From the Heartland News Desk!

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Barbara J. Seaworth, MD

March 25, 2025

World TB Day • March 25, 2025 • Webcast

Lisa Y. Armitige, MD, PhD

Has the following disclosures to make:

- No conflict of interests
- No relevant financial relationships with any commercial companies pertaining to this activity

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3HP for Tiny Humans

Lisa Y Armitige, MD, PhD

Co-Medical Director

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LTBI Treatment Options for Children < 2 y/o

- Rifampin daily for 4 months (120 doses)
- Isoniazid daily for 6-9 months (180-270 doses)
- Everybody else can have INH/rifapentine weekly (12 doses)

Risk for active TB by Age

Table 1. Pooled estimates of risk for active TB among household contacts stratified by age and baseline LTBI status as compared with the general population

Age (years)	LTBI-positive at baseline				Regardless of baseline LTBI status			
	Follow-up < 12 months		Follow-up < 24 months		Follow-up < 12 months		Follow-up < 24 months	
	No. of studies	Risk ratio	No. of studies	Risk ratio	No. of studies	Risk ratio	No. of studies	Risk ratio
General population	–	1.0 (reference)	–	1.0 (reference)	–	1.0 (reference)	–	1.0 (reference)
0–4	2	24.3 (0.73–811.0)	3	22.9 (7.7–68.6)	3	25.9 (16.9–39.7)	5	14.8 (9.8–22.3)
5–14	2	27.1 (17.5–54.1)	3	8.2 (2.3–29.4)	3	24.1 (16.9–34.4)	5	6.3 (2.9–13.7)
≥ 15	1	30.7 (17.5–54.1)	2	13.4 (9.5–18.8)	1	24.7 (14.2–43.0)	3	11.7 (7.6–18.0)

WHO **Latent tuberculosis infection** - Updated and consolidated guidelines for programmatic management

Risk of Progression to TB Disease by Age

Age @ primary infection	Risk of Disease	
• Birth - 12months	Disease	50%
	Pulmonary Dis	30-40%
	Miliary or TBM	10-20%
• 1-2 years	Disease	20-25%
	Pulmonary Dis	75%
	Miliary or TBM	2-5%

Marais BJ. *Int J Tuberc Lung Dis* 2004;8:392-402

The Announcement

TAG
Treatment Action Group

About Us HIV HCV TB Resources Support Us

Finally, Children of All Ages Can Benefit from 3HP to Prevent TB!

Statements Finally, Children of All Ages Can Benefit from 3HP to Prevent TB!

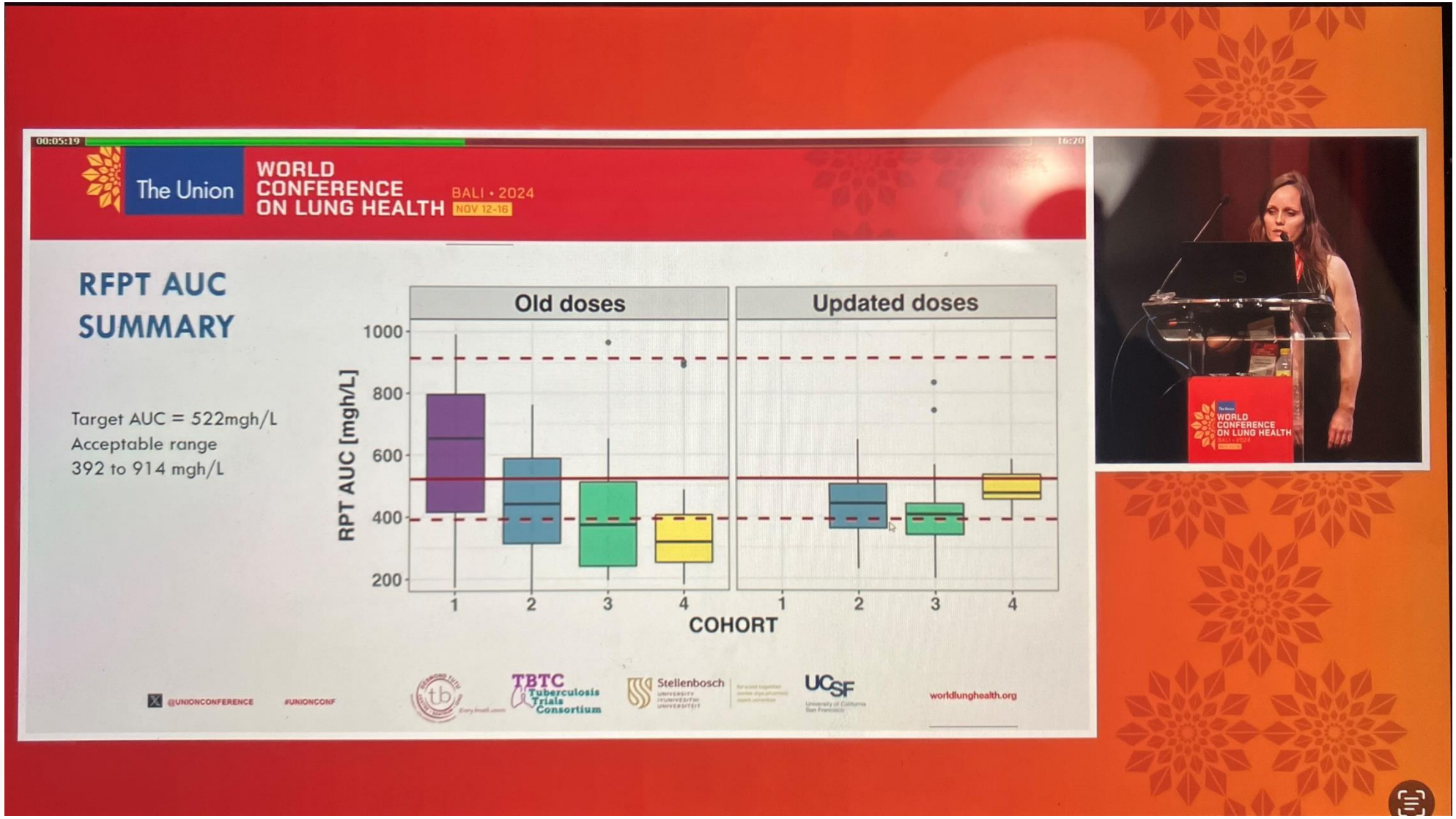
CRAG
TB Community Research Advisors Group

Community Research Advisors Group's statement on the results of TBTC Study 35: an *open-label, phase I/II dose finding and safety study of rifapentine and isoniazid in HIV- positive and HIV- negative children with latent tuberculosis infection*

13 November 2024 — The Community Research Advisors Group (CRAG) celebrates both the findings and the methodology of Study 35, a phase I/II clinical trial of the tuberculosis (TB) preventive treatment regimen known as 3HP in children. Conducted by the Tuberculosis Trials Consortium (TBTC) at the U.S. Centers for Disease Control and Prevention, TBTC Study 35 results were presented today at the Union World Conference on Lung Health in Bali, Indonesia.

Enrollment

Cohort	Age	Number Enrolled (Targeted)
1	≥ 4 to ≤ 12 years old	18 (12)
2	≥ 24 months to < 4 years old	12 (12)
3	≥ 12 to < 24 months old	18 (18)
4	0 to < 12 months old	18 (18)
	Total	66



Union 2024 Bali – Louvina van der Laan

Operational handbook (2)

Drug dosage for TPT according to body weight band

different weight bands

TPT regimens and drug formulations	No. of tablets or quantity of solution by body weight band												
	3–5.9 kg (< 3 months)	3–5.9 kg (≥ 3 months)	6–9.9 kg (< 6 months)	6–9.9 kg (≥ 6 months)	10–14.9 kg	15–19.9 kg	20–24.9 kg	25–29.9 kg	30–34.9 kg	35–39.9 kg	40–44.9 kg	45–49.9 kg	> 50 kg
3HP													
H 100 mg dispersible	0.6 (6 mL)	0.7 (7 mL)	1	1.5	2.5	3	4.5	4.5	6	6	7.5	7.5	9
H 300 mg tab	–	–	–	–	–	1	1.5	1.5	2	2	2.5	2.5	3
P 150 mg dispersible	0.5 (5 mL)	0.7 (7 mL)	1.5	1.5	2	3	4	4	5	6	6	6	6
P 300 mg tab	–	–	–	–	–	1.5	2	2	2.5	3	3	3	3
P 300 mg and H 300 mg FDC tab	–	–	–	–	–	–	–	–	–	–	–	–	3
One month of daily rifapentine plus isoniazid (1HP): age ≥ 13 years													
H 300 mg tab	–	–		–	–	–	–	1	1	1	1	1	1
P 300 mg tab	–	–		–	–	–	–	2	2	2	2	2	2
Six months daily levofloxacin (6Lfx)													
Lfx 100 mg dt	0.5	1	1	1.5	2	2.5	3	3.5	–	–	–	–	–
Lfx 250 mg tab	0.25 (2.5 mL)	0.5 (5 mL)	0.5 (5 mL)	1 (10 mL)	1	1.5	–	2	2	2	2	2	3
Lfx 500 mg tab	–	–	–	–	–	–	–	1	1	1	1	1	1.5

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The Union

WORLD CONFERENCE ON LUNG HEALTH

BALI • 2024 NOV 12-16

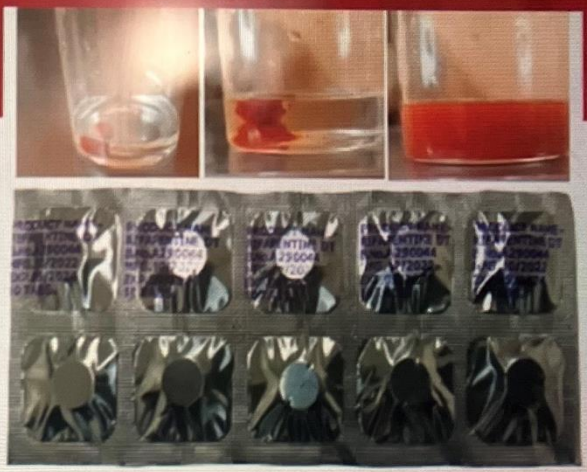
Rifapentine and Isoniazid products for children and adolescents

Palatable tablets of both medicines are available, that can be dispersed in water and are therefore easier to administer to children. This allows for more accurate dosing compared to crushing adult tablets.

LUPIN PHARMACEUTICALS INC.	NEW Rifapentine 150mg scored dispersible tablet (GF ERP approved, under review by WHO PQ) – *taste-masked for increased palatability*	**$1.38** per 10 pack
MACLEODS MICRO LABS	Isoniazid 100mg scored dispersible (WHO Prequalified) – *taste-masked for increased palatability* *Already in use*	**$8.95 - $9.16** per 100 pack
LUPIN PHARMACEUTICALS INC.	Isoniazid 100mg scored dispersible tablet (under development) – *taste-masked for increased palatability*	**$3.00** per 100 pack[2]

[1]*Although there is a conditional recommendation, there is currently no suitable child-friendly option for 4R.*

[2]*Contingent upon successful development and regulatory approval*



About the new RPT 150mg scored dispersible tablet (Lupin)

- Functionally scored tablet to provide 75mg dose increments
- Disperses rapidly in a small volume of water (about 10ml)
- Taste masked with raspberry mint flavoring
- Stability data generated at ICH Zone IVb conditions (30°C/75% Relative Humidity (RH))
- Proposed shelf-life: 24 months
- Proposed Packaging:
  - Aluminum strips (10ct and 28ct)
  - Aluminum/Aluminum blister (10ct and 12ct)
  - PVC/PVDC blister with Aluminum lidding foil (10ct)
- Can be ordered via the Stop TB Partnership Global Drug Facility (GDF) or other country procurement mechanisms directly from the manufacturer

worldlunghealth.org

@UNIONCONFERENCE #UNIONCONF

Points to Consider

- This study was done with dispersible tablets ….that we can’t get
- Crushing rifapentine tablets still offers good bioavailability
- Achieving the appropriate dose without liquid formulations is likely to be complicated in the smallest children
- Coming soon:
  - Smile-TB looking at 8 weeks of HPMZ for children < 10 years old

Artificial Intelligence in TB

Barbara J. Seaworth, MD
Co-Medical Director
Heartland National TB Center

A Quick Look at How AI Can Help Address the TB Epidemic

A Birdseye view

Disclaimer:

I am the very least qualified person to do this!

How can AI Help ?

- Diagnosis of TB Disease
  - Screening
  - Triage (Assessing next steps in symptomatic patient)
- Radiographic diagnosis of Drug Resistance
- Prediction of treatment outcomes
- Identifying new compounds for treatment of MTB
- Identifying host directed therapies
- Basic education of patients and families
- Discussion of challenges patients face with TB treatment

Ling et al, Frontiers in Medicine, July 2022

TABLE 1 | A brief summary of the included studies.

Section	Study proportion	Purpose	Reference standard	Primary materials	Algorithm	Evaluation indicators	References
Tuberculosis detection	48.5%	Diagnose pulmonary tuberculosis or disease evaluation	Pathogenic detection, radiology reports, clinical records, etc.	CXR and CT images	CNN and ML	AUC, sensitivity, specificity, accuracy, etc.	(31–41, 43–47)
Tuberculosis discrimination	18.2%	Discriminate between pulmonary tuberculosis and lung cancer or NTM-LD	Pathogenic detection, pathology, or follow-up confirmation	CT and PET/CT images	CNN and radiomics		(52–55, 59, 60)
Tuberculosis drug resistance prediction	33.3%	Recognize MDR-TB or drug resistance of *Mycobacterium tuberculosis* up to 14 anti-tuberculosis drugs	Drug susceptibility testing	CXR, CT images, and gene sequences	ANN, CNN, GNN, and ML		(63–65, 68–73)

CXR, chest X-ray; CT, computed tomography; CNN, convolutional neural network; ML, machine learning; AUC, area under the curve; NTM-LD, non-tuberculous mycobacterium lung disease; PET/CT, positron emission tomography/computed tomography; MDR-TB, multi-drug resistant tuberculosis; ANN, artificial neural network; GNN, graph neural network.

Ling et al; Frontiers in Medicine Review July 2022

Can I Trust AI?

- Modeling shows accuracy of physicians' interpretations was highest when accompanied by accurate, interpretable AI tools. *Jabbour; JAMA, 2023;330*
    - Physicians need to be able to find and use correct tool
- After analysis of AI based CAD (computer aided detection) in 2021, **WHO issued conditional recommendation that CAD solutions may be used i**n place of human readers for both TB screening and triage. *Int J TB Lung Dis 2023 The Union*

Can I Trust AI?

- Several CAD programs are commercially available and have accuracy of near 90% with sensitivity close to 90% and specificity of ~70% compared to + Xpert and/or culture
  - Shown to preform on par with radiologists
  - **Thresholds vary with population characteristics and need to be set by each program and adjusted for populations**
  - Not validated in kids; cannot process a lateral CXR
  - Accuracy in non-TB abnormalities needs to be evaluated

Int J Tuberc Lung Dis 2023 The Union

CAD of TB from CXR in TB prevalence survey in South Africa: validation and modelled impacts of commercially available AI software

Qin et al Lancet Digital Health 2024

- Evaluated 12 CAD products against +Xpert and/or culture for MTB in a high HIV and high TB burden setting
  - Evaluated against WHO target product profile sensitivity of 90% and specificity 70%
  - First evaluated each across all thresholds; found that closest to 90% sensitivity and then checked its specificity against 70% target.
- **Results**
  - 5 had overall performance (AUC – measure of accuracy) > 0.86
  - For the same criteria there were differences in threshold scores across different CAD products
  - Several performed worse with prior TB RX and in older persons
  - **Different products needed different thresholds**

CAD of TB from CXR in TB prevalence survey in South Africa: evaluation and modelled impacts of commercially available AI software

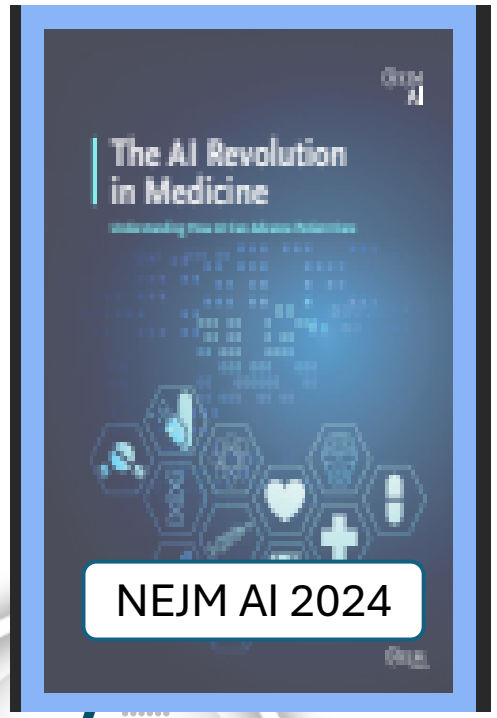
Qin et al Lancet Digital Health 2024

- **Threshold adjustments helped meet programmatic targets in different sub-populations**
- Different thresholds were needed for same criterion from different products.

  Refutes the notion that a universally recommend threshold could be appropriate
  Implementers such as national TB programs should develop own
- None of the 12 CAD evaluated were included in prior WHO guidance list; some were updated models.
  - But no guarantee performance was the same

Can I Trust AI?

Jabbour; JAMA 2023; 330



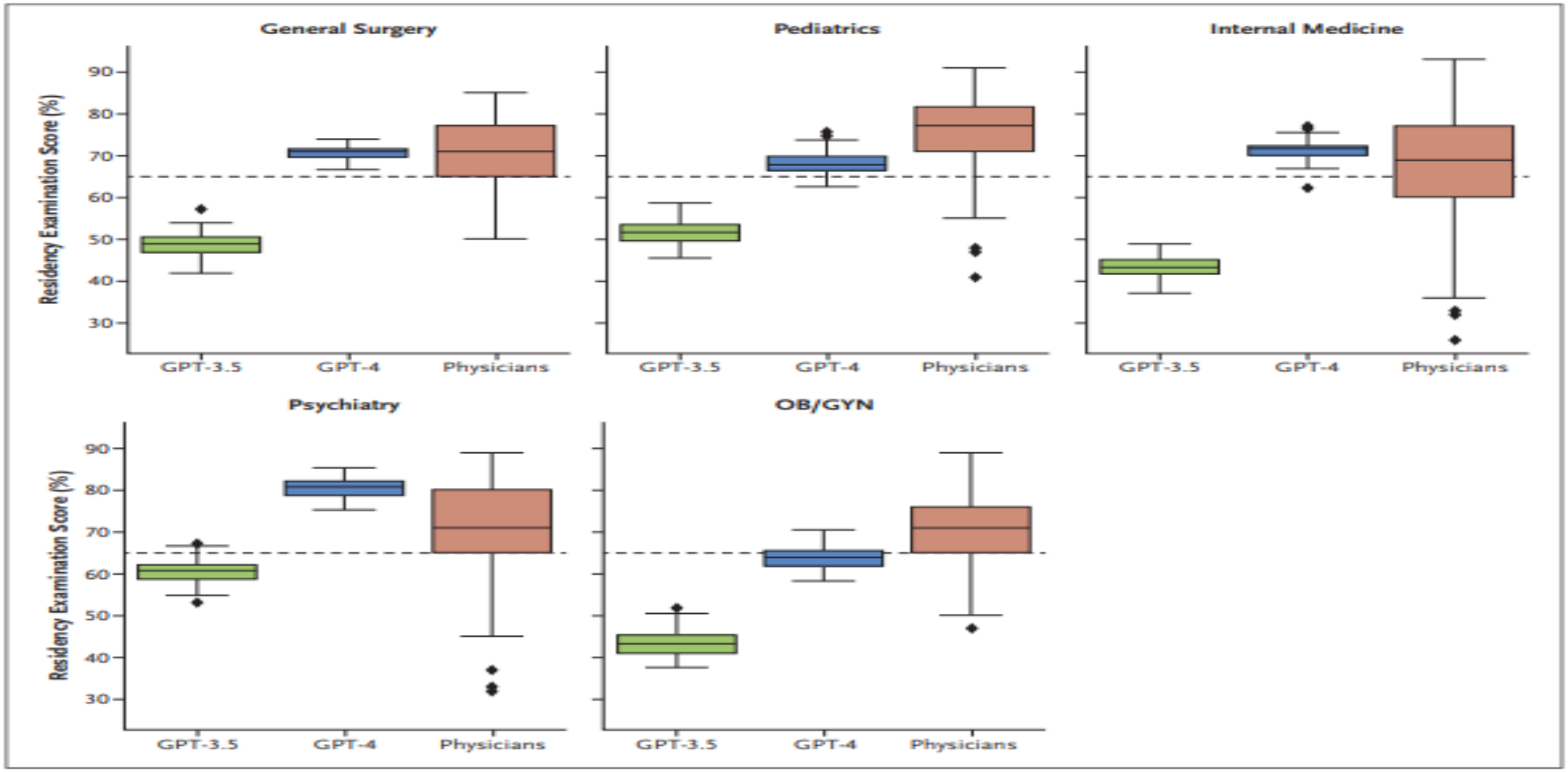


Figure 2. GPT and Physician Examination Scores.

ormance of different generative pretrained transformer (GPT) models across the different specialties is shown. The dotted lines esent the passing threshold. Dots represent outlier scores. The variance of GPT scores in repeated exam attempts is a result of del stochasticity. The variance in physician scores arises from differences between individual test-takers. The graphic was created by authors using data from the 2022 Israeli board residency examinations and results from the GPT models. OB/GYN denotes tetrics and gynecology.

Maybe AI Can be Trusted and Can Help

ai.nejm.org The AI Revolution in Medicine

NEJM AI

NEJM AI 2023; 1 (1
DOI: 10.1056/AIp230003

PERSPECTIVE

Use of GPT-4 to Diagnose Complex Clinical Cases

Alexander V. Eriksen, M.D.,[1,2] Sören Möller, M.Sc., Ph.D.,[3,4] and Jesper Ryg, M.D., Ph.D.[1,2]

Received: July 10, 2023; Revised: September 15, 2023; Accepted: September 29, 2023; Published: November 9, 2023

Abstract

We assessed the performance of the newly released AI GPT-4 in diagnosing complex medical case challenges and compared the success rate to that of medical-journal readers. GPT-4 correctly diagnosed 57% of cases, outperforming 99.98% of simulated human readers generated from online answers. We highlight the potential for AI to be a powerful supportive tool for diagnosis; however, further improvements, validation, and addressing of ethical considerations are needed before clinical implementation. (No funding was obtained for this study.)

Correctly diagnosed 57% of cases
Outperforming 99.8% of humans

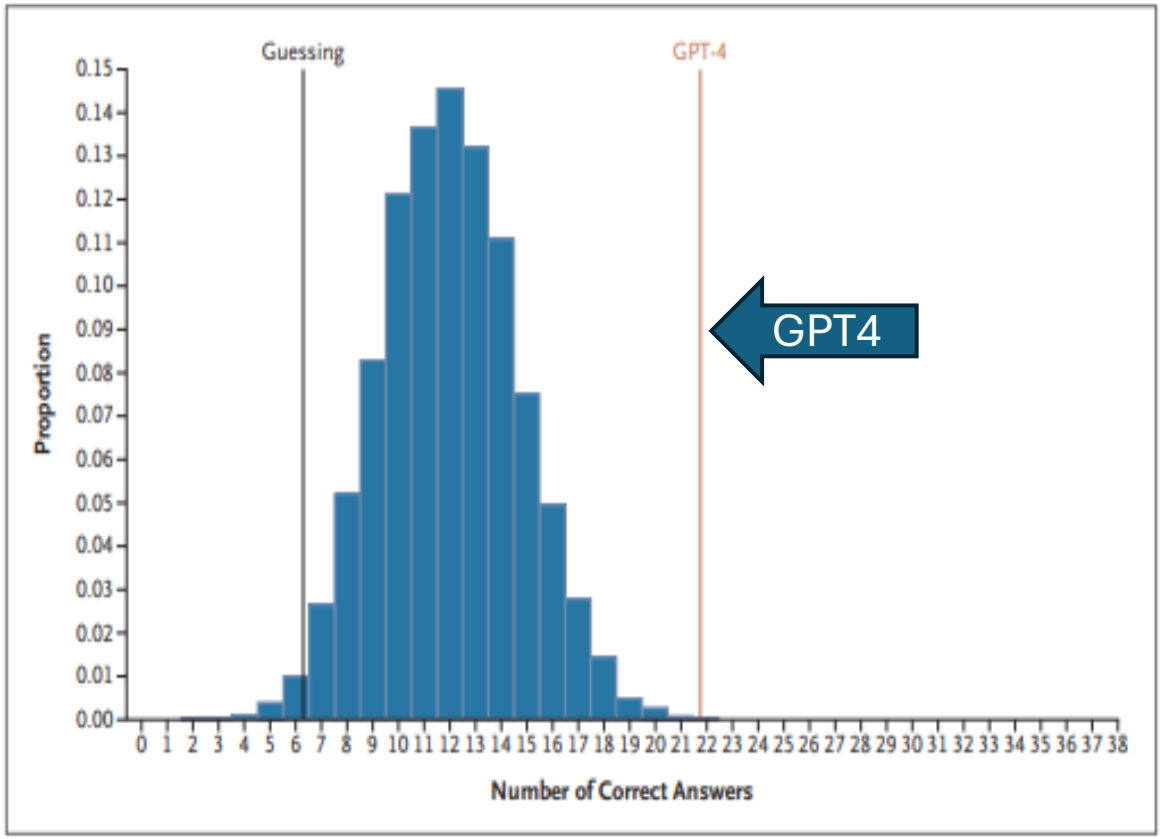


Figure 1. Number of Correct Answers of GPT-4 Compared with Guessing and a Simulated Population of Medical-Journal Readers.

AI assisted human interactions

Tested Chatbot with ethically fraught role-play dialogues

As I read through the dialogue I, like the author, believe that the Chatbot likely performed as well as I would have; maybe better!

And computers have unlimited time!!!

PERSPECTIVE

Who's Training Whom?

Jonathan H. Chen, M.D., Ph.D.[1,2,3]

Received: January 2, 2024; Revised: February 9, 2024; Accepted: March 1, 2024; Published: April 12, 2024

Abstract

My experience trying to break this large language model artificial intelligence system inspired me to consider how such human-computer interactions may not only automate many mundane paperwork tasks but actually stimulate some of the most human activities needed in medicine. With the ability to practice high-stakes conversations in a low-stakes environment, I hope such computer systems will make us better in our next human-human interactions.

Use of AI in TB Education and Counselling

- *Accepted/Pending publication*
- Testing of the accuracy and effectiveness of AI chatbot configured to draw information from international and local TB guidelines and was **tasked to provide education response**
  - Tested on 39 FAQ
    - These were appraised by team of 91 global experts by modified Delphi consensus
- **Findings:**
  - Overall able to answer questions in all domains (epidemiology, presentation, prevention of TB, diagnosis and treatment) and cited source
  - Unable to distinguish LTBI from disease
  - Out of date on definition of MDR TB
  - **Helpful but not able to replace a healthcare provider for patient's unique circumstances.**

Challenges – Data Paucity Cycle

- Physician trust in AI
- Success in other areas relied on access to large and comprehensive and high-quality datasets.
- We consider the principal issue currently hindering replication of the previous achievements of AI-based medicine in TB, being a “data paucity cycle” - a profound lack of data, particularly for validation purposes,
  - leads to unsuccessful efforts to develop translatable tools
  - resulting in a lack of evidence to convince further investment
  - ultimately leading back to data paucity

Breathe Viewpoint 2024, McClean et al

PZA

New Understanding and…. Could One Size Fit All?

Lisa Armitige, MD, PhD

Co-Medical Director

Heartland National TB Center

ORIGINAL ARTICLE

Pyrazinamide Safety, Efficacy, and Dosing for Treating Drug-Susceptible Pulmonary Tuberculosis

A Phase 3, Randomized Controlled Clinical Trial

Ava Y. Xu[1,2], Gustavo E. Velásquez[3,4], Nan Zhang[1,3], Vincent K. Chang[1,3], Patrick P. J. Phillips[3,5], Payam Nahid[3,5], Susan E. Dorman[6], Ekaterina V. Kurbatova[7], William C. Whitworth[7], Erin Sizemore[7], Kia Bryant[7], Wendy Carr[7], Nicole E. Brown[7], Melissa L. Engle[8], Nguyen Viet Nhung[9,10], Pheona Nsubuga[11], Andreas Diacon[12], Kelly E. Dooley[13], Richard E. Chaisson[14], Susan Swindells[15], and Radojka M. Savic[1,3]; Tuberculosis Trials Consortium (TBTC) Study 31/AIDS Clinical Trials Group (ACTG) A5349 Study Team

- Known facts:
  - WHO and US guidelines suggest dosing PZA at 20-30 mg/kg daily (max 2000 mg)
  - Some PK/PD studies suggest higher doses might achieve increased efficacy
  - Increasing the PZA dose raises concerns about increasing toxicity

- Authors sought to determine PZA dosing strategies to optimize benefit/minimize risk

- Took advantage of TBTC Study 31 that compared standard 6 month RIPE (HRZE) regimen to HEPZ (substituting rifapentine for rifampin) and HMPZ (replacing rifapentine for rifampin and moxifloxacin for EMB)

Analysis: How and Whom?

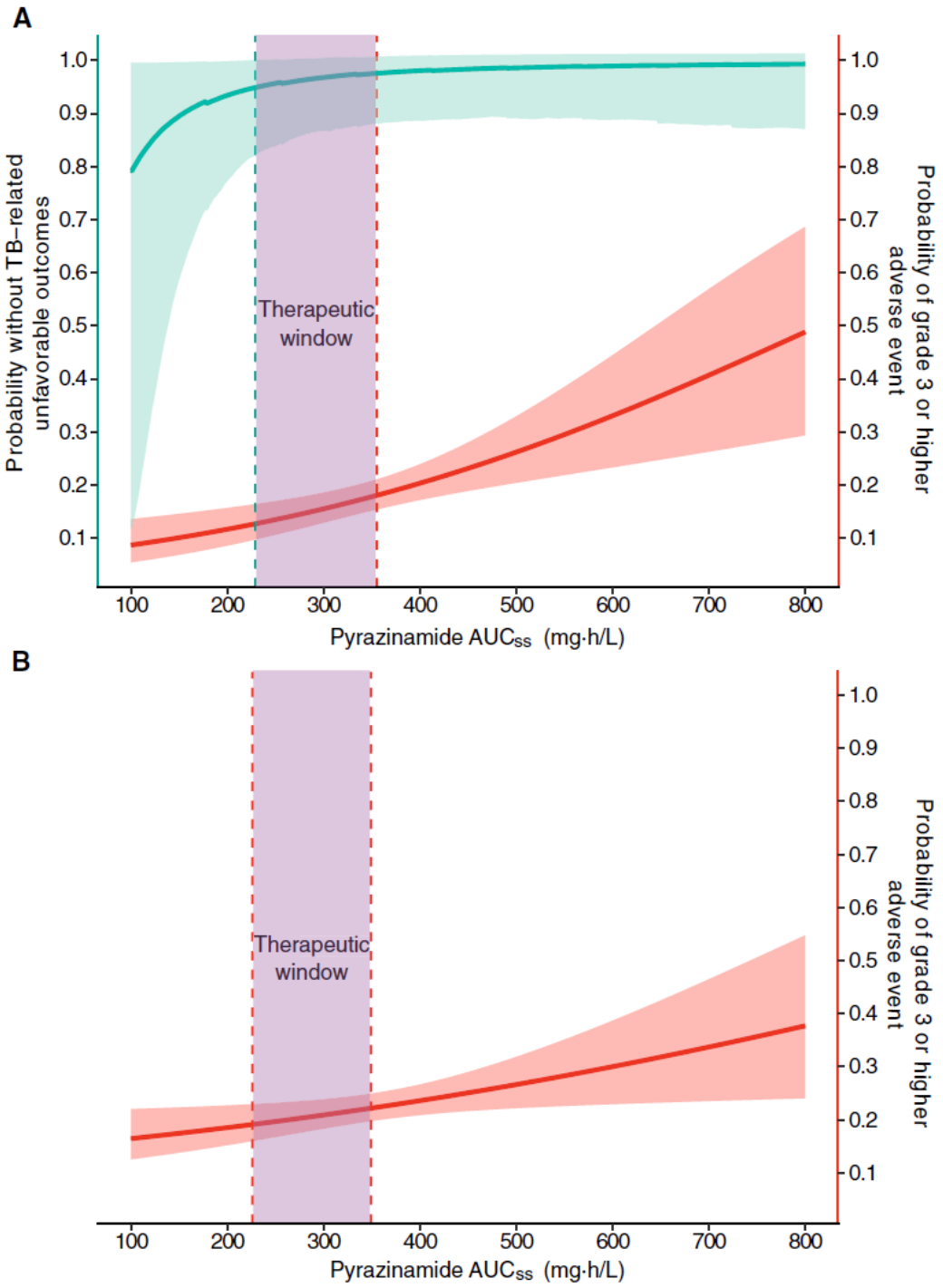
- ≥12 y/o (ages 13-81), weights 40-122 kg, 71% men
- Standard daily PZA dosing:
  - 40 to <55 kg 1000 mg
  - 55 to 75 kg 1500 mg
  - >75 kg 2000 mg
- Plasma specimens collected and analyzed by HPLC
- Measured peak concentration (Cmax) and total drug exposure over time (AUC)
- Measured primary efficacy as time to unfavorable outcome over 12 months
- Measured primary safety as any grade 3 or higher adverse treatment while on treatment

Findings

- Overall, 39 of 2255 participants (2%) experienced hepatotoxicity

- Covariate (age, race, sex) effect on PZA PK profile
  - Higher doses (1500 mg daily [80%] and 2000 mg daily [70%]) had lower bioavailability compared to 1000 mg daily
  - Women had 16.3% higher bioavailability
  - Individuals identifying as Asian absorbed PZA faster than those identifying as Black
  - PZA was absorbed 51.9% faster on an empty stomach (though exposure was not affected)

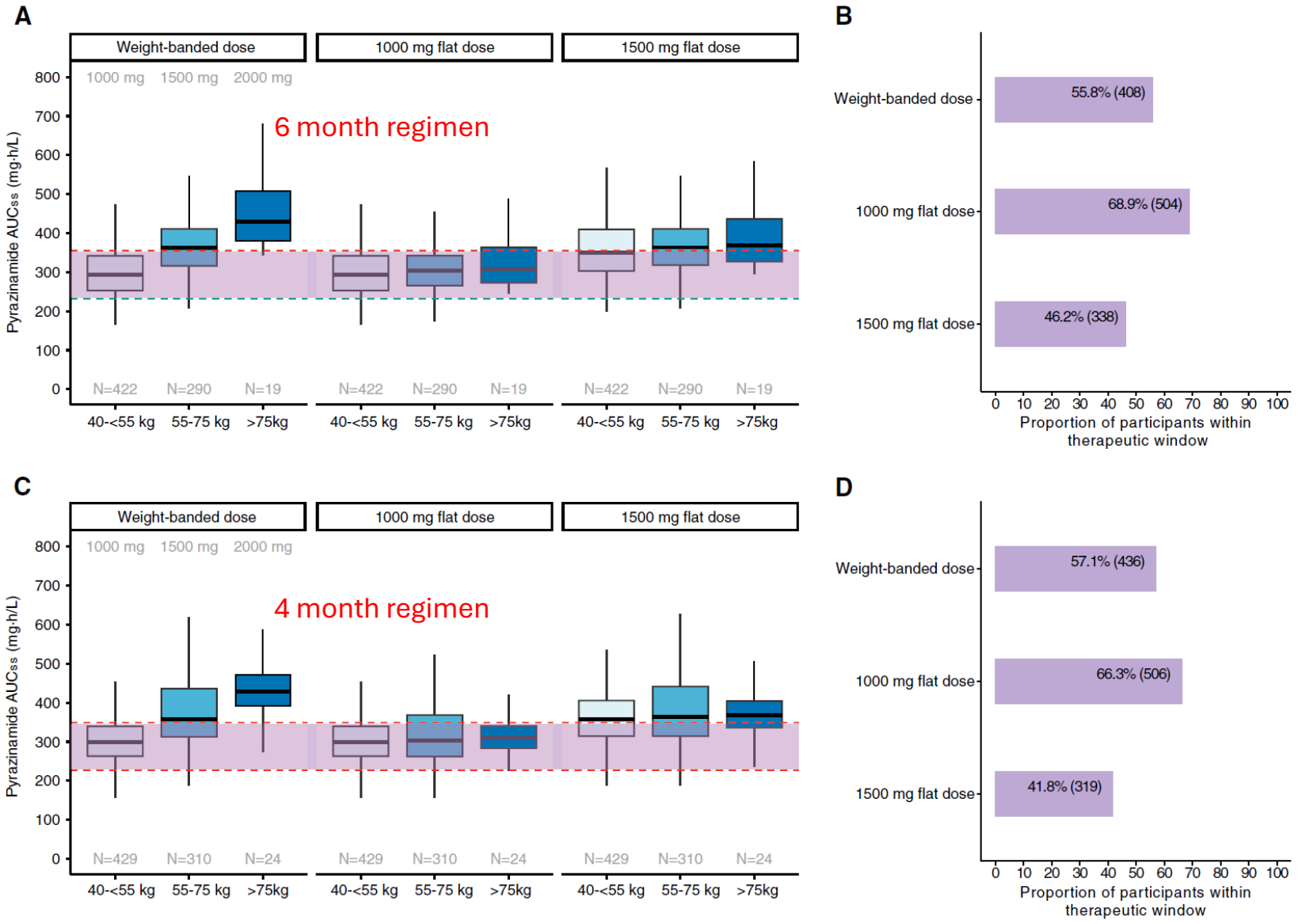
- PZA Efficacy and Safety
  - Decreasing PZA lead to lower Ct by Xpert
  - In advanced age, PZA was associated with unfavorable outcomes with 6 month regimen while in the 4 month regimen, rifapentine exposure was the most important influence on unfavorable outcomes
  - As PZA AUC increased, risk of grade 3 or higher adverse events increased



The authors estimated the therapeutic window based on the AUC needed to achieve:

- 95% durable cure at 12 months and
- <18% probability of grade 3 or higher adverse events

PZA Weight-Banded Dosing vs. Flat Dosing



Questions to Consider

- Bioavailability decreases as the dose increases.
  - Does clearance increase with dose increase?
  - Does absorption decrease after a certain dose?
- Since PZA is always administered with other drugs that cause hepatotoxicity, will we ever understand PZA's role in hepatotoxicity?
- What role do PZA metabolites play in these findings?
- Are we over dosing our patients? Does one size actually fit all……?

Class A Drug Resistance

Barbara J. Seaworth, MD

Co-Medical Director

Heartland National TB Center

WHO Classification: Drug Resistant TB

January 2021

Group A Drugs
Levofloxacin/Moxifloxacin
Bedaquiline
Linezolid

- **Rifampin Resistant (RR)/MDR** (INH and rifampin resistant)
  - Grouped together
- **Pre-XDR-TB:** TB caused by M. tuberculosis strains that fulfill the definition of MDR/RR-TB and are also resistant to **any fluoroquinolone**
- **XDR-TB: TB** caused by M. tuberculosis strains that fulfill the definition of MDR/RR-TB and that are also resistant to any **fluoroquinolone and at least one additional Group A drug.**

Fluoroquinolone Resistance

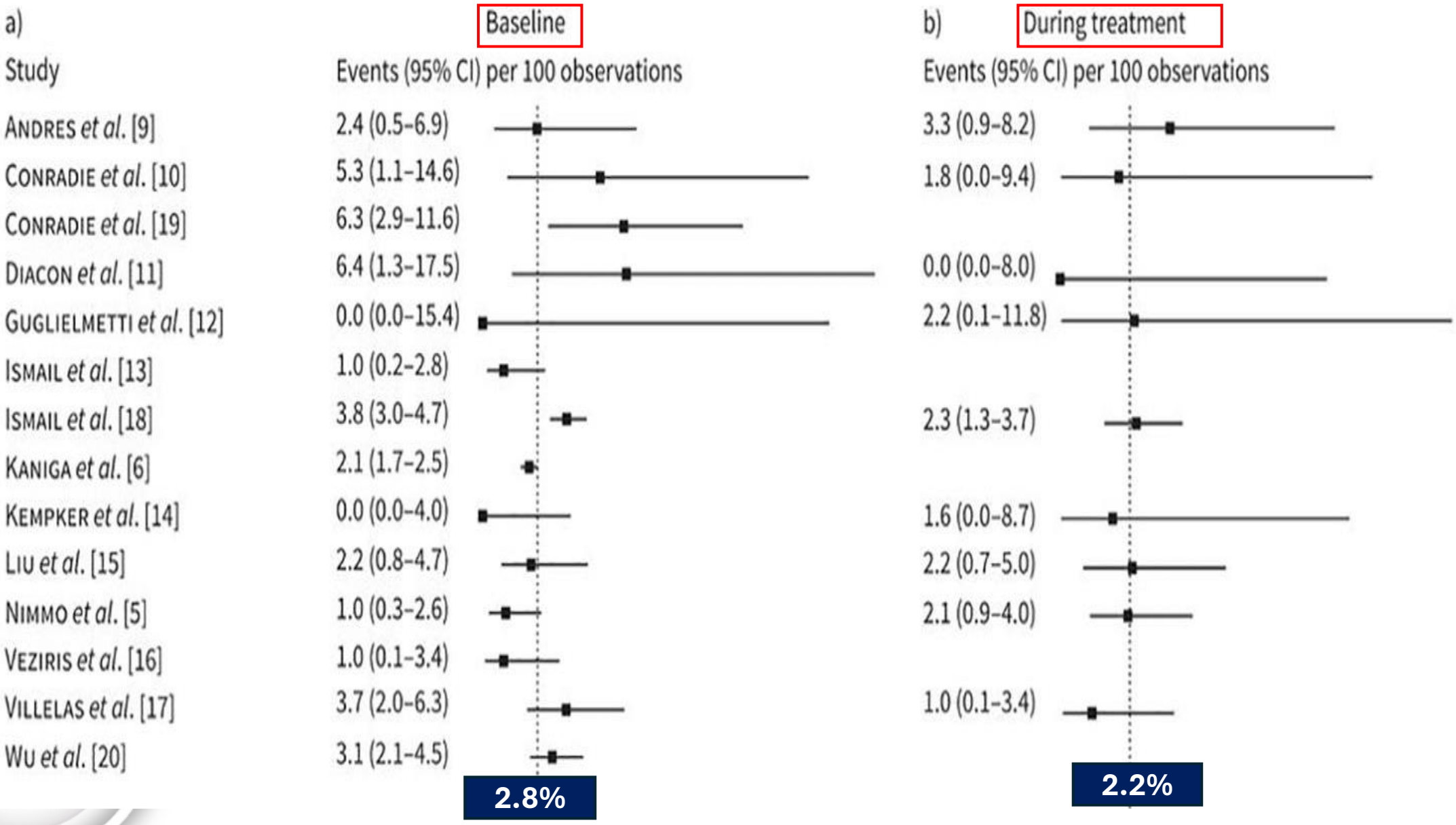
- Associated with poorer outcomes
    - *WHO Global tuberculosis report 2024*
- Globally in 2023, 19% estimated proportion of MDR/RR TB cases with pre-XDR TB (resistance to any FQN tested)
- Some areas with very high rates
    - Mumbai ~36% of MDR/RR TB has resistance to fluoroquinolones
        - *Dreyer et al, Genome Medicine 2022*
    - England – 1.4% overall, 23.9% MDR TB
        - survey of 16,000 unselected isolates *Ferran et al, CID March 2025*
    - United States – 16 of 88 (18%) MDR TB cases were pre-XDR (FQN or Inject)
        - *Reported TB in U.S. 2022 CDC*

Bedaquiline Resistance

- First described in 2015
- Detection challenging; access to DST limited, genotype unpredictable
- Association with poor Treatment Outcomes
- South African Study (2015-2019); baseline BDQ R = 3.8%
  - *Ismail et al, Lancet Infect Dis 2022*
  - Resistance to CFZ significantly associated with BDQ in South Africa
- German WHO Supranational Ref Cent (6/2018-3/2019), BDQ R - 5.6%
  - 4 pt took BDQ or CFZ prior to BDQ resistance (200 isolates from 124 patients)
  - Patients treated in hospital; resistance likely due to lack of protection of BDQ by other drugs
    Andres et al, Am J Resp and CC Med June 2020
- Several U.S. cases noted

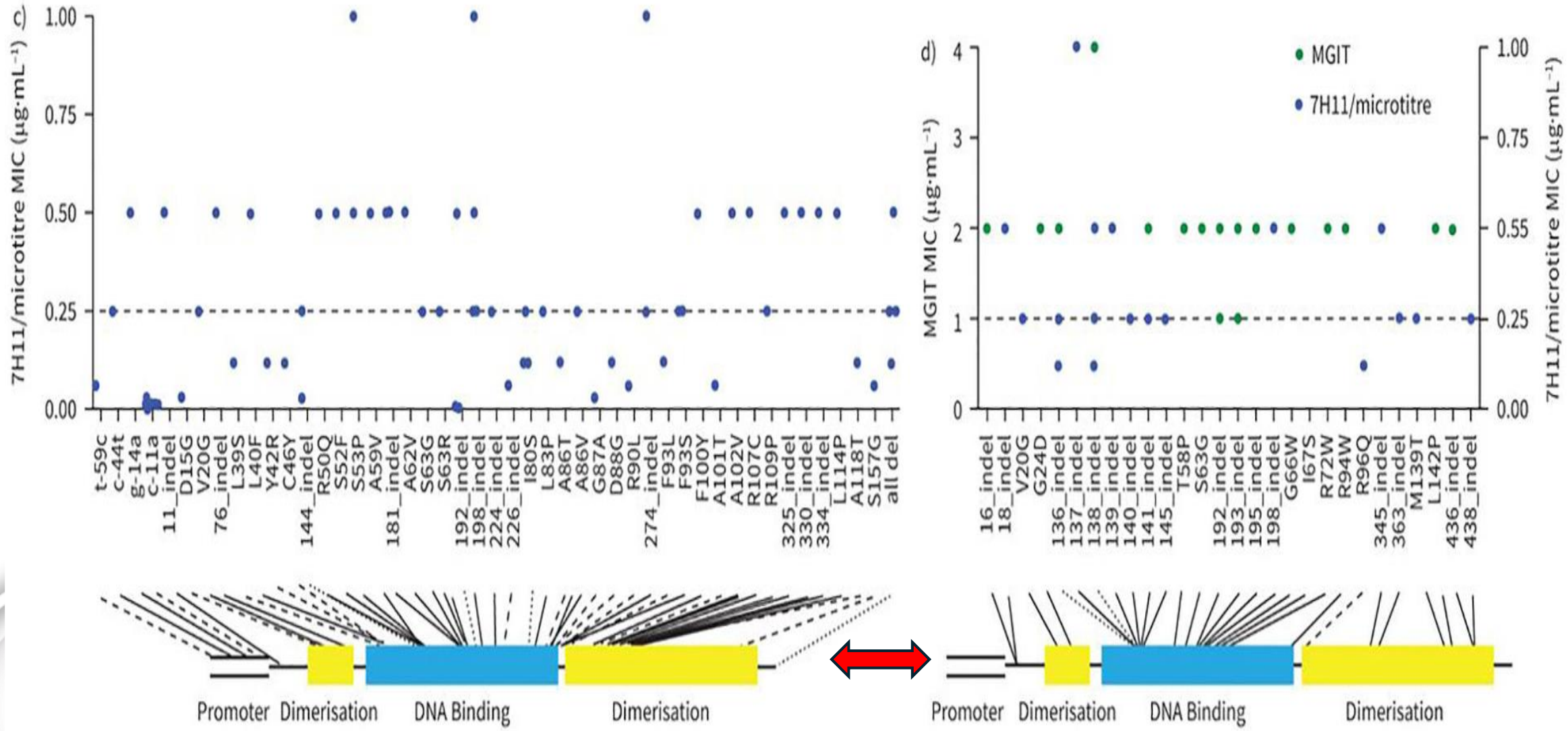
Pooled Prevalence of BDQ Resistant TB

Systematic Review Baseline and Acquired During Treatment *Eur Resp J, April 2023*



Baseline and Treatment-emergent resistance associated variants (RAVs) and associated minimum inhibitory concentrations (MICs)

Eur Resp J, April 2023



Solid black line = intermediate or resistant MIC, dashed = susceptible MIC, dotted RAVs with either susceptible, intermediate or resistant MICs

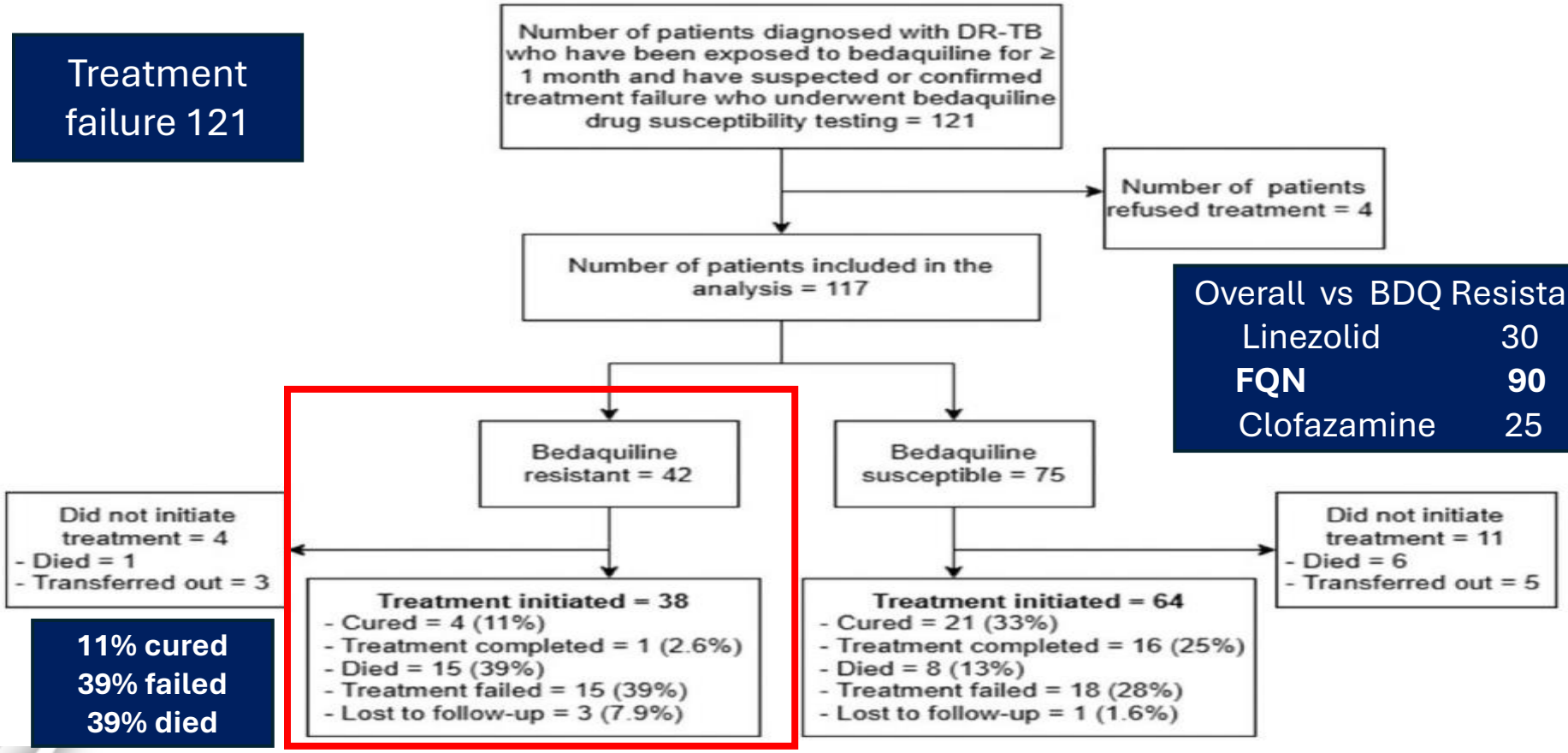
Clinical Infectious Diseases
MAJOR ARTICLE

Bedaquiline Resistance and Treatment Outcomes Among Patients With Tuberculosis Previously Exposed to Bedaquiline in India: A Multicentric Retrospective Cohort Study

July 2024

Rupak Singla,[1] Samsuddin Khan,[2,a] Arunima Silsarma,[2,a] Vijay Chavan,[2,a] Raman Mahajan,[2,a] Homa Mansoor,[2] Ravindra Kumar Devan,[1] Neeta Singla,[1] Manpreet Bhalla,[1] Gavish Kumar,[1] Pramila Singh,[2] Aparna Iyer,[2] Mabel Morales,[2,b] Satish Chandra Devkota,[2] Alpa Dalal,[3] Hannah Spencer,[4,a] and Petros Isaakidis[4,5,a]

Treatment failure 121



Overall vs BDQ Resistance %		
Linezolid	30	37
FQN	**90**	**93**
Clofazamine	25	44

11% cured
39% failed
39% died

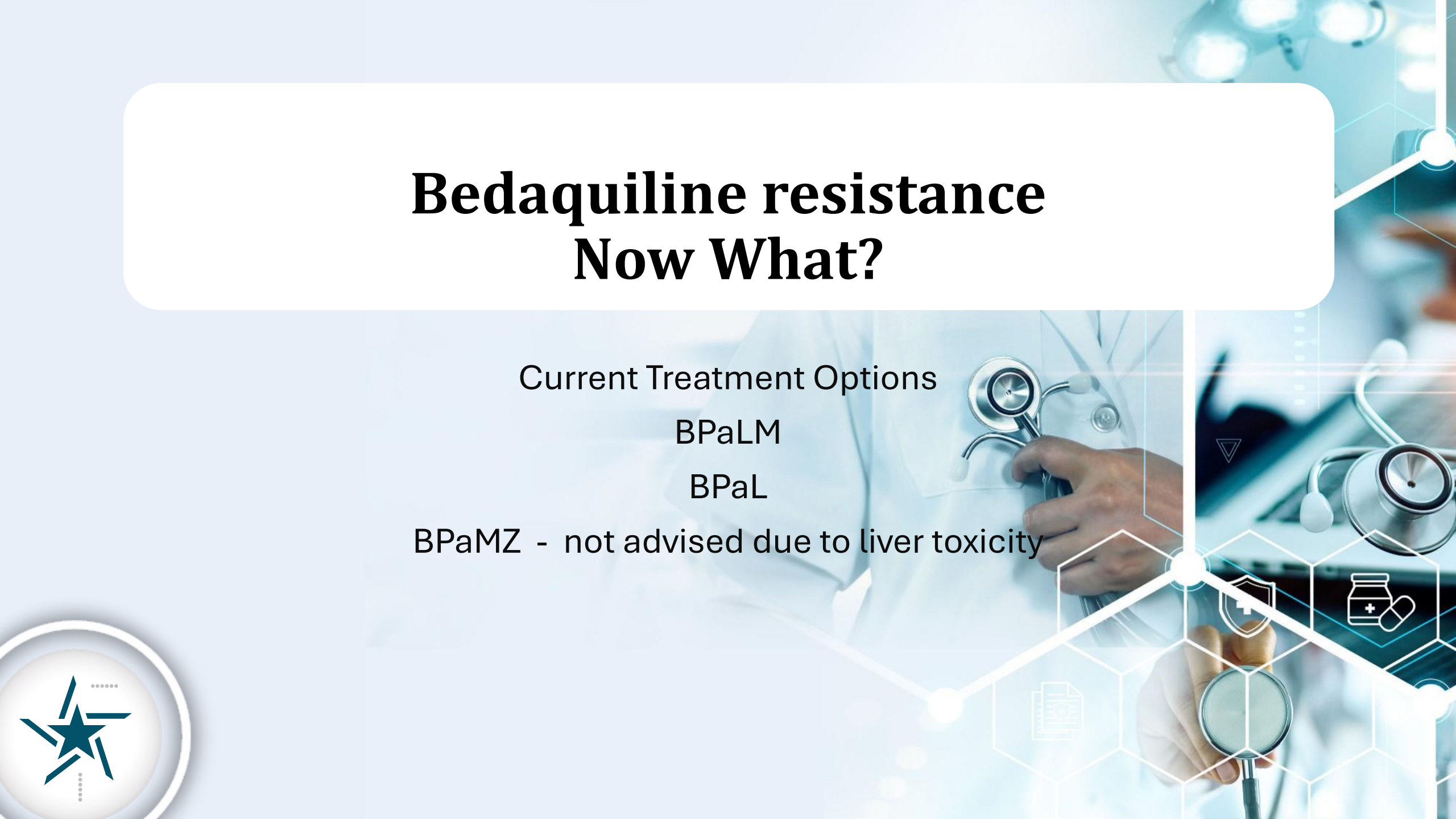
Bedaquiline resistance
Now What?

Current Treatment Options

BPaLM

BPaL

BPaMZ - not advised due to liver toxicity



end TB (9 month regimens)

WHO now recommends #1-3 and if BDQ resistance #4

Non-inferior to SOC

Superior

Higher failure & acquired drug resistance

Trial regimens	Bedaquiline	Delamanid	Clofazimine	Linezolid	Fluoroquinolone	Pyrazinamide
9BLMZ	B			L	M	Z
9BCLLfxZ	B		C	L	Lfx	Z
9BDLLfxZ	B	D		L	Lfx	Z
9DCLLfxZ		D	C	L	Lfx	Z
9DCMZ		D	C		M	Z
Control	Standard of care for the treatment of rifampicin-resistant and fluoroquinolone-susceptible tuberculosis. Composed according to latest World Health Organization guidelines, as they evolved during the trial. This group included mostly participants treated with the 18-month conventional regimen.					

Figure 1. Composition of endTB trial regimens

B denotes bedaquiline, L linezolid, M moxifloxacin, Z pyrazinamide, C clofazimine, Lfx levofloxacin, D delamanid

9mo D-C-Lzd-Lfx-Z may give an option other than older individualized regimen when isolate is resistant to or patient is intolerant to Bedaquiline –

MDR-END 9 D-Lfx-Lzd-Z No BDQ or Pretomanid (Korea)

MDR-END
NCT02619994

(MDR-TB; 214; PLHIV not included)

(a) 9DLzLxZ

(b) [20mo IA-containing regimen]

Non – inferior to SOC but longer regimen with IA Had a better outcome 75% versus 70.6%

Primary Efficacy Outcome:
The nine-month delamanid-based regimen demonstrated non-inferiority to a 20-month injectable-containing regimen– the standard of care in 2014 (mITT). The NI margin was -10%.

Unfavorable outcomes:		**Risk difference, experimental-control (95% confidence interval)**
(a)	25 (29.4%)	4.4 (-9.5 to ∞)
(b)	18 (25%)	NA

Primary Safety Outcome:
No statistically significant differences in safety were detected between arms.

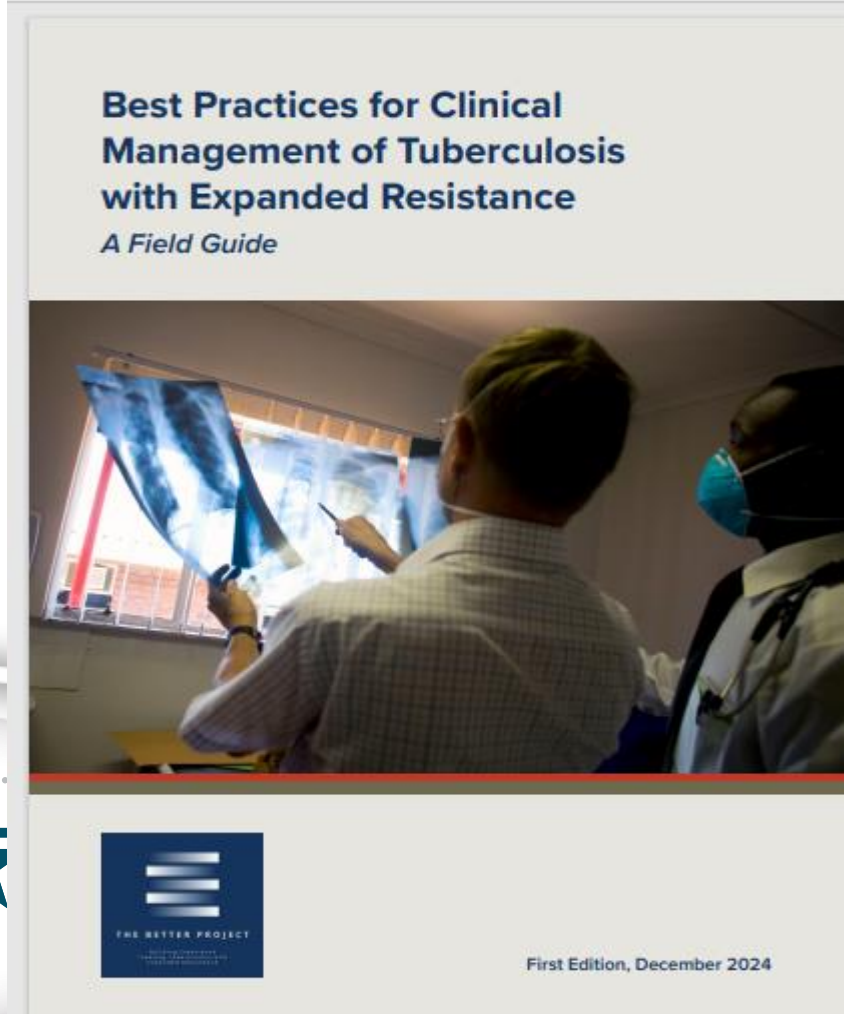
	Any grade 3 or 4 AEs	Any serious AEs	Deaths
(a)	29 (36.7%)	20 (25.3%)	5 (6%)
(b)	26 (29.2%)	19 (21.3%)	2 (2%)

Mok J, Lee M, Kim DK, et al. 9 months of delamanid, linezolid, levofloxacin, and pyrazinamide versus conventional therapy for treatment of fluoroquinolone-sensitive multidrug-resistant tuberculosis (MDR-END): a multicentre, randomised, open-label phase 2/3 non-inferiority trial in South Korea. Lancet. 2022 Oct 29;400(10362):1522–1530. doi: 10.1016/S0140-6736(22)01883-9.

The Better Project

Best Practices for Clinical Management of TB with Expanded Resistance

1st Edition December 2024



Back to Buidling Individualized Regimens

When designing an individualized regimen for a person with TB who has possible or known expanded resistance, consideration should be given to both the WHO groupings and the bactericidal/sterilizing activity. Regimens need to include a combination of drugs that are bactericidal and drugs that are sterilizing. We suggest the following steps below:

Step 1: Choose as many core drugs as you can

Core drugs are group A drugs that are both sterilizing and bactericidal and include Bdq, Lzd and the third-generation Flqs.

These drugs should be included if susceptibility is documented or uncertain. If low-level resistance has been demonstrated, the third-generation Flqs can be given at higher doses. High-dose Bdq could also be considered. Of note, for high-dose Bdq, there are no clinical studies that demonstrate the effectiveness of this approach. Rather, it is based on modeling data. If high-dose Bdq is given, it should be only done so when there are no other options and when there is close monitoring for toxicity.

Step 2: Choose as many oral agents as you can for their bactericidal activity, including a nitroimidazole (Pa or Dlm) and/or Cs. Depending on the resistance mutations detected, then either high-dose Inh could be given (if only an *inhA* mutation) or Eto (if only a *katG* mutation).

Step 3: Choose from the following oral agents for their sterilizing activity as you need to construct a 5-drug regimen:

Sterilizing: Pza (if susceptible), Cfz

Step 4: Choose as many injectable agents for their bactericidal activity as you need to construct a 5-drug regimen including Am and the carbapenems + clavulanic acid. It is essential that regimens have sufficient numbers of bactericidal agents, especially in the first weeks/months of treatment and thus many individualized regimens will need to have one of these injectable drugs. Of note, some experts would place step 4 above step 3 in the regimen design process to ensure there are adequate bactericidal drugs.

Step 5: Choose other drugs if more are needed to reach a total of at least 5 effective drugs in the regimen

Bactericidal: PAS, Emb (if susceptible), rifabutin (if there is susceptibility to rifabutin demonstrated, although in most settings, testing to this drug is not available nor is the drug).

Step 6: Consider pre-approval access/compassionate use drugs

Please see the section on pre-approval access for more details. Some possible agents that have already completed at least phase 2b include quabodepistat, ganfeborole, and telacebec.