unsure

0%

Panel Discussion

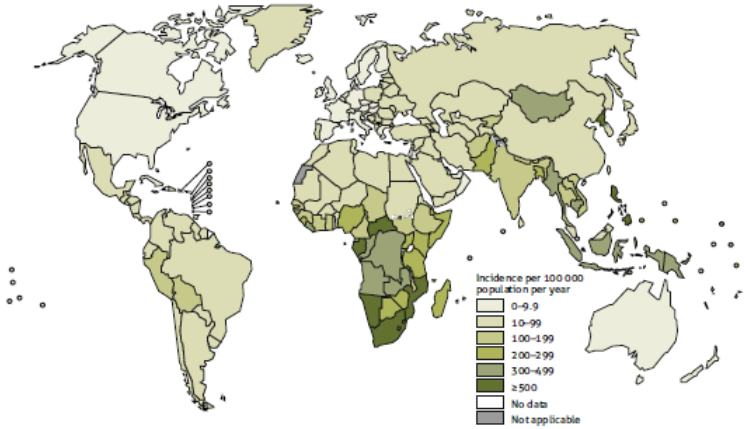
Recommendation 4: Determining whether community based RIR is indicated

- ***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

CTBCP Recommended Framework for Individualized Decisions on Community-based Respiratory Isolation and Restrictions

TB Treatment Status	Pre-treatment bacterial burden in the respiratory tract	Level of infectiousness	Isolation indicated	Level of isolation/restriction
Pre-treatment	high	highest	yes	extensive
Pre-treatment	low	moderate	yes	moderate or extensive
Treatment ≤ 5 days	high	moderate	yes	moderate
Treatment ≤ 5 days	low	moderate	yes	moderate
Treatment > 5 days	high	low**	Individualized*	none or moderate
Treatment > 5 days	low	lowest	no	none
Extrapulmonary TB	N/A	None	No	None



JOHNS HOPKINS
MEDICINE

Case 1

Example 1: Low initial bacterial burden, low community risks

- 34 year old M, from Honduras, works on local farm and presents to the hospital with intermittent fevers and cough for 3 months with weight loss, and diagnosed with pulmonary TB.
  - Smear-Negative
  - GeneXpert Positive (rpoB negative)
  - No Cavity
  - No concerns for drug resistance epidemiologically

PRIOR to treatment initiation, how would you judge this PWTB (smear-neg, non-cavitary) level of infectiousness/

A. Very High/Highest 0%

B. High 0%

C. Moderate 0%

D. Low 0%

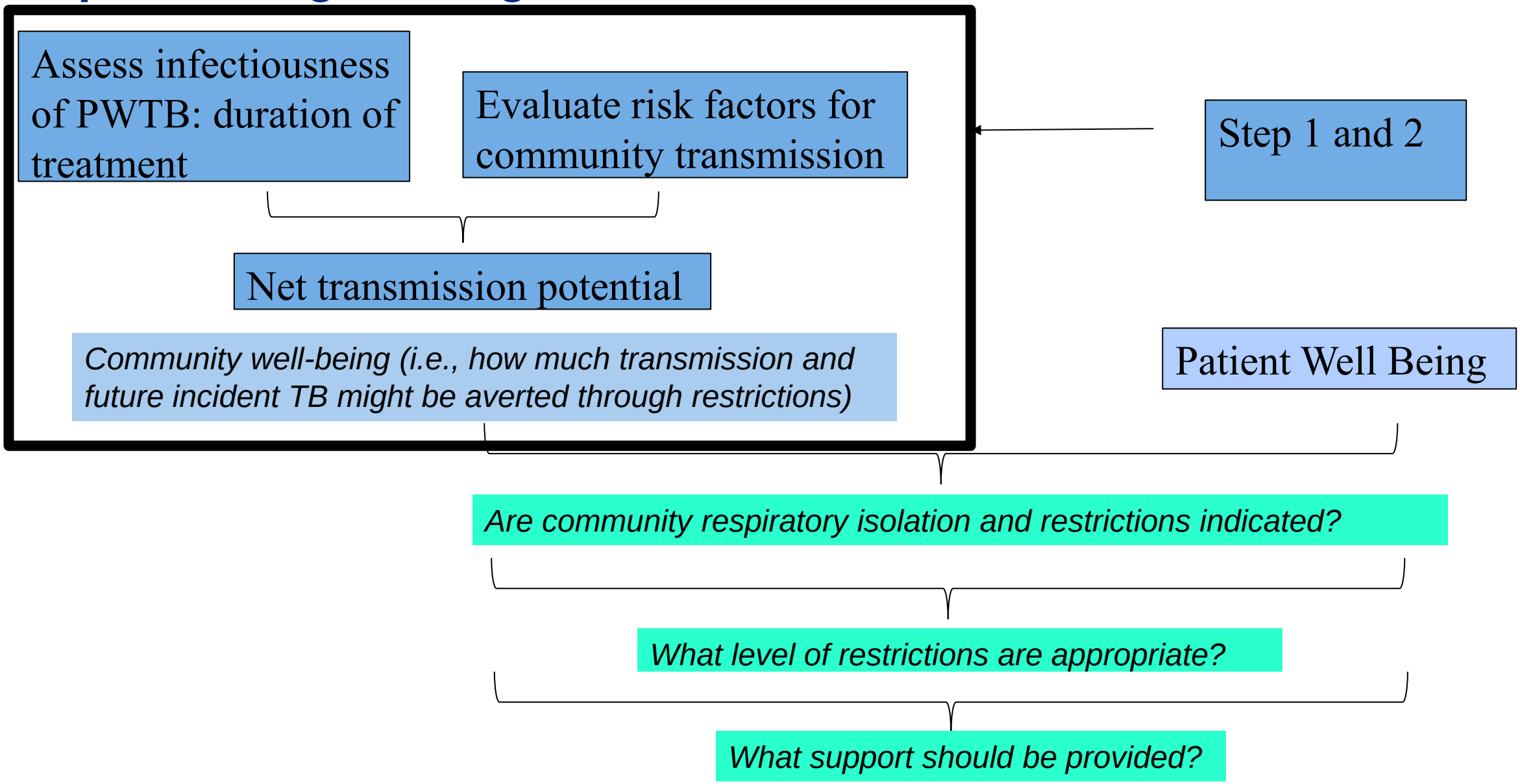
E. Very Low/Lowest 0%

Panel Discussion

CTBCP Recommended Framework for Individualized Decisions on Community-based Respiratory Isolation and Restrictions

TB Treatment Status	Pre-treatment bacterial burden in the respiratory tract	Level of infectiousness	Isolation indicated	Level of isolation/restriction
Pre-treatment	high	highest	yes	extensive
Pre-treatment	low	moderate	yes	moderate or extensive
Treatment ≤ 5 days	high	moderate	yes	moderate
Treatment ≤ 5 days	low	moderate	yes	moderate
Treatment > 5 days	high	low**	Individualized*	none or moderate
Treatment > 5 days	low	lowest	no	none
Extrapulmonary TB	N/A	None	No	None

Implementing NTCA guidelines



Assess infectiousness and overall community risks

Approach	Result	Notes/Thoughts
1.Infectiousness prior to treatment: --sputum smear-microscopy --sputum culture --sputum NAAT --Imaging --Cough	• Smear-negative, • GeneXpert MTB/RIF-positive • No Cavity • Has Cough	Person is not on treatment (at their highest infectious potential) Bacterial burden is low (relatively lower infectious potential)
2.Review available drug susceptibility testing	• GeneXpert MTB/RIF—no rpoB mutation detected • No known contacts to MDR-TB	• Presumed drug susceptible • Clinical decision to treat with standard RHZE

3.Assess overall community risks	• Lives with 4 roommates
	• Works in open spaces
	• No expected contact with children or immunosuppressed
		• Overall risks of transmission to new previously unexposed individuals is **?**
		  • Frequency of new contacts
		  • Duration of new contacts
		  • Intensity of new contacts

How would you judge the overall risk factors for community transmission (if patient were infectious)?

A. Very High/Highest 0%

B. High 0%

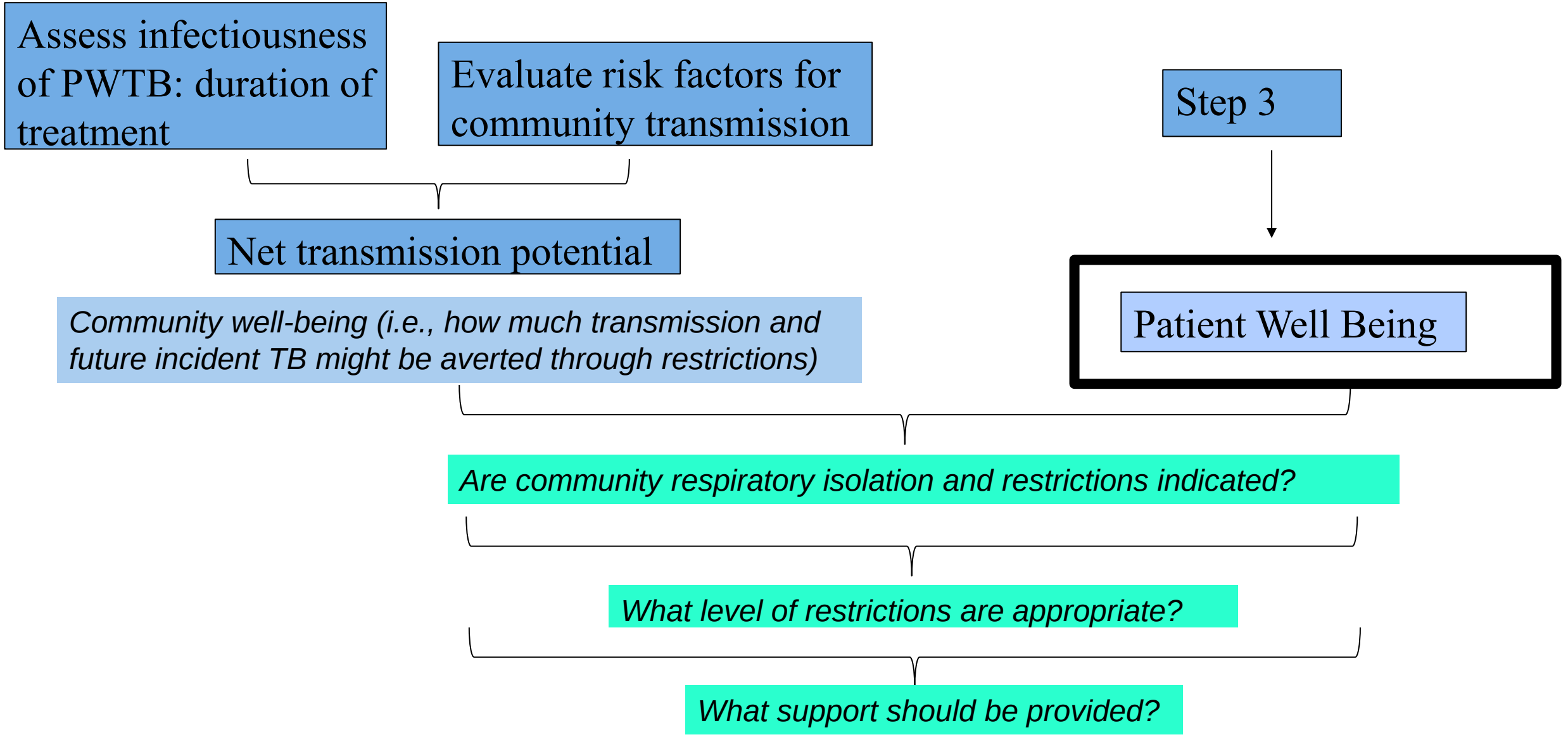
C. Moderate 0%

D. Low 0%

E. Very Low/Lowest 0%

Panel Discussion

Implementing NTCA guidelines



Step 3: Determine whether community based RIR is indicated: *assess benefits and harms*

- Formally assess **potential harms** of RIR for PWTB to aid decision-making:
  - **Financial stability**: *Patient indicates he can take a few days off of work but expresses concern that his employer will not retain him if he misses extended time*
  - **Housing stability**: *Patient has a home with multiple adult roommates (previously exposed), none of whom are immunosuppressed*
  - **Food stability**: *Patient indicates his roommates can assist with obtaining food*
  - **Mental health**: *multiple scales and tools available (PHQ-9, GAD-7)*
  - *Appendix 1 of the guidelines includes some possible signaling questions (not a validated tool, but represents possible questions derived from literature review)*

How would you rate the level of negative impact of isolation on patient well being?

A. High

0%

B. Moderate

0%

C. Low

0%

Panel Discussion

Case-example continued: Initial Evaluation Summary

- 34 year old with newly diagnosed pulmonary TB started on HRZE by hospital and discharged to home
  - Pre-treatment smear negative, GXP positive with no rpoB mutation
  - **Tolerating medication and has taken 3 days by DOT/vDOT**
  - Contact investigation was initiated by the health department
    - Four household contacts
    - No employment related contacts identified
    - Identifies five close friends he has spent time with regularly
  - **Health department recommended home-isolation (moderate restrictions)**
    - **Indicated he could go outdoors for exercise provided he had limited to no contact with previously unexposed individuals**
  - No concerns for food or housing
  - **Expresses concerns for missing work, as he is paid on an hourly basis. Is worried employer will not retain him if he misses too many days of work**

Case-example continued: > 5 days of treatment

- 34 year old with newly diagnosed pulmonary TB
  - Pre-treatment smear negative, GXP positive with no rpoB mutation
  - **Has completed 5 days of HRZE with DOT/vDOT** and is clinically improving
  - **Has remained in home isolation during this time**
  - **Growing anxious about ongoing missed days of work**

Discussion: Please discuss your approach to determining the appropriate duration of restrictions?

CTBCP Recommended Framework for Individualized Decisions on Community-based Respiratory Isolation and Restrictions

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Pre-treatment	high	highest	yes	extensive
Pre-treatment	low	moderate	yes	moderate or extensive
Treatment ≤ 5 days	high	moderate	yes	moderate
Treatment ≤ 5 days	low	moderate	yes	moderate
Treatment > 5 days	high	low**	Individualized*	none or moderate
Treatment > 5 days	low	lowest	no	none
Extrapulmonary TB	N/A	None	No	None

Snapshot of documentation

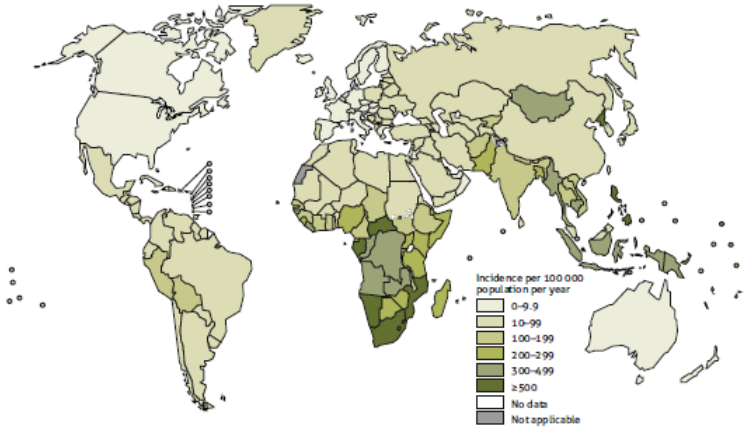
****
ISOLATION
(Assessment based on NTCA Guidelines for Respiratory Isolation and Restrictions to Reduce Transmission of Pulmonary Tuberculosis in Community Settings, February 2024)
a) Initial pre-treatment infectiousness: LOW
b) Initial community risk assessment: LOW
c) Is there drug-susceptibility testing? NO
    If not, is there any concern for drug resistance based on epi risks? NO
d) Initial Restriction level: MODERATE
e) Restriction start date: 3/28/2024

WEEKLY RE-EVALUATION
a) Duration of effective treatment: 9 DAYS
b) Assessment of infectiousness: LOWEST
c) Restriction end date: 4/1/2024
d) Restriction evaluation dates: 4/5/2024
e) Restriction harm assessment:
    --Financial: YES
    --Stigma: UNK
    --Housing: YES
    --Food: UNK
    --Mental Health: UNK
f) Current level of RIR: NONE

****

Quick Reference Guide

Patient Characteristics	MDH Recommendations	Added Considerations	Patient Considerations
Extrapulmonary Only Normal CXR	No Respiratory Isolation or Restrictions	Ensure evaluation for TB of respiratory tract with chest imaging and sputum bacteriologic testing	Evaluate weekly 1.Assess Financial impact and support as resources allow 2.Assess Housing 3.Assess Mental Health and refer for additional counseling/support 4.Assess Food security Tailor restrictions: 1.Consider Moderate restrictions in most instances (allow outdoor activities that do not involve close, prolonged contact) 2.Evaluate employment setting and make tailored recommendation)
Children <10 with intrathoracic TB	No isolation except for older children and adolescents with adult-type disease	Individuals with sputum bacteriologic tests that are positive may be considered as having adult-type disease	
Low pre-treatment infectiousness (e.g., sputum smear-negative & non-cavitary) + GXP available (Rifampin S)	All settings and contacts: RIR through at least 5 days of verified treatment*	Request GXP. See below if not available.	
Moderate or High pre-treatment infectiousness (e.g., sputum smear-positive OR cavitation or extensive/multilobar) + GXP available (Rifampin S)	Lower risk settings and contacts RIR through 5-10 days of verified treatment* Higher risk settings and contacts[b]: RIR through 10-14 days of verified treatment, and documented clinical response (symptom improvement) and/or microbiologic response (reducing sputum smear grade)*	1.Request GXP. See below if not available. 2.If High pre-treatment infectiousness (sm+ and cavitation) with high risk setting (e.g., vulnerable population), request MDDR to verify INH S; Consider HPMZ or high dose rifamycin to improve EBA of first line therapy	
GXP unavailable	Low bacterial burden and Lower Risk Settings: 10-14 days of verified treatment and clinical improvement* High bacterial burden OR Higher Risk Settings[b]: At least 14 days of verified treatment* and clinical improvement and microbiologic response (reducing smear grade)	1.Request GXP and/or MDDR, particularly for high bacterial burden or higher risk settings 2.Collect weekly sputum x 3 to evaluate microbiologic response to assess appropriateness of treatment	
Rifampin Resistant	Minimum 14 days of laboratory confirmed effective therapy + clinical improvement, and demonstrated	1.Request MDDR and phenotypic DST 2.Effective treatment is defined based on microbiological	Higher risk for negative patient impact. Evaluate as above, and



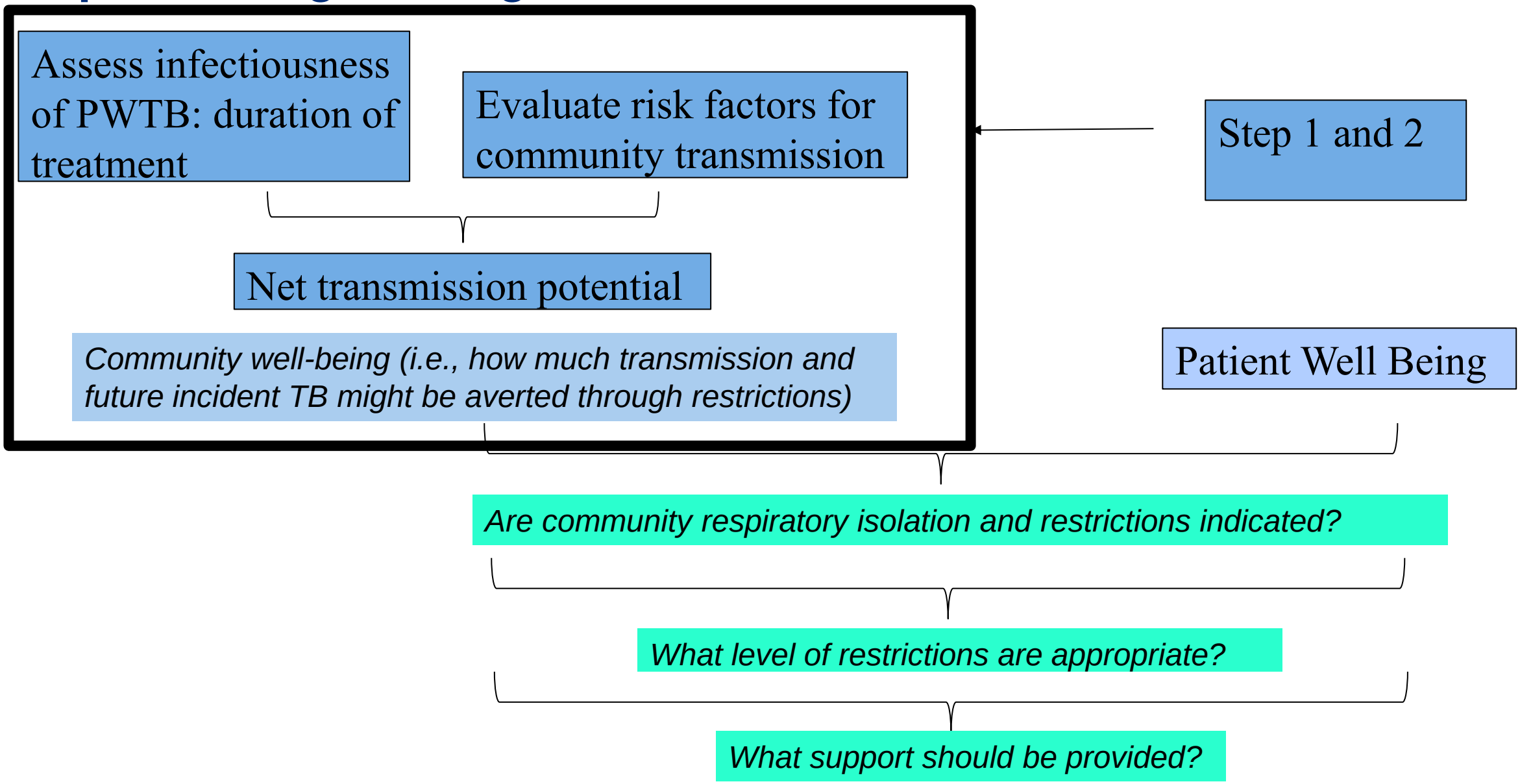
JOHNS HOPKINS MEDICINE

Case 1a: low bacterial burden, higher community risks and higher patient harms

Case 1a : Low pre-treatment bacterial burden

- 17 yo moved to US from India in February. Enrolled in High-school the following school year (Sept).
- December has a fall/rib injury and incidentally found on CXR to have a RLL cavity. Initially given azithromycin and augmentin
- Serial CXR one month later: persistent cavity
  - IGRA positive
  - Microbiology: Smear negative, GXP NAAT negative, Cultures negative
  - Asymptomatic
- Decision to start empiric therapy with RHZE
- Social History:
  - Works on weekends at a local donut store
  - High School: 7 periods each with ~20-30 kids
  - Tennis team
- Amenable to treatment—very concerned with missing class, and possible stigma

Implementing NTCA guidelines



PRIOR to treatment initiation, how would you judge this PWTB (smear-neg, non-cavitary, GXP negative) level of infectiousness?

A. Very High/Highest 0%

B. High 0%

C. Moderate 0%

D. Low 0%

E. Very Low/Lowest 0%

How would you judge the overall risk factors for community transmission (if patient were infectious) given high school setting?

A. Very High/Highest 0%

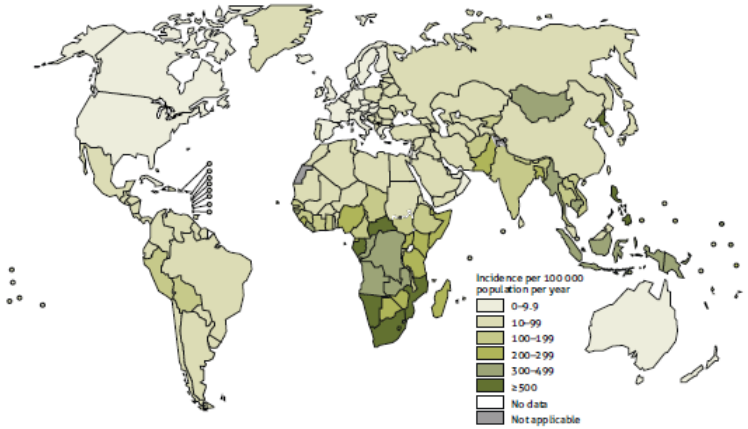
B. High 0%

C. Moderate 0%

D. Low 0%

E. Very Low/Lowest 0%

Panel Discussion



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Case 1b: low bacterial burden, higher community risks and higher patient harms

Case 1b : Low pre-treatment bacterial burden

- 44 yo immigrated from Philipines many years ago.
- Seen at local hospital in February
  - Smear-positive→No GeneXpert Done
  - Cultures positive (three weeks later): no DST available yet
  - Asymptomatic
- New sputum testing:
  - Smear-negative/NAAT negative, cultures pending
- Started on HRZE
- Social History:
  - Special needs teacher at local elementary school (pre-K to 5th grade)
  - Inner circle of school: ~50-60 kids and teachers (~10 under age 5)
  - Outer circle: 295 kids

Investigation and Follow-up

- School based investigation to occur within 1 week
- Some parents and staff have heard of a ‘TB outbreak’, but thus far identity of the individual has not been revealed
- Patient assessment:
  - Financial security: no immediate concerns, but asking about duration
  - Stigma: Very concerned about work, and her identity being revealed and backlash. Anxious about getting back to work as longer absence may reveal her identity

Quick Reference Guide

Patient Characteristics	MDH Recommendations	Added Considerations	Patient Considerations
Extrapulmonary Only Normal CXR	No Respiratory Isolation or Restrictions	Ensure evaluation for TB of respiratory tract with chest imaging and sputum bacteriologic testing	Evaluate weekly 1.Assess Financial impact and support as resources allow 2.Assess Housing 3.Assess Mental Health and refer for additional counseling/support 4.Assess Food security Tailor restrictions: 1.Consider Moderate restrictions in most instances (allow outdoor activities that do not involve close, prolonged contact) 2.Evaluate employment setting and make tailored recommendation)
Children <10 with intrathoracic TB	No isolation except for older children and adolescents with adult-type disease	Individuals with sputum bacteriologic tests that are positive may be considered as having adult-type disease	
Low pre-treatment infectiousness (e.g., sputum smear-negative & non-cavitary) + GXP available (Rifampin S)	All settings and contacts: RIR through at least 5 days of verified treatment*	Request GXP. See below if not available.	
Moderate or High pre-treatment infectiousness (e.g., sputum smear-positive OR cavitation or extensive/multilobar) + GXP available (Rifampin S)	Lower risk settings and contacts RIR through 5-10 days of verified treatment* Higher risk settings and contacts[b]: RIR through 10-14 days of verified treatment, and documented clinical response (symptom improvement) and/or microbiologic response (reducing sputum smear grade)*	1.Request GXP. See below if not available. 2.If High pre-treatment infectiousness (sm+ and cavitation) with high risk setting (e.g., vulnerable population), request MDDR to verify INH S; Consider HPMZ or high dose rifamycin to improve EBA of first line therapy	
GXP unavailable	Low bacterial burden and Lower Risk Settings: 10-14 days of verified treatment and clinical improvement* High bacterial burden OR Higher Risk Settings[b]: At least 14 days of verified treatment* and clinical improvement and microbiologic response (reducing smear grade)	1.Request GXP and/or MDDR, particularly for high bacterial burden or higher risk settings 2.Collect weekly sputum x 3 to evaluate microbiologic response to assess appropriateness of treatment	
Rifampin Resistant	Minimum 14 days of laboratory confirmed effective therapy + clinical improvement, and demonstrated	1.Request MDDR and phenotypic DST 2.Effective treatment is defined based on microbiological	Higher risk for negative patient impact. Evaluate as above, and

Panel Discussion: Smear-negative, NAAT Negative

- How would you assess effectiveness of therapy and would you consider any alternative regimens?
- If DST is not available, how do you assess ‘effectiveness’ of therapy for a smear-negative/NAAT negative patient?
- Would you allow return to work at 5 days? 14 days? Some other duration?
- How would you handle if DST returns with some drug resistance?

Rapid Fire Case: Low pre-treatment bacterial burden

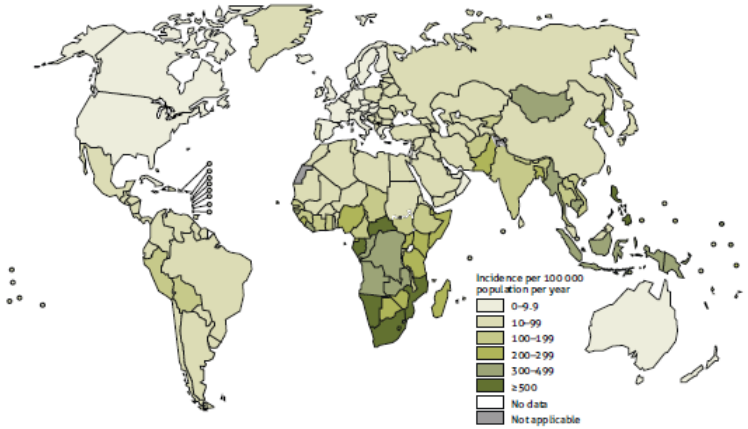
- 65 year old from Vietnam, seen for shortness of breath
- Chest Imaging:
- Not coughing
- BAL: smear-negative, NAAT negative, culture positive, DST: PZA resistant
- Now readmitted for care: HR(high dose), Moxi, Ethambutol
- Repeat testing: sputum smear-negative, NAAT negative x 2

- Social history: Homeless—living in shelter
  - Previously owned nail salons, successful business
  - ETOH abuse, eventually lost businesses
  - Living out of car for much of 2024, eventually sold it to rent room in motel
  - For last few months living in a shelter

How long should he stay in hospital isolation before discharge?

- Patient will return to shelter—no other home
- Not asking to be discharged, but is clinically well
- Inpatient team ready to discharge clinically, but continuing to hospitalize

- How long should he remain in isolation before dc to shelter?



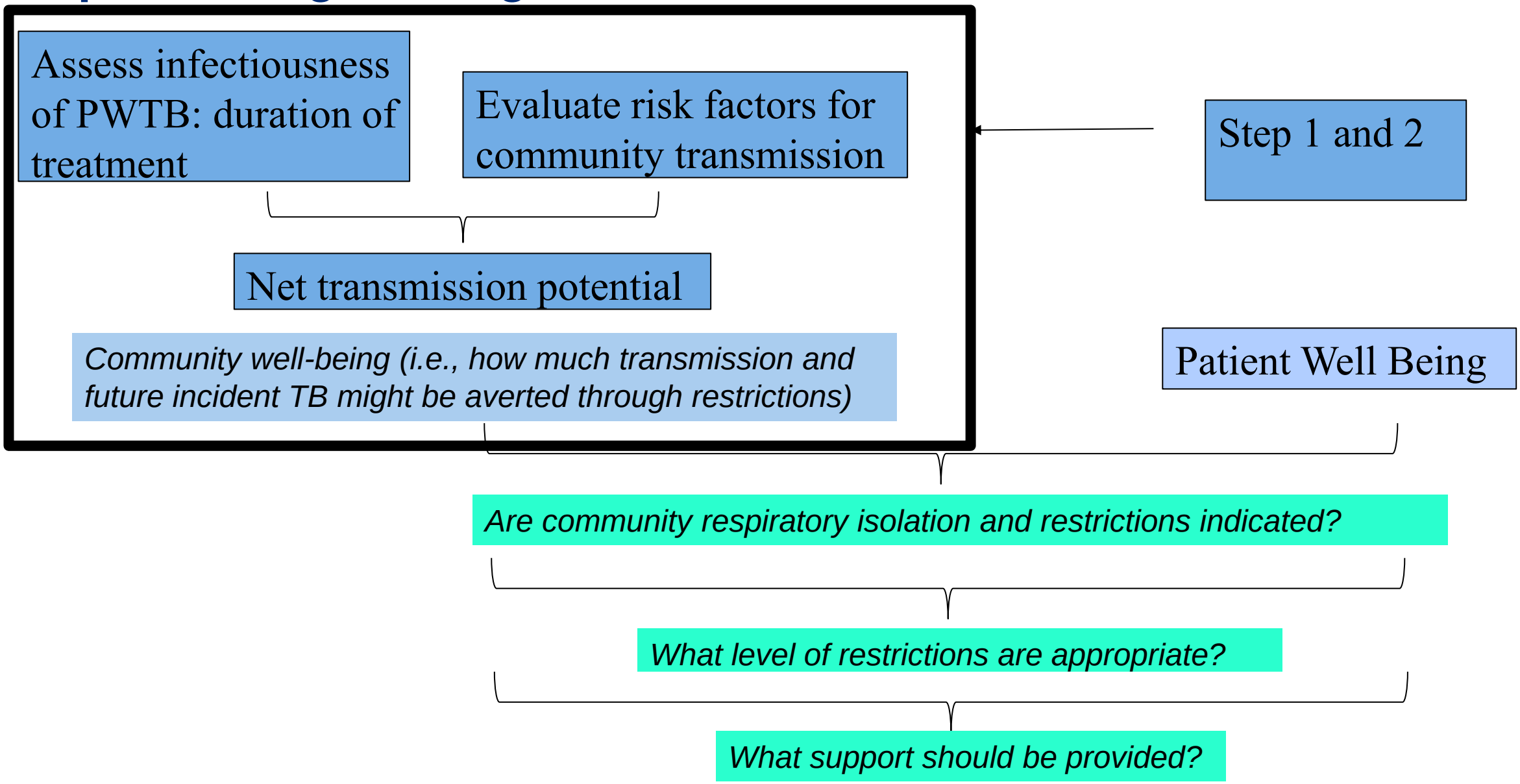
JOHNS HOPKINS MEDICINE

Case-study 2: high bacterial burden; moderate community risk, low patient harm

Case 2 : High pre-treatment bacterial burden

- 55 year old F, diagnosed with pulmonary TB after presenting with fevers x 2 weeks and productive cough.
  - Microbiology: Smear-positive, GeneXpert MTB/RIF positive (no rpoB)
  - Coughing
  - Cavity on chest imaging
  - Intermittent cough for 3 months
- Social History:
  - Born in India, living in the US since 2003,
  - Works in IT: 20 coworkers in single-floor office
  - Married with 3 children
  - Attends church on weekends (~50 individuals)

Implementing NTCA guidelines



PRIOR to treatment initiation, how would you judge this PWTB (smear-positive, Cavitary) level of infectiousness?

A. Very High/Highest 0%

B. High 0%

C. Moderate 0%

D. Low 0%

E. Very Low/Lowest 0%

How would you judge the overall risk factors for community transmission (if patient were infectious) given employment and social activities?

A. Very High/Highest 0%

B. High 0%

C. Moderate 0%

D. Low 0%

E. Very Low/Lowest 0%

Panel Discussion

CTBCP Recommended Framework for Individualized Decisions on Community-based Respiratory Isolation and Restrictions

TB Treatment Status	Pre-treatment bacterial burden in the respiratory tract	Level of infectiousness	Isolation indicated	Level of isolation/restriction
Pre-treatment	high	highest	yes	extensive
Pre-treatment	low	moderate	yes	moderate or extensive
Treatment ≤ 5 days	high	moderate	yes	moderate
Treatment ≤ 5 days	low	moderate	yes	moderate
Treatment > 5 days	high	low**	Individualized*	none or moderate
Treatment > 5 days	low	lowest	no	none
Extrapulmonary TB	N/A	None	No	None

CTBCP Recommended Framework for Individualized Decisions on Community-based Respiratory Isolation and Restrictions

TB Treatment Status	Pre-treatment bacterial burden in the respiratory tract	Level of infectiousness	Isolation indicated	Level of isolation/restriction
Pre-treatment	high	highest	yes	extensive
Pre-treatment	low	moderate	yes	moderate or extensive
Treatment ≤ 5 days	high	moderate	yes	moderate
Treatment ≤ 5 days	low	moderate	yes	moderate
Treatment > 5 days	high	low**	Individualized*	none or moderate
Treatment > 5 days	low	lowest	no	none
Extrapulmonary TB	N/A	None	No	None

Re-evaluation: High initial bacterial burden, moderate community risks, on therapy for 5 days

- 55 year old F with smear-positive, GXP positive (rpoB negative), cavitary, pulmonary TB initiated on HRZE, with **moderate restrictions**
  - Moderate RIR: Agreed to limit movement to the home. When she feels up for it, she has permission to telework. She asks friends not to visit while she is ill.
    - She indicates good family support and is in good spirits
    - No concerns for housing, food, or financial insecurity
  - On HRZE with good adherence and has taken 5 days of treatment (DOT+vDOT)
  - Fevers have subsided, but still has a cough, and repeat sputum is still smear-positive
  - Contact investigation has not yet been initiated at the site of employment

How would you approach duration of restrictions in this smear-positive patient (who remains smear-positive)?

Isolation until smear-negative x 3 and at least 14 days of therapy 0%

Isolation until 14 days of therapy and clinical improvement and smear-grade reduction 0%

Isolation until 14 days and then discontinue irrespective of improvement or smear-grade 0%

Discontinue isolation--patient has completed 5 days of therapy 0%

Something else 0%

Panel Discussion

CTBCP Recommended Framework for Individualized Decisions on Community-based Respiratory Isolation and Restrictions

TB Treatment Status	Pre-treatment bacterial burden in the respiratory tract	Level of infectiousness	Isolation indicated	Level of isolation/restriction
Pre-treatment	high	highest	yes	extensive
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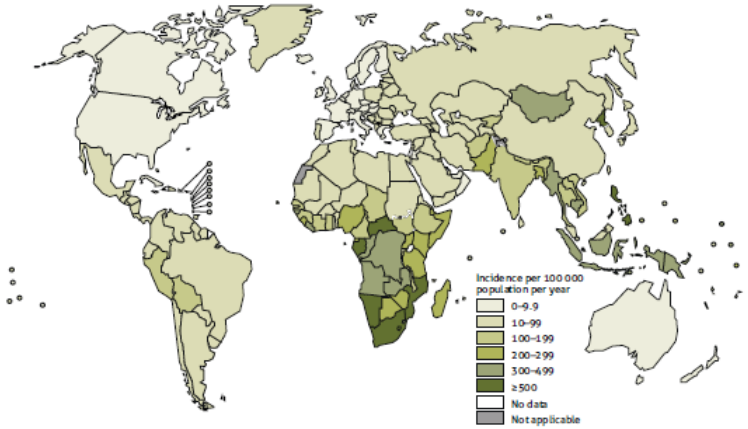
Treatment ≤ 5 days	high	moderate	yes	moderate
Treatment ≤ 5 days	low	moderate	yes	moderate
Treatment > 5 days	high	low**	Individualized*	none or moderate
Treatment > 5 days	low	lowest	no	none
Extrapulmonary TB	N/A	None	No	None

Quick Reference Guide

Patient Characteristics	MDH Recommendations	Added Considerations	Patient Considerations
Low pre-treatment infectiousness (e.g., sputum smear-negative & non-cavitary) + GXP available (Rifampin S)	All settings and contacts: RIR through at least 5 days of verified treatment*	Request GXP. See below if not available.	
Moderate or High pre-treatment infectiousness + GXP available (Rifampin S)	Lower risk settings and contacts RIR through 5-10 days of verified treatment* Higher risk settings and contacts[b]: RIR through 10-14 days of verified treatment, and documented clinical response (symptom improvement) and/or microbiologic response (reducing sputum smear grade)*	1.Request GXP. See below if not available. 2.If High pre-treatment infectiousness (sm+ and cavitation) with high risk setting (e.g., vulnerable population), request MDDR to verify INH S; Consider HPMZ or high dose rifamycin to improve EBA of first line therapy	
[illegible]	[illegible] of verified treatment and clinical improvement* High bacterial burden OR Higher Risk Settings[b]: At least 14 days of verified treatment* and clinical improvement and microbiologic response (reducing smear grade)	[illegible] or higher risk settings 2.Collect weekly sputum x 3 to evaluate microbiologic response to assess appropriateness of treatment	
Rifampin Resistant	Minimum 14 days of laboratory confirmed effective therapy + clinical improvement, and demonstrated microbiologic response (reduced smear grade or increasing time to culture positivity on serial testing)	1.Request MDDR and phenotypic DST 2.Effective treatment is defined based on microbiological testing. Emerging data suggests BPaL/M reduces infectiousness rapidly, but data is limited. 3.For higher risk settings and contacts, a higher degree of certainty of treatment effectiveness (DST, 14-28 days of therapy, micro/clinical response) may be considered	Higher risk for negative patient impact. Evaluate as above, and engage with MDH and local social work or patient advocacy services to support patients.



JOHNS HOPKINS MEDICINE

Case-study: Moderate bacterial burden, moderate risks in the community; moderate/high patient harm

Example : Initial history

- 24 year old HIV negative born in Nicaragua, presented with abdominal pain and found to have pulmonary and GI TB
  - Microbiology: Sputum Smear-negative, GeneXpert MTB/RIF positive (no rpoB)
    - Stool AFB smear (culture positive)
  - Not Coughing
  - 1cm nodule, diffuse tree-in-bud opacities throughout lung fields 1.4cm cavity RUL
- Social History:
  - Born in Nicaragua and entered US 2022
  - Reports brother treated for PTB 2 years ago
  - Works part-time in a mail room (varying other employees depending on shift)

- Patient concerned about missing time from work

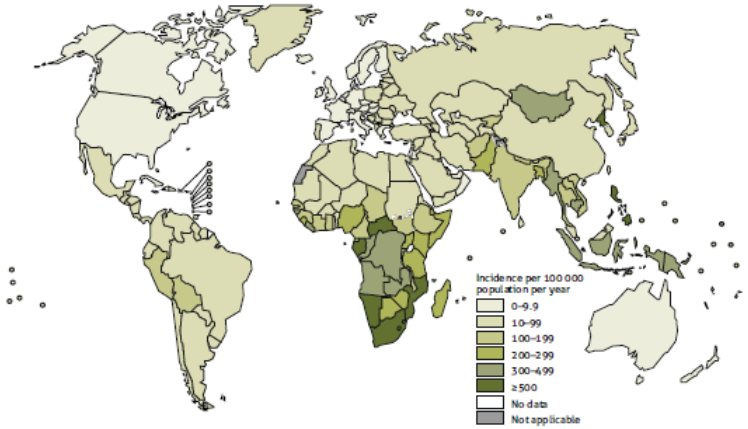
Example: Moderate initial bacterial burden, low/moderate community risks

- 24 yo w pulmonary smear-negative TB, stable housing, works mostly alone

Step	Result	Notes/Thoughts
1.Infectiousness prior to treatment: --sputum smear-microscopy --sputum culture --sputum NAAT --Imaging --Cough	• Smear-negative, • GeneXpert MTB/RIF-positive • Small Cavity • No Cough	Person is not on treatment (at their highest infectious potential) **Bacterial burden is low/moderate** **Infectiousness: moderate/high (before treatment)**
2.Review available drug susceptibility testing	• GeneXpert MTB/RIF—no rpoB mutation detected	• Presumed drug susceptible • Clinical decision to treat with standard RHZE
3.Assess overall community risks:	3 roommates in rented house Part-time work	• Low/Moderate risk: works alone, but poor ventilation

Panel Discussion

- Initial infectiousness
- Community risk
- Patient harm



JOHNS HOPKINS MEDICINE

Case-study: High bacterial burden, Moderate/High Community Risk, high patient harm

Example : Initial history

- 42 year old HIV-negative, diabetic, US born individual, prior contact while staying in a homeless shelter
  - Treated with INH for 9 mo 14 years ago (positive PPD)
- Fevers, cough, chest pain: Smear positive,GXP positive (rpoB neg)
- 4cm cavitary lung lesion

- Social history:
  - Marginally housed. Stays in a hotel with a husband and 2 grandchildren (both under 5)
  - Works in a daycare center (40 children ranging from infants to pre-K)
  - Pay for hotel weekly and concerned for herself and grandchildren becoming homeless

- Patient asks for the shortest possible treatment regimen

What is the shortest treatment for TB currently included in national guidelines?

HPMZ x 4 months

0%

HRZE x 6 months

0%

BPaL/M x 6 months

0%

Other

0%

Updates on the Treatment of Drug-Susceptible and Drug-Resistant Tuberculosis: An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline

Published by ATS Journals, 12/30/2024

Treatment of isoniazid-susceptible, rifampin-susceptible TB in adults with a 4-month rifapentine-moxifloxacin versus 6-month regimen

Question: In adolescents and adults with drug-susceptible pulmonary tuberculosis (TB), is a 4-month regimen composed of 2 months of isoniazid, rifapentine, pyrazinamide, and moxifloxacin followed by 2 months of isoniazid, rifapentine, and moxifloxacin (2HPZM/2HPM) as efficacious and safe as the standard 6-month drug-susceptible TB regimen of 2 months of isoniazid, rifampin, pyrazinamide, and ethambutol (2HRZE) followed by 4 months of isoniazid, and rifampin (4HR) endorsed by the American Thoracic Society (ATS)/U.S. Centers for Disease Control and Prevention (CDC)/European Respiratory Society (ERS)/Infectious Diseases Society (IDSA) guidelines?

Recommendation: In people aged 12 years or older with drug-susceptible pulmonary tuberculosis, we conditionally recommend the use of a 4-month regimen of isoniazid, rifapentine, moxifloxacin, and pyrazinamide (conditional recommendation, moderate certainty of evidence). See Table 1 for dosing details.

Table 1. Recommended Drug Regimens

Q1: Treatment of Isoniazid-Susceptible, Rifampin-Susceptible TB in Adults	
Recommended 4-mo Rifapentine-Moxifloxacin–Containing Regimen*	
Isoniazid†	300 mg daily for 17 wk
Rifapentine	1,200 mg daily for 17 wk
Pyrazinamide	Weight-based dosing daily for 8 wk: 40 to <55 kg: 1,000 mg; ⩾55–75 kg: 1,500 mg >75 kg: 2,000 mg
Moxifloxacin	400 mg daily for 17 wk

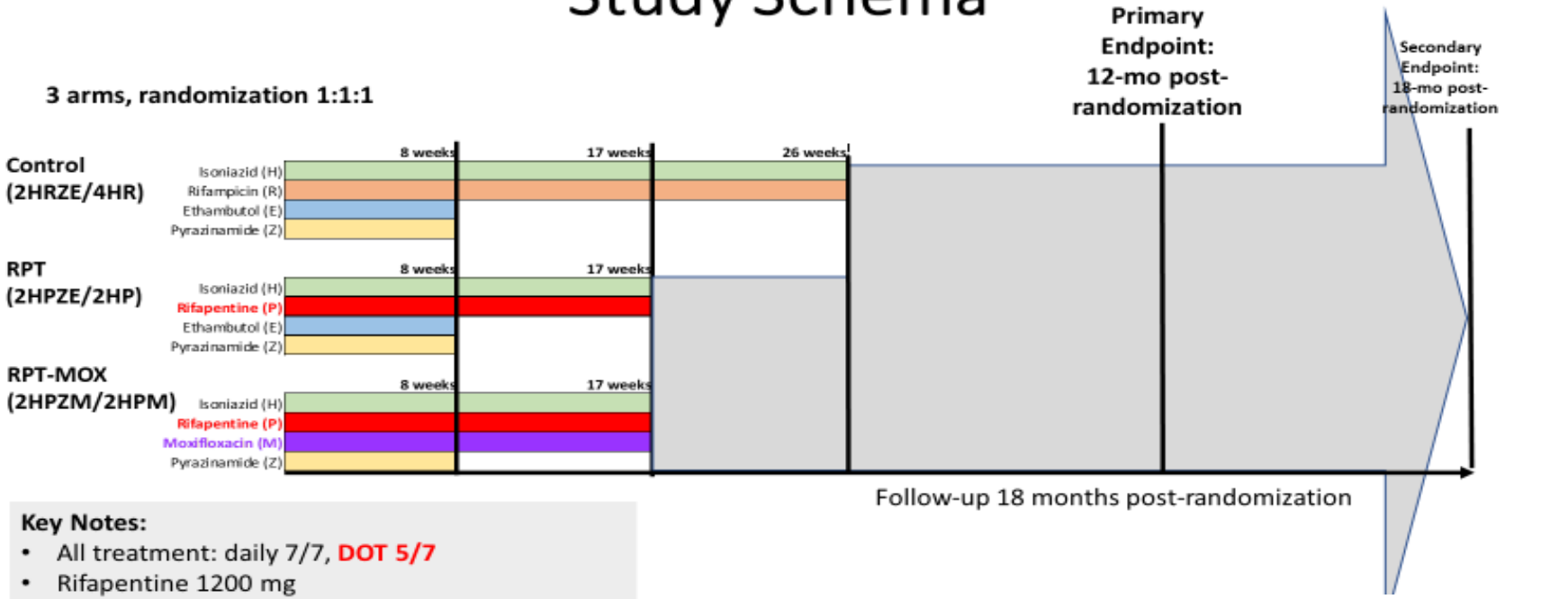
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis

S.E. Dorman, P. Nahid, E.V. Kurbatova, P.P.J. Phillips, K. Bryant, K.E. Dooley, M. Engle, S.V. Goldberg, H.T.T. Phan, J. Hakim, J.L. Johnson, M. Lourens, N.A. Martinson, G. Muzanyi, K. Narunsky, S. Nerette, N.V. Nguyen, T.H. Pham, S. Pierre, A.E. Purfield, W. Samaneka, R.M. Savic, I. Sanne, N.A. Scott, J. Shenje, E. Sizemore, A. Vernon, Z. Waja, M. Weiner, S. Swindells, and R.E. Chaisson, for the AIDS Clinical Trials Group and the Tuberculosis Trials Consortium

Study Schema

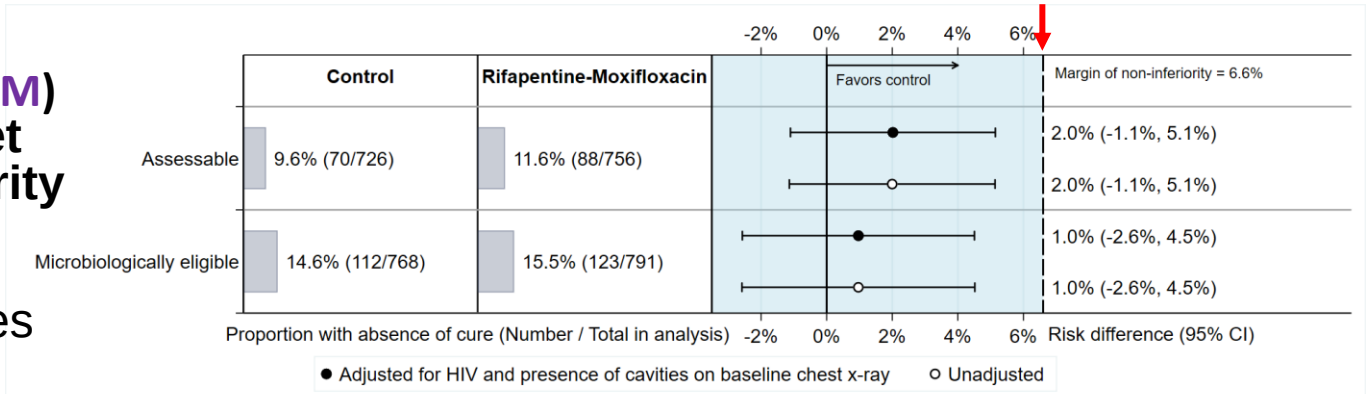


Key Notes:

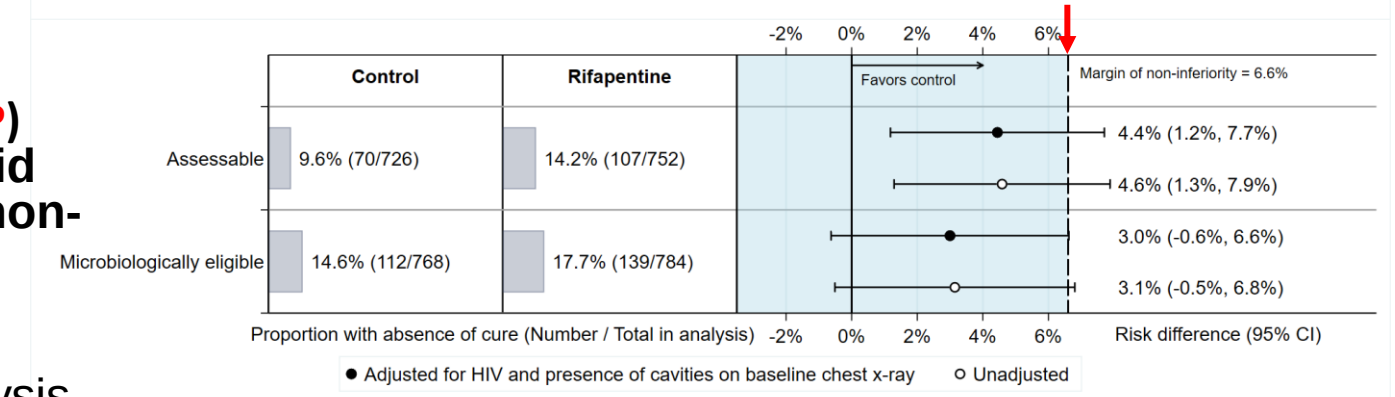
- All treatment: daily 7/7, **DOT 5/7**
- Rifapentine 1200 mg
- Moxifloxacin 400 mg
- Non-inferiority trial, NI margin 6.6%

Primary Efficacy Results

RPT-MOX (2HPZM/2HPM) regimen met non-inferiority criteria for efficacy in <u>both</u> analyses



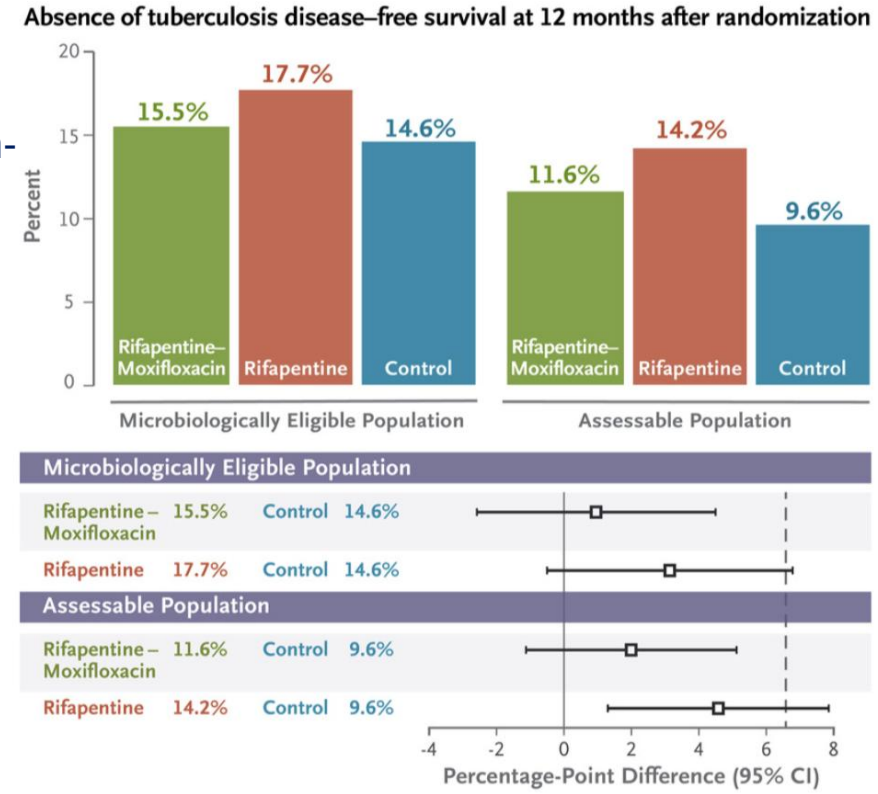
RPT (2HPZE/2HP) regimen did not meet non-inferiority criteria for efficacy in either analysis

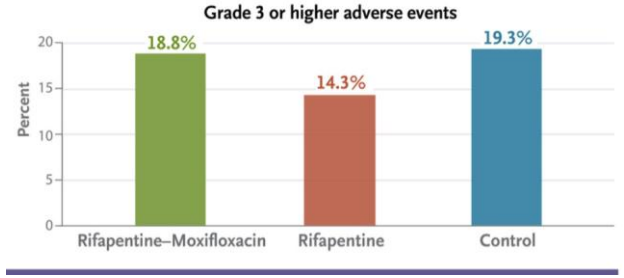


Four Month Regimen for Drug-Sensitive TB

- N=2516
- Open-label non-inferiority trial
- 4m vs 6m
- 13 countries

- 71% male
- 73% cavity
- 55% 2+ higher AFB smear+
- 8% HIV+
  - EFV-based





CONCLUSIONS

A 4-month regimen containing rifapentine and moxifloxacin was noninferior in efficacy and similar in safety and premature discontinuation to a standard 6-month antimicrobial regimen for the treatment of tuberculosis.

Dorman et al. NEJM (2021): PMID 33951360

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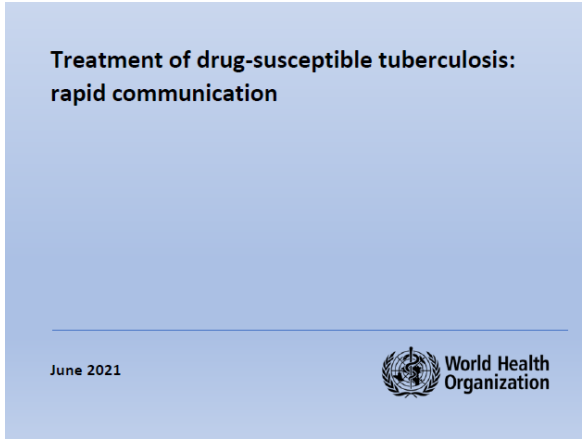
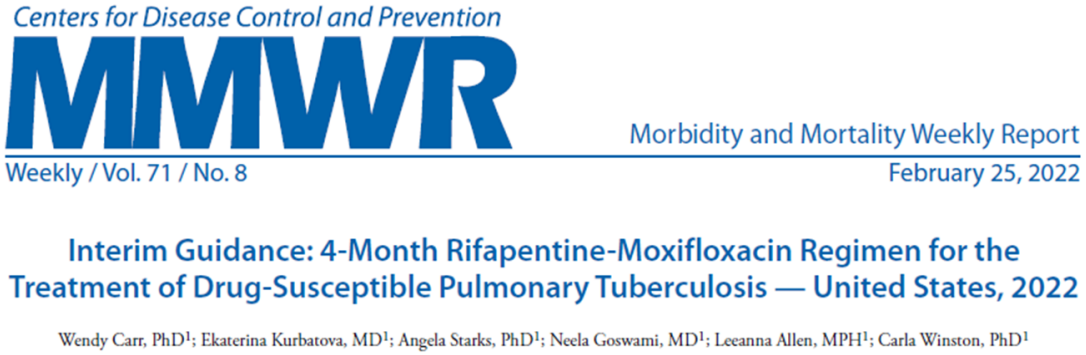
DIVISION OF INFECTIOUS DISEASES

WHO Rapid Communication on S31/A5349 Released June 14, 2021



Conclusions/Summary

The available evidence reviewed by the GDG on the **4-month regimen for treatment of drug-susceptible pulmonary TB supports the use of this regimen as a possible alternative to the current standard 6-month regimen**. The shorter regimen has showed similar performance to the current standard regimen, both in terms of efficacy and safety. The 4-month regimen, which is shorter, effective and all-oral, would be a preference for many patients and also national TB programmes, allowing faster cure and easing the burden on both patients and the healthcare system.

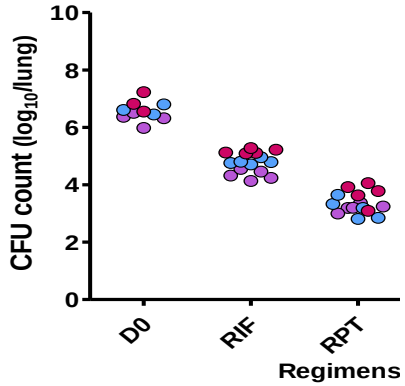


Recommendation for Use of the 4-month Rifapentine-Moxifloxacin Regimen

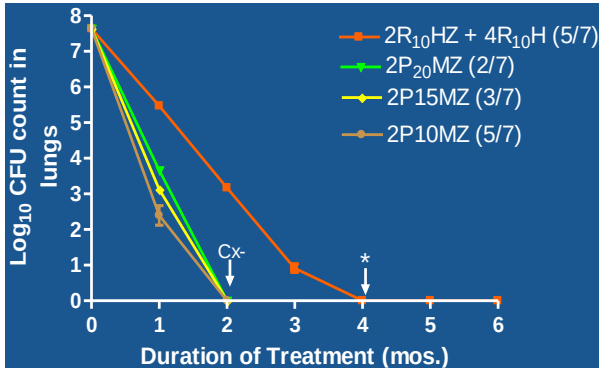
- Adults and adolescents ≥12 y.o.
- Weight ≥40 kg
- No known or suspected resistance

What else do we know?

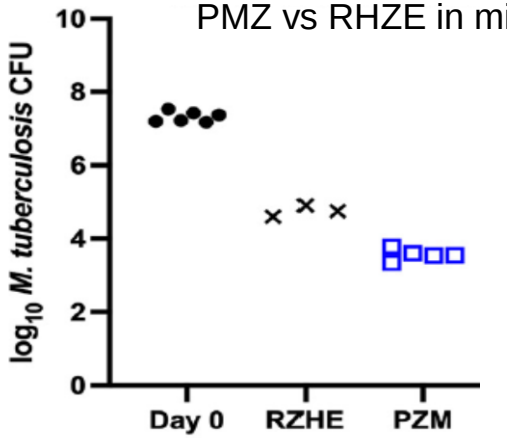
Rif vs RPT in mice (4 weeks)



Time to cx negativity in mice w RPT+M+Z



PMZ vs RHZE in mice



	Proportion of mice relapsing after treatment for:			
Regimen	2 mo.	3 mo.	4 mo.	6 mo.
RZHE		19/19	7/19	1/18
PZMH	13/18	1/19	0/19	

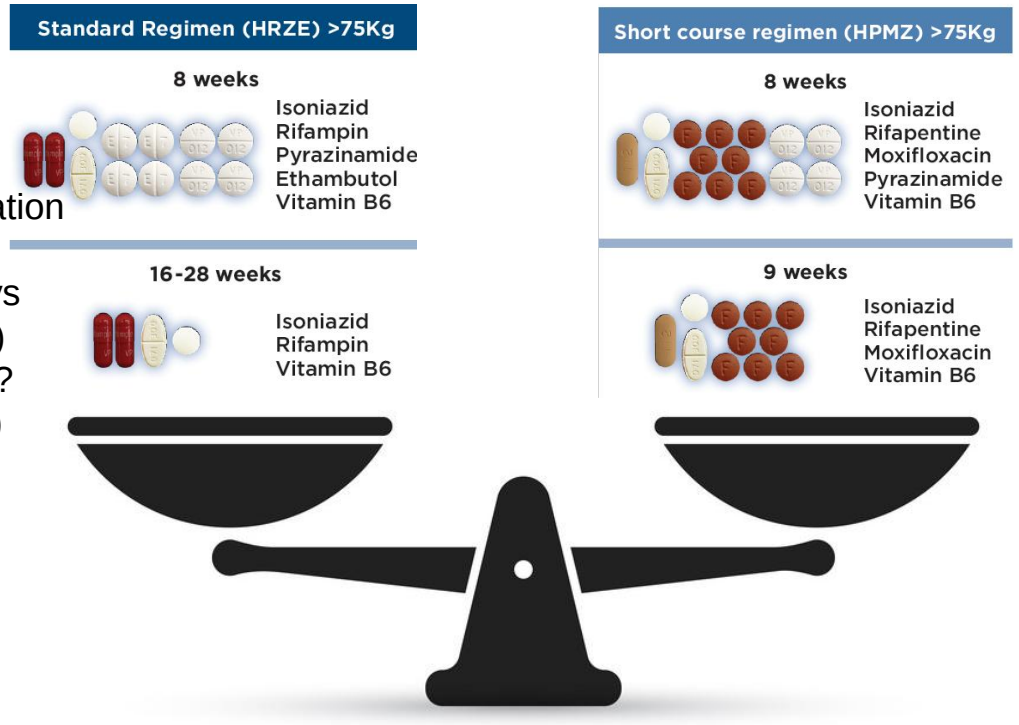
- PMZ(H) has **stronger bactericidal and sterilizing** activity in mouse models of TB
- For equal amount of time, PMZH likely has superior activity than RHZE
- PMZH should have other benefits based on pre-clinical data including:
  - **Faster response to treatment**
  - **More forgiving of missed doses**
  - **Greater efficacy against INH-monoresistant TB**

Slides adapted from presentation by Dr. Eric Nuermberger

Patient, clinicians, an programs may value these outcomes differently

RHZE

- Less Pills
- Longer Duration
- ?Costs (patient costs vs Program costs)
- Side effects?
- (Resources)



HPMZ

- More Pills
- Shorter Duration
- ?Costs (patient costs vs program costs)
- Side effects?
- (Resources)

Example : Initial history

- 42 year old HIV-negative, diabetic, US born individual, prior contact while staying in a homeless shelter
  - Treated with INH for 9 mo 14 years ago (positive PPD)
- Fevers, cough, chest pain: Smear positive,GXP positive (rpoB neg)
- 4cm cavitary lung lesion

- Social history:
  - Marginally housed. Stays in a hotel with a husband and 2 grandchildren (both under 5)
  - Works in a daycare center (40 children ranging from infants to pre-K)
  - Pay for hotel weekly and concerned for herself and grandchildren becoming homeless

- Patient asks for the shortest possible treatment regimen

Assessing effectiveness of therapy

- GXP positive, rpoB negative
- Prior INH exposure

- Would you consider MDDR? What are the other options for rapid drug susceptibility testing?

- How would you approach treatment?

- How would you assess the effectiveness of therapy?

Panel Discussion

- Initial infectiousness
- Community risk
- Patient harm
- Initial regimen selection

Example: High initial bacterial burden, moderate community risks

- 42 yo w smear positive, cavitary TB, expressing concerns for any isolation or work restrictions

Step	Result	Notes/Thoughts
1.Infectiousness prior to treatment: --sputum smear-microscopy --sputum culture --sputum NAAT --Imaging --Cough	• Smear-positive, • GeneXpert MTB/RIF-positive • Cavity • Has Cough	Person is not on treatment (at their highest infectious potential) **Bacterial burden is high**
2.Review available drug susceptibility testing	• GeneXpert MTB/RIF—no rpoB mutation detected	• Presumed drug susceptible (but had INH exposure) • Clinical decision to treat with standard RHZE
3.Assess overall community risks:	• 5-10 children heavily exposed • ~40 children	• **HIGH** • Presume poor ventilation and long durations in close proximity • Vulnerable population

How do you approach the considerations of community risk and patient harm in this situation?

- How would the provision of window prophylaxis and contact investigations factor into your decision making?
- How does the presence of vulnerable populations factor into your decision-making?
- What steps should be taken to mitigate harms to the patient and her family?

Summary (Maryland Quick Reference)

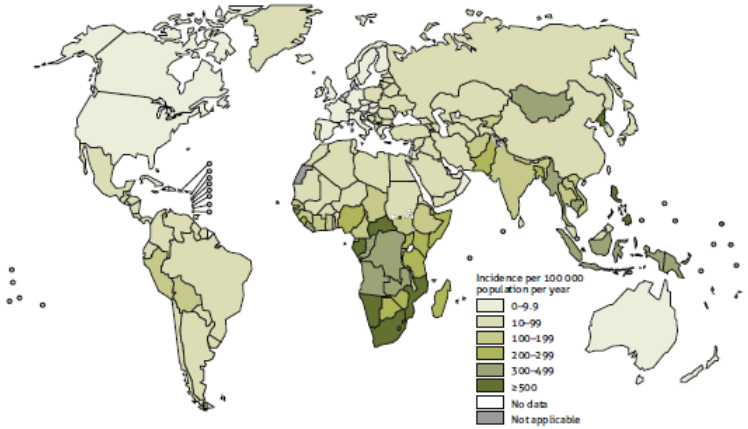
Patient Characteristics	MDH Recommendations	Added Considerations	Patient Considerations
Extrapulmonary Only Normal CXR	No Respiratory Isolation or Restrictions	Ensure evaluation for TB of respiratory tract with chest imaging and sputum bacteriologic testing	Evaluate weekly 1.Assess Financial impact and support as resources allow 2.Assess Housing 3.Assess Mental Health and refer for additional counseling/support 4.Assess Food security Tailor restrictions: 1.Consider Moderate restrictions in most instances (allow outdoor activities that do not involve close, prolonged contact) 2.Evaluate employment setting and make tailored recommendation)
Children <10 with intrathoracic TB	No isolation except for older children and adolescents with adult-type disease	Individuals with sputum bacteriologic tests that are positive may be considered as having adult-type disease	
Low pre-treatment infectiousness + GXP available (Rifampin S)	All settings and contacts: RIR through at least 5 days of verified treatment*	Request GXP. See below if not available.	
Moderate or High pre-treatment infectiousness + GXP available (Rifampin S)	Lower risk settings and contacts RIR through 5-10 days of verified treatment* Higher risk settings and contacts[b]: RIR through 10-14 days of verified treatment, and documented clinical response (symptom improvement) and/or microbiologic response (reducing sputum smear grade)*	1.Request GXP. See below if not available. 2.If High pre-treatment infectiousness (sm+ and cavitation) with high risk setting (e.g., vulnerable population), • request MDDR to verify INH S; • Consider HPMZ or • Consider high dose rifamycin to improve EBA of first line therapy	

Maryland Quick Reference

Patient Characteristics	MDH Recommendations	Added Considerations	Patient Considerations
GXP unavailable	Low bacterial burden and Lower Risk Settings: 10-14 days of verified treatment and clinical improvement* High bacterial burden OR Higher Risk Settings[b]: At least 14 days of verified treatment* and clinical improvement and microbiologic response (reducing smear grade)	1.Request GXP and/or MDDR, particularly for high bacterial burden or higher risk settings 2.Collect weekly sputum x 3 to evaluate microbiologic response to assess appropriateness of treatment	Evaluate weekly 1.Assess Financial impact and support as resources allow 2.Assess Housing 3.Assess Mental Health and refer for additional counseling/support 4.Assess Food security Tailor restrictions: 1.Consider Moderate restrictions in most instances (allow outdoor activities that do not involve close, prolonged contact) 2.Evaluate employment setting and make tailored recommendation)
Rifampin Resistant	Minimum 14 days of laboratory confirmed effective therapy + clinical improvement, and demonstrated microbiologic response (reduced smear grade or increasing time to culture positivity on serial testing)	1.Request MDDR and phenotypic DST 2.Effective treatment is defined based on microbiological testing. Emerging data suggests BPaL/M reduces infectiousness rapidly, but data is limited. 3.For higher risk settings and contacts, a higher degree of certainty of treatment effectiveness (DST, 14-28 days of therapy, micro/clinical response) may be considered	Higher risk for negative patient impact. Evaluate as above, and engage with MDH and local social work or patient advocacy services to support patients.

Panel Discussion

- How would you approach duration of restrictions?
- Final comments?



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Case-study: GXP positive/Rif resistance

Case

- 40 year old from Ukraine admitted with chest pain and intermittent fevers
- Chest CT: multilobar infiltrates and effusion
- Sputum:
  - Sputum smear-negative x 3
  - Sputum GXP negative x 3
  - BAL Smear-negative, GXP positive, Rifampin resistance detected
- Lives at home with several roommates (no children)
- Unemployed

Panel Discussion

- What would be your choice of holding regimen while awaiting bedaquiline?
- Can the person return to home (with isolation)?
- How would you approach duration of restrictions?

Quick Reference Guide

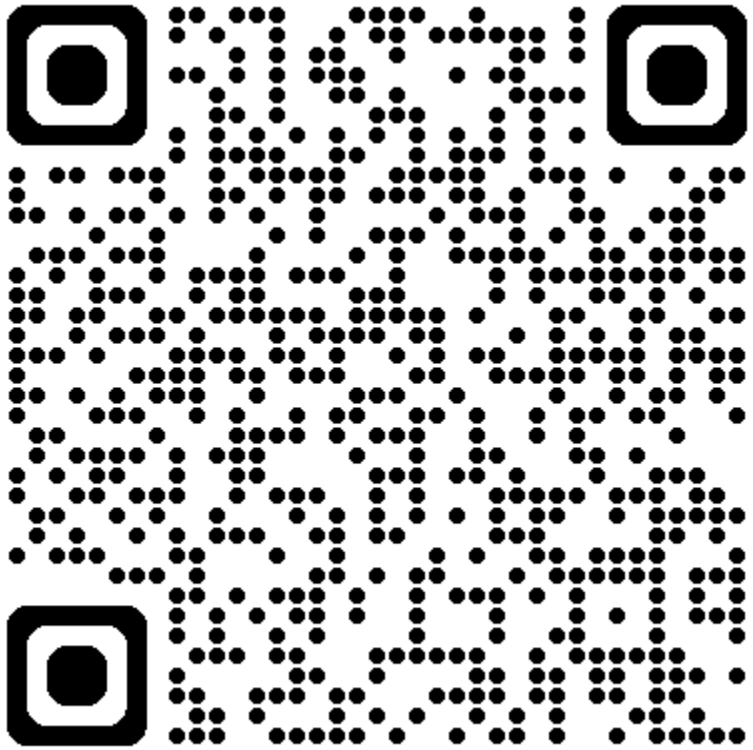
Patient Characteristics	MDH Recommendations	Added Considerations	Patient Considerations
Low pre-treatment infectiousness (e.g., sputum smear-negative & non-cavitary) + GXP available (Rifampin S)	All settings and contacts: RIR through at least 5 days of verified treatment*	Request GXP. See below if not available.	
Moderate or High pre-treatment infectiousness + GXP available (Rifampin S)	Lower risk settings and contacts RIR through 5-10 days of verified treatment* Higher risk settings and contacts[b]: RIR through 10-14 days of verified treatment, and documented clinical response (symptom improvement) and/or microbiologic response	1.Request GXP. See below if not available. 2.If High pre-treatment infectiousness (sm+ and cavitation) with high risk setting (e.g., vulnerable population), request MDDR to verify INH S; Consider HPMZ or high dose rifamycin to improve EBA of first line therapy	
Rifampin Resistant	Minimum 14 days of laboratory confirmed effective therapy + clinical improvement, and demonstrated microbiologic response (reduced smear grade or increasing time to culture positivity on serial testing)	1.Request MDDR and phenotypic DST 2.Effective treatment is defined based on microbiological testing. Emerging data suggests BPaL/M reduces infectiousness rapidly, but data is limited. 3.For higher risk settings and contacts, a higher degree of certainty of treatment effectiveness (DST, 14-28 days of therapy, micro/clinical response) may be considered	Higher risk for negative patient impact. Evaluate as above, and engage with MDH and local social work or patient advocacy services to support patients.

Guidelines and Commentary: Clinical Infectious Diseases Available as Advance Articles

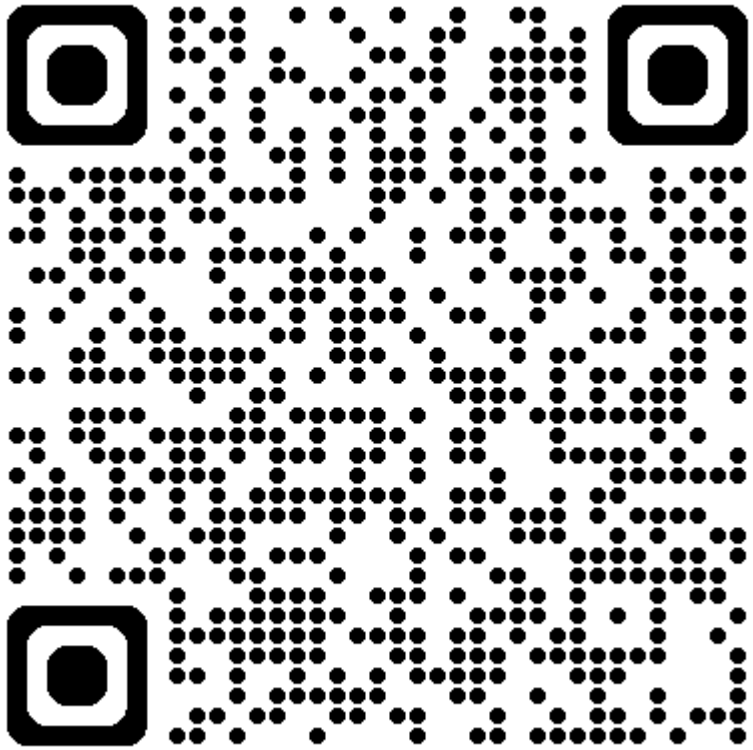
NTCA Guidelines:
https://academic.oup.com/cid/article-lookup/doi/10.1093/cid/ciae199

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

Additional manuscripts



Determinants of Infectiousness



Historical Perspective