Key Research in TB and NTM

2025.4.12

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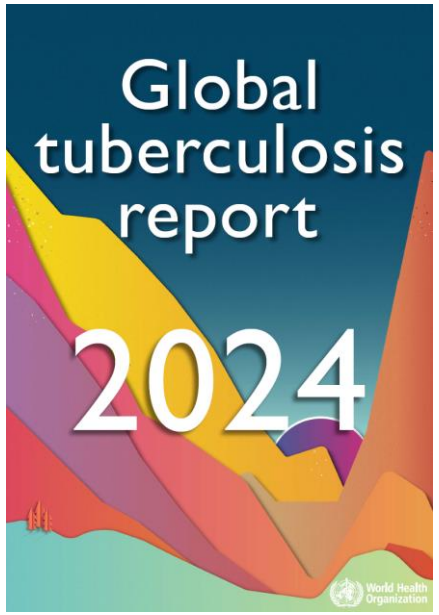
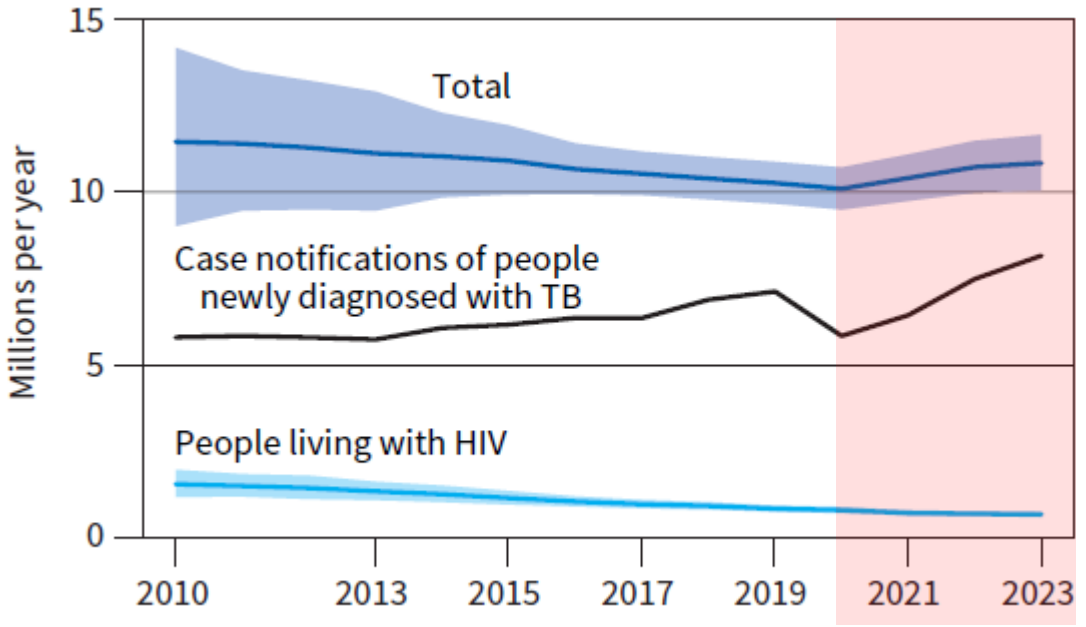
Contents

Global TB Report 2024 (WHO)



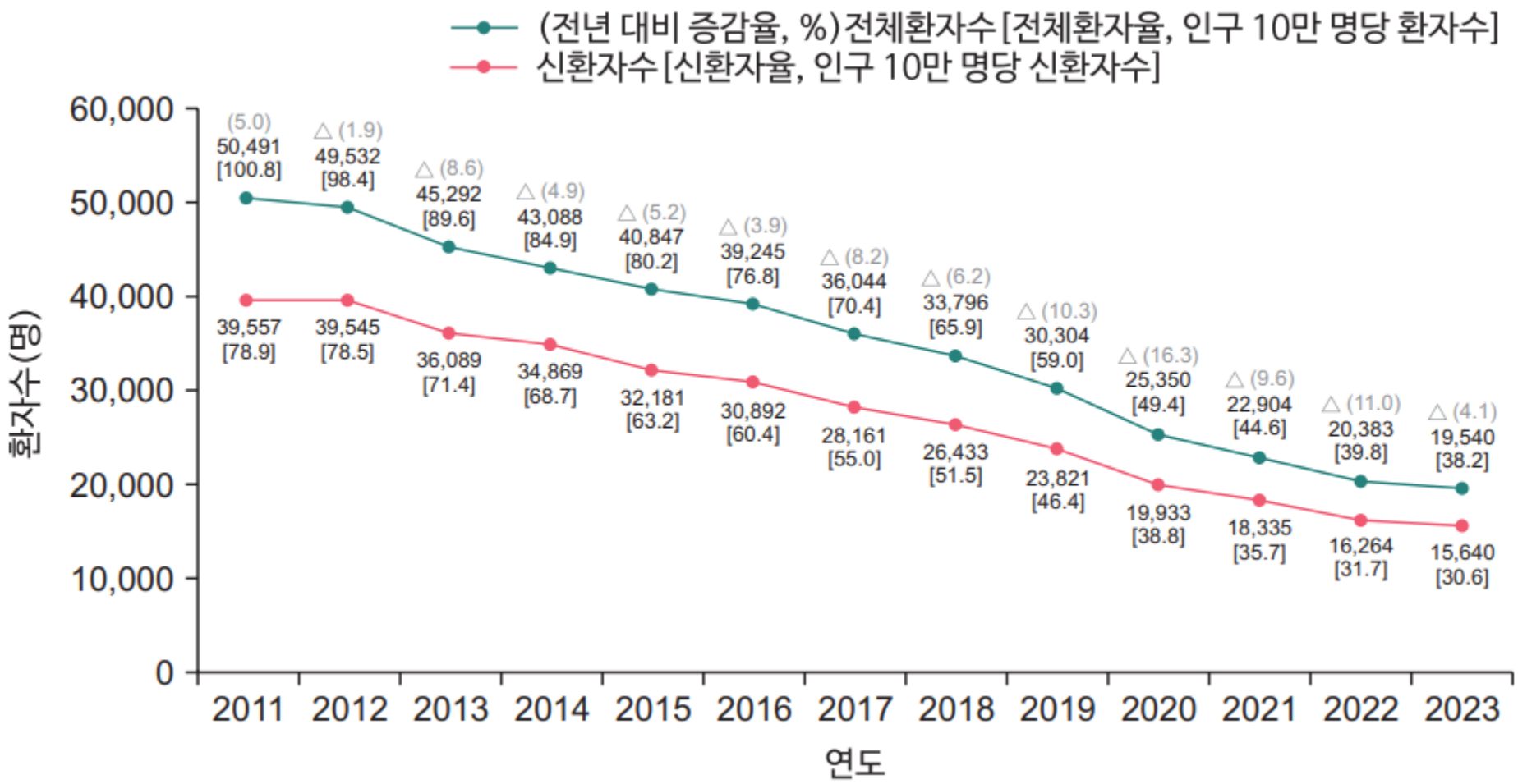
Global trends in the estimated number of incident TB cases (left) 2010–2023



(2023)
10.8 million
New: 8.2 million

(2022)
10.7 million
New: 7.5 million

연도별 국내 결핵 (신)환자수



Public Health Weekly Report 2024; 17(37): 1591-1608

Contents

1. Tuberculosis (TB)

- **Diagnosis**
- Treatment
- MDR/RR-TB
- Prevention of TB exposure

Targeted next-generation sequencing to diagnose drug-resistant tuberculosis: a systematic review and meta-analysis

Lancet Infect Dis 2024; 24: 1162–76

Published Online May 22, 2024

Tiana Carina Schwab, Lisa Perrig, Pauline Carlotta Göller, Freddy Fernando Guebely De la Hoz, Adrien Philippe Lahousse, Beatrice Minder, Gunar Günther, Orestis Efthimiou, Shaheed Vally Omar, Matthias Egger, Lukas Fenner

Background

- Limitations of existing methods for diagnosing drug-resistant TB:
  - ✓ Phenotypic DST: Time-consuming (weeks), reliability issues for some drugs
  - ✓ Commercial NAATs: Limited to detect only specific drugs and mutations
  - ✓ Whole-genome sequencing (WGS): Comprehensive but costly and requires culture
- Targeted next-generation sequencing (NGS) has emerged as an intermediate approach between NAATs and WGS

Targeted next-generation sequencing to diagnose drug-resistant tuberculosis: a systematic review and meta-analysis

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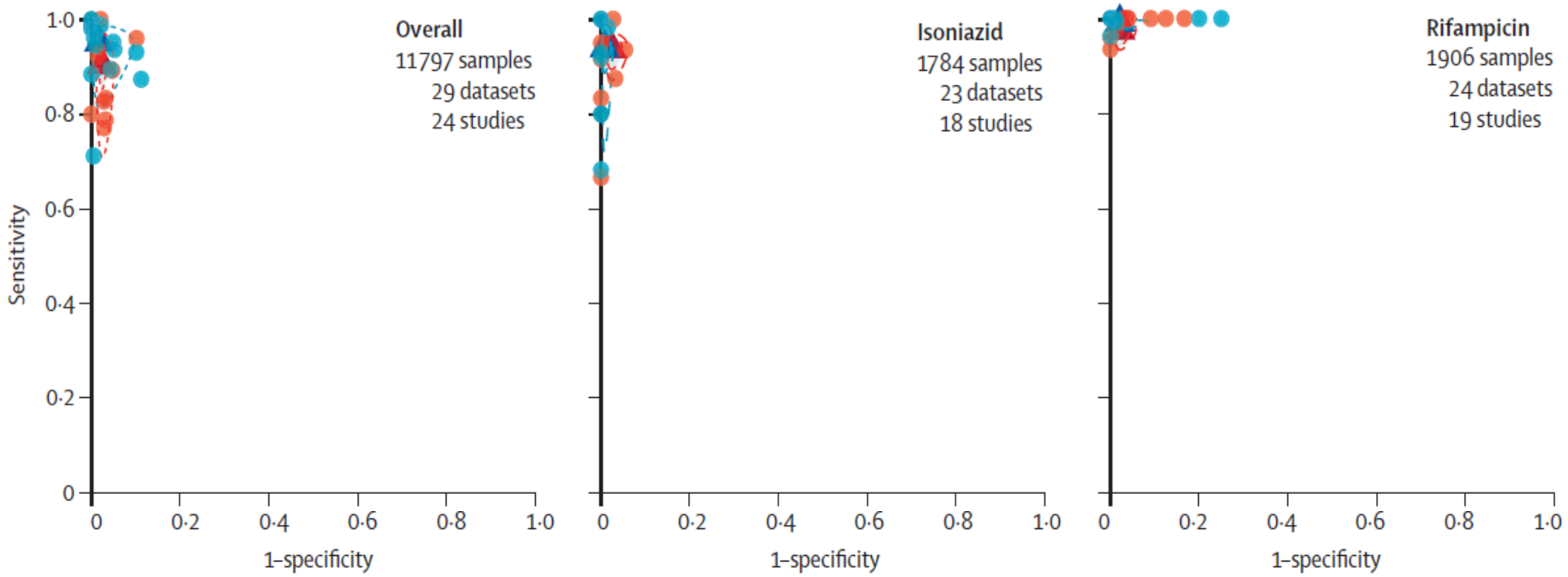
Tiana Carina Schwab, Lisa Perrig, Pauline Carlotta Göller, Freddy Fernando Guebely De la Hoz, Adrien Philippe Lahousse, Beatrice Minder, Gunar Günther, Orestis Efthimiou, Shaheed Vally Omar, Matthias Egger, Lukas Fenner

Question of this study

- How accurate is targeted NGS for the diagnosis of drug-resistant TB?
- Does the performance of targeted NGS differ by sample type?
  (culture isolates vs. direct clinical samples)
- Where is targeted NGS technology being used, and what are the barriers to its clinical implementation?

Key findings

- Diagnostic accuracy:
  - ✓ Overall - **Sensitivity: 94.1%, Specificity: 98.1%**
  - ✓ Rifampicin - **Sensitivity: 99.1%, Specificity: 97.6%**
  - ✓ Isoniazid - **Sensitivity: 95.6%, Specificity: 98.9%**



Lancet Infect Dis 2024; 24: 1162–76

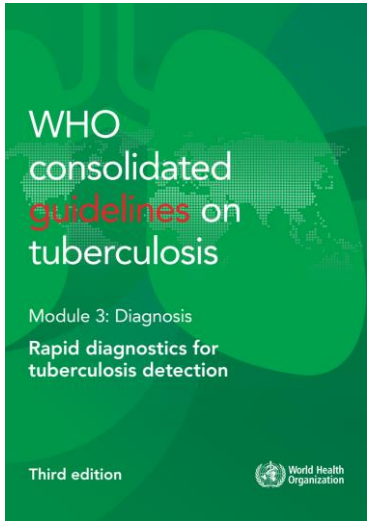
Key findings

- Global utilization:
  - ✓ Samples collected from 53 countries (including 27 WHO high-burden countries)
  - ✓ Sequencing mainly performed in USA (16%), Western Europe (11%), India (11%), China (10%)
  - ✓ Limited local sequencing in resource-constrained regions, especially in Africa

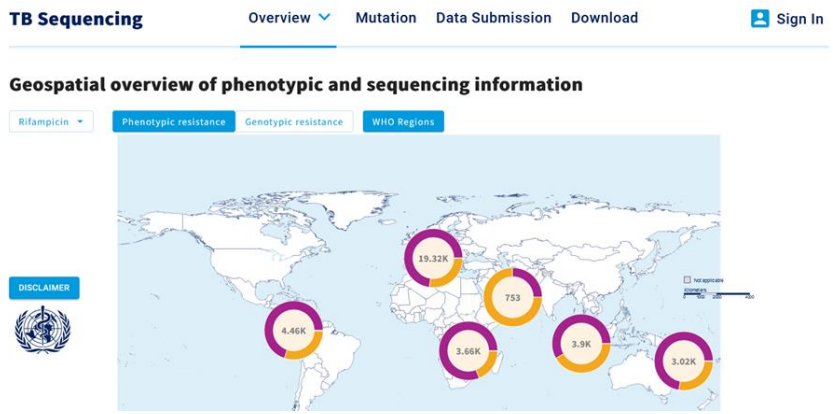
Lancet Infect Dis 2024; 24: 1162–76

Clinical Implications

- Targeted NGS demonstrates **high accuracy** for diagnosing drug-resistant TB
- Effective performance on direct clinical samples enables **rapid diagnosis** (1–10 days)
- Limited data for newer drugs (bedaquiline, linezolid, etc.) indicates the need for additional research
- **WHO** conditionally recommended targeted NGS as a complementary tool for genotypic DST of drug-resistant TB in March 2024



20 March 2024



WHO TB sequencing portal

Lancet Infect Dis 2024; 24: 1162–76

Contents

1. Tuberculosis (TB)

- Diagnosis
- **Treatment**
- MDR/RR-TB
- Prevention of TB exposure

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

Background

- Pyrazinamide (PZA) essential for non-replicating TB bacilli
- Current guidelines: weight-based dosing (20–30 mg/kg, max, 2g/day)
- High PK variability challenges optimal dosing

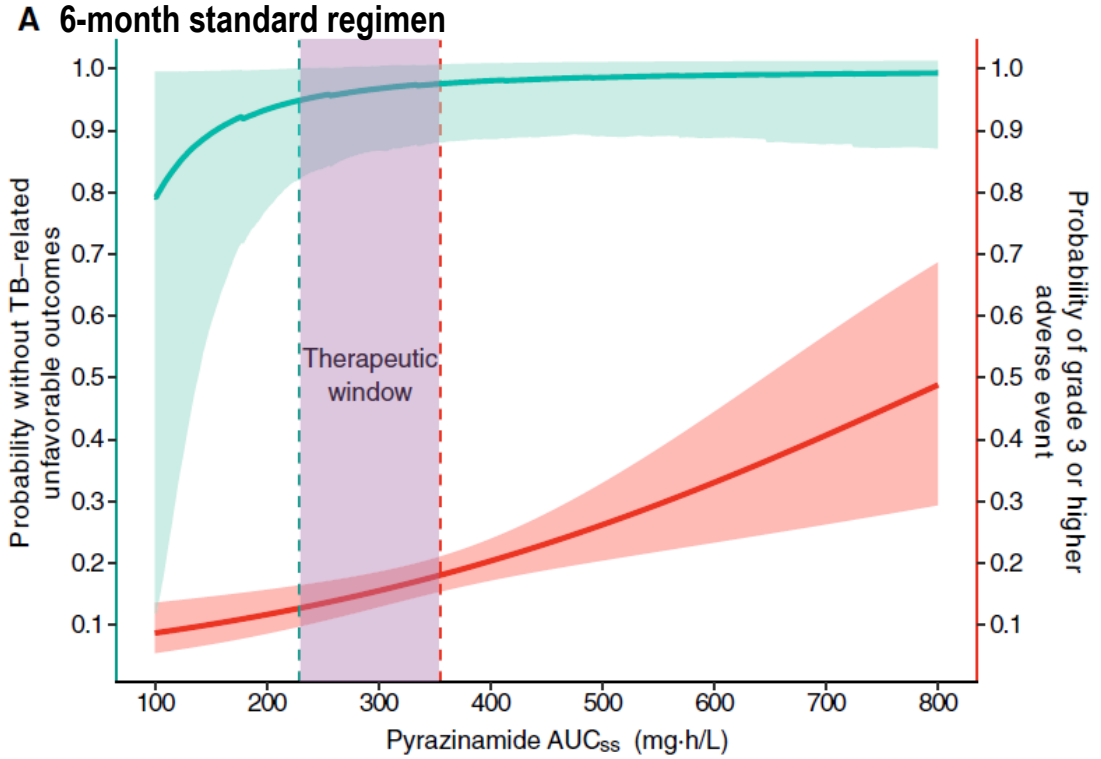
Question of this study

- Can flat dosing of PZA optimize efficacy-safety balance in drug-susceptible TB(DSTB)?

Am J Respir Crit Care Med. 2024 Dec 1;210(11):1358-1369

Key findings

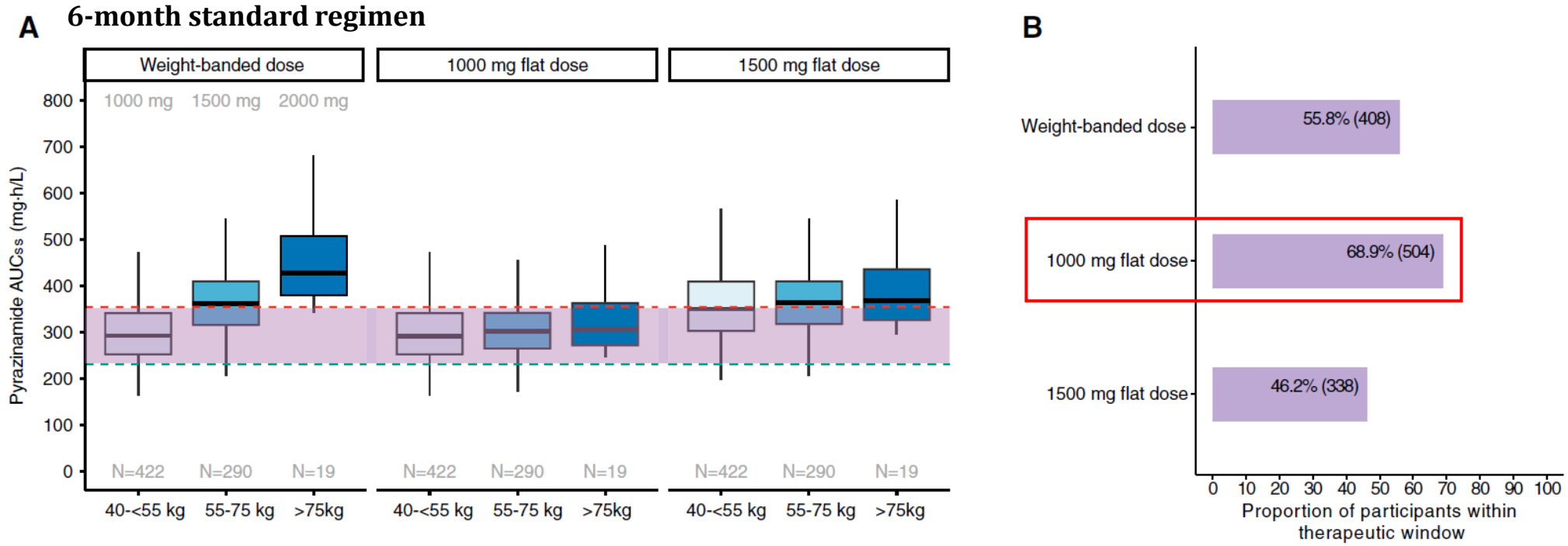
- **PZA** showed **7-fold** exposure variability (151–1,053 mg·h/L)
- Therapeutic windows:
  - ✓ 6-month standard regimen (A): 231–355 mg·h/L
  - ✓ 4-month rifapentine-moxifloxacin regimen (B): 226–349 mg·h/L



Am J Respir Crit Care Med. 2024 Dec 1;210(11):1358-1369

Key findings

- Body weight **was not** clinically relevant predictor of drug clearance
- **Flat dosing (1,000 mg/day)** would improve dosing precision, ensuring **13.1%** more participants (n=96, control) within the therapeutic window compared to weight-banded dosing.



Am J Respir Crit Care Med. 2024 Dec 1;210(11):1358-1369

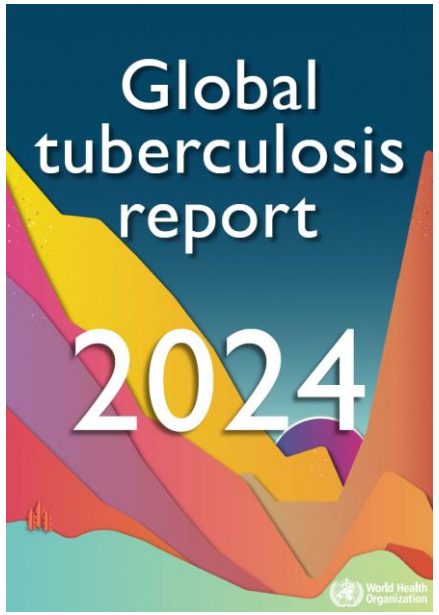
Clinical Implications

- **Flat dosing of pyrazinamide at 1,000 mg/day** provides a **better balance of efficacy and safety** than weight-banded dosing for drug-susceptible tuberculosis**.**
  - ✓ Placed **13.1% more patients within therapeutic window** *vs.* weight-based dosing
  - ✓ Reduced overdosing risk in higher weight bands
  - ✓ Simplified administration for patients and providers
  - ✓ Facilitates fixed-dose combinations development
- Since **body weight was not a significant predictor of drug clearance**, flat dosing allowed more patients to achieve optimal drug exposure while reducing toxicity risks
- **Recommendation: Consider flat dosing (1,000 mg/day) for DSTB**

Am J Respir Crit Care Med. 2024 Dec 1;210(11):1358-1369

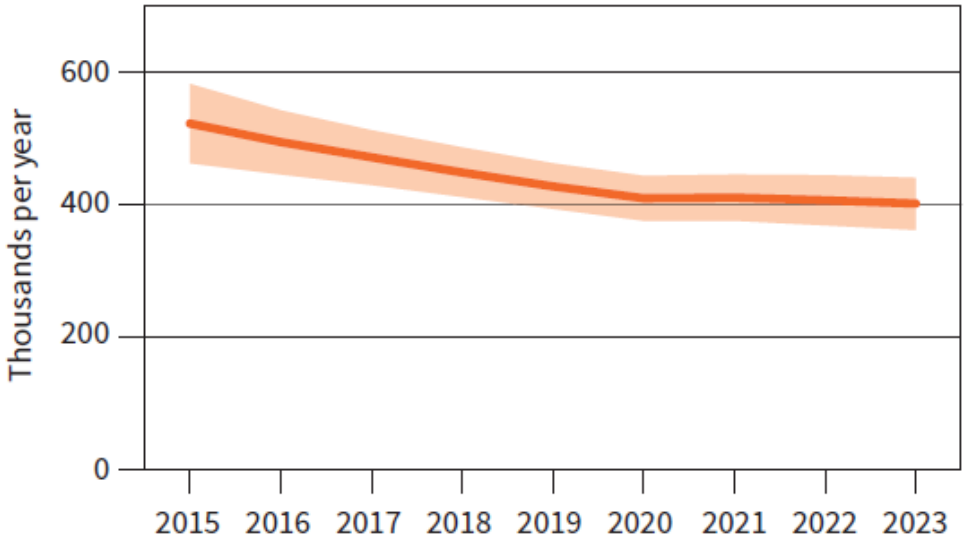
Contents

Global TB Report 2024 (WHO)



Global trend in the estimated number of people who developed MDR/RR-TB (incident cases), 2015–2023

The shaded area represents the 95% uncertainty interval.



(2023)
400,000
New case: 3.2%
Previously treated: 16%

SimpliciTB Trial: BPaMZ Regimen for TB Treatment

Bedaquiline-pretomanid-moxifloxacin-pyrazinamide for drug-sensitive and drug-resistant pulmonary tuberculosis treatment: a phase 2c, open-label, multicentre, partially randomised controlled trial

Muge Cevik, Lindsay C Thompson, Caryn Upton, Valéria Cavalcanti Rolla, Mookho Malahleha, Blandina Mmbaga, Nosipho Ngubane, Zamzurina Abu Bakar, Mohammed Rassool, Ebrahim Variava, Rodney Dawson, Suzanne Staples, Umesh Lalloo, Cheryl Louw, Francesca Conradie, Marika Eristavi, Anastasia Samoilova, Sergey N Skornyakov, Niyanda Elias Ntinginya, Frederick Haraka, George Praygod, Harriett Mayanja-Kizza, Janice Caoili, Vincent Balanag, Margareth Pretti Dalcolmo, Timothy McHugh, Robert Hunt, Priya Solanki, Anna Bateson, Angela M Crook, Stella Fabiane, Juliano Timm, Eugene Sun, Melvin Spigelman, Derek J Sloan, Stephen H Gillespie, on behalf of SimpliciTB Consortium

Lancet Infect Dis 2024; 24: 1003–14

Published Online May 17, 2024

Background

- **BPaMZ** combination (bedaquiline, pretomanid, moxifloxacin, pyrazinamide) showed promising results in preclinical & phase 2 studies, with potential to shorten TB treatment for both DS-TB and DR-TB.

Question of this study

- Can 4-month BPaMZ reduce treatment time while maintaining efficacy compared to 6-month HRZE for DS-TB?
- Is 6-month BPaMZ effective for DR-TB?

Lancet Infect Dis. 2024 Sep;24(9):1003-1014.

SimpliciTB Trial: BPaMZ Regimen for TB Treatment

Key findings

- SimpliciTB, Phase 2c, open-label clinical trial at 26 sites in 8 countries, ≥18 years with sputum smear-positive pulmonary TB.
- DS-TB Group: 303 randomly assigned (BPaMZ 4M: 150; HRZE 6M: 153)
  DR-TB Group: 152 received BPaMZ 6M
- **Primary endpoint**: Time to culture-negative status by 8 weeks

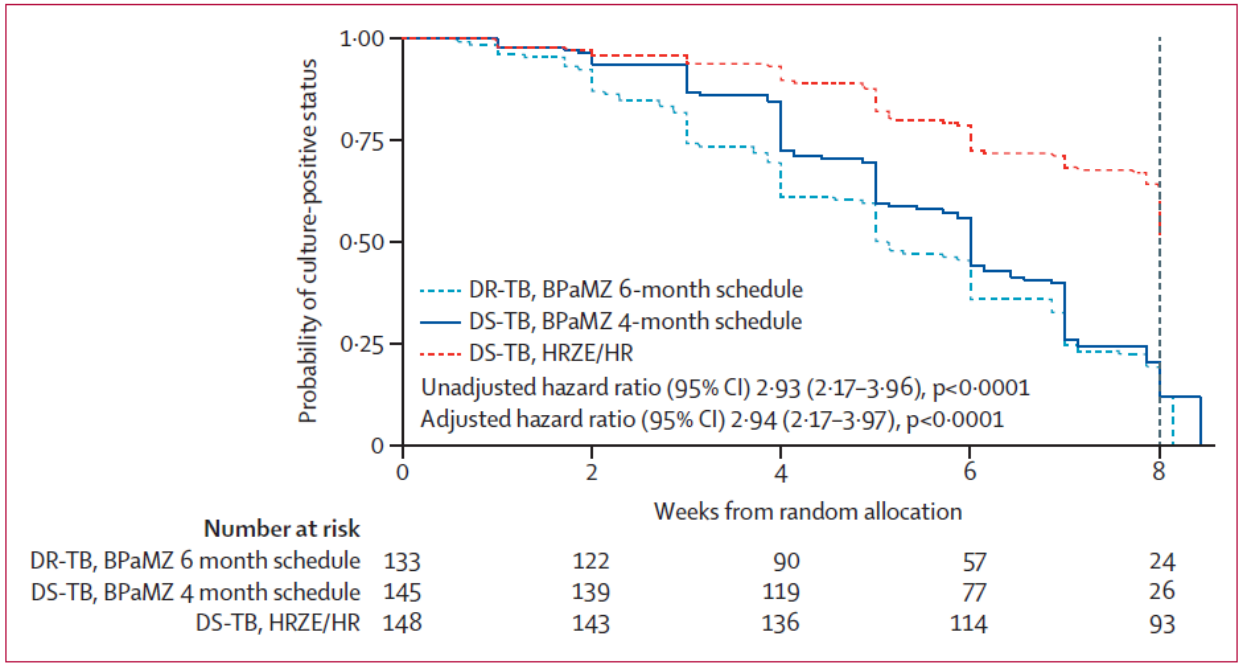


Figure 2: **Primary efficacy analysis in the mITT population—time to culture-negative status by 8 weeks**

Lancet Infect Dis. 2024 Sep;24(9):1003-1014.

Key findings (Safety)

- **Hepatotoxicity** led to treatment discontinuation:
  - ✓ Any liver-related AEs:

    DS-TB: HRZE **25%,** 4-month BPaMZ **30%**

    DR-TB: 6-month BPaMZ **22%**
  - ✓ **Serious liver-related AEs:**

    DS-TB: HRZE **1%**, 4-month BPaMZ **7%**

    DR-TB: 6-month BPaMZ **5%**

	DS-TB		DR-TB 6 months of BPaMZ (N=149)
	2 months of HRZE plus 4 months of HR (N=153)	4 months of BPaMZ (N=150)	
TEAE of grade 3 or above	61 (40%)	68 (45%)	47 (32%)
Any study drug related TEAE	99 (65%)	119 (79%)	123 (83%)
Any serious TEAE	7 (5%)	17 (11%)	16 (11%)
Any TEAE leading to death	1 (1%)	3 (2%)	2 (1%)
Any liver-related TEAE	38 (25%)	45 (30%)	33 (22%)
Any serious liver-related TEAE	1 (1%)	11 (7%)	8 (5%)
ALT, AST, or both at 3 × ULN or over	17 (11%)	24 (16%)	21 (14%)
ALT, AST, or both 3–8 × ULN	14 (9%)	12 (8%)	12 (8%)
ALT, AST, or both over 8 × ULN	3 (2%)	12 (8%)	9 (6%)
Any TEAE leading to study drug discontinuation	3 (2%)	17 (11%)	16 (11%)
Any TEAE leading to study discontinuation	0	6 (4%)	2 (1%)

Table 2: **Safety and premature discontinuation of assigned regimen (safety population)**

Lancet Infect Dis. 2024 Sep;24(9):1003-1014.

Clinical Implications

- **BPaMZ** regimen for **DS-TB** and **DR-TB** showed potential of treatment-shortening
- BPaMZ achieved sputum culture conversion for DS-TB,
  but **failed to meet the key secondary efficacy endpoint** due to treatment withdrawals from adverse events, particularly **hepatotoxicity**
- Future research needed: Modified regimens with reduced hepatotoxicity while maintaining efficacy

Lancet Infect Dis. 2024 Sep;24(9):1003-1014.

endTB Trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral Regimens for Rifampin-Resistant, Fluoroquinolone-Susceptible Tuberculosis

L. Guglielmetti, U. Khan, G.E. Velásquez, M. Gouillou, A. Abubakirov, E. Baudin, E. Berikova, C. Berry, M. Bonnet, M. Cellamare, V. Chavan, V. Cox, Z. Dakenova, B.C. de Jong, G. Ferlazzo, A. Karabayev, O. Kirakosyan, N. Kiria, M. Kunda, N. Lachenal, L. Lecca, H. McIlleron, I. Motta, S.M. Toscano, H. Mushtaque, P. Nahid, L. Oyewusi, S. Panda, S. Patil, P.P.J. Phillips, J. Ruiz, N. Salahuddin, E.S. Garavito, K.J. Seung, E. Ticona, L. Trippa, D.E.V. Vasquez, S. Wasserman, M.L. Rich, F. Varaine, and C.D. Mitnick, for the endTB Clinical Trial Team*

Background

- MDR-TB treatment historically challenging:
  18–24 month regimens, injectable drugs, poor outcomes
- Previous trials (STREAM, TB-PRACTECAL) showed promise for all-oral regimens,
  but optimal drug combinations remain unclear.

Question of this study

- Can **9-month all-oral regimens** containing **new drugs (bedaquiline, delamanid)** and **repurposed drugs (clofazimine, linezolid)** effectively treat fluoroquinolone-susceptible rifampin-resistant TB(RR-TB)?

N Engl J Med. 2025 Jan 30;392(5):468-482.

Key findings

- endTBtrial, Phase 3, open-label clinical trial at 12 sites in 7 countries
  ≥15 years with fluoroquinolone-susceptible, RR-TB
- Evaluating five 9-month, all-oral regimens:
  BLMZ [118], **B**CLLfxZ [115], **BD**LLfxZ [122], **D**CLLfxZ [118], **D**CMZ [107] vs. Standard (18–24mo) [119]
- Primary endpoint: Favorable outcome at week 73

N Engl J Med. 2025 Jan 30;392(5):468-482.

Key findings

Primary end point: favorable outcome at **week 73**, defined by 2 negative sputum culture results or favorable bacteriologic, clinical, and radiologic evolution (noninferiority margin: −12 %)

Table 2. Primary Efficacy End Points at Week 73 (Modified Intention-to-Treat Population).*

Outcome	BLMZ (N=118)	BCLLfxZ (N=115)	BDLLfxZ (N=122)	DCLLfxZ (N=118)	DCMZ (N=107)	Standard Therapy (N=119)	Total (N=699)
Favorable†							
Participants with favorable outcome — no. (%)	105 (89.0)	104 (90.4)	104 (85.2)	93 (78.8)	89 (83.2)	96 (80.7)	591 (84.5)
Difference from standard therapy (95% CI) — percentage points	8.3 (−0.8 to 17.4)	9.8 (0.9 to 18.7)	4.6 (−4.9 to 14.1)	−1.9 (−12.1 to 8.4)	2.5 (−7.5 to 12.5)	—	—
Negative culture results, wk 65 and wk 73 — no. (%)	102 (86.4)	100 (87.0)	102 (83.6)	90 (76.3)	87 (81.3)	91 (76.5)	572 (81.8)
Favorable bacteriologic, clinical, and radiologic evolution — no. (%)‡	3 (2.5)	4 (3.5)	2 (1.6)	3 (2.5)	2 (1.9)	5 (4.2)	19 (2.7)
Unfavorable†							
Participants with unfavorable outcome — no. (%)	13 (11.0)	11 (9.6)	18 (14.8)	25 (21.2)	18 (16.8)	23 (19.3)	108 (15.5)
Death from any cause — no. (%)§	2 (1.7)	1 (0.9)	3 (2.5)	3 (2.5)	2 (1.9)	2 (1.7)	13 (1.9)
Positive culture results — no. (%)¶	1 (0.8)	3 (2.6)	4 (3.3)	12 (10.2)	8 (7.5)	1 (0.8)	29 (4.1)
Recurrence — no. (%)‖	0	0	0	1 (0.8)	2 (1.9)	0	3 (0.4)
Permanent treatment discontinuation due to adverse event — no. (%)	3 (2.5)	3 (2.6)	1 (0.8)	1 (0.8)	1 (0.9)	2 (1.7)	11 (1.6)
Poor treatment adherence or loss to follow-up — no. (%)	3 (2.5)	2 (1.7)	3 (2.5)	3 (2.5)	4 (3.7)	8 (6.7)	23 (3.3)
Withdrawal of consent — no. (%)	1 (0.8)	1 (0.9)	4 (3.3)	3 (2.5)	0	7 (5.9)	16 (2.3)
Other unfavorable outcome — no. (%)**	3 (2.5)	1 (0.9)	3 (2.5)	2 (1.7)	1 (0.9)	3 (2.5)	13 (1.9)

N Engl J Med. 2025 Jan 30;392(5):468-482.

Key findings

Analysis Population	Standard Therapy	Experimental Therapy	Risk Difference (95% CI)
	no. with favorable outcome/total no. (%)		*percentage points*
Standard therapy vs. BLMZ			
Modified intention-to-treat population	96/119 (80.7)	105/118 (89.0)	8.3 (–0.8 to 17.4)
Per-protocol population	71/74 (95.9)	94/98 (95.9)	0.0 (–6.0 to 5.9)
Standard therapy vs. BCLLfxZ			
Modified intention-to-treat population	96/119 (80.7)	104/115 (90.4)	9.8 (0.9 to 18.7)
Per-protocol population	71/74 (95.9)	91/95 (95.8)	–0.2 (–6.2 to 5.9)
Standard therapy vs. BDLLfxZ			
Modified intention-to-treat population	96/119 (80.7)	104/122 (85.2)	4.6 (–4.9 to 14.1)
Per-protocol population	71/74 (95.9)	97/103 (94.2)	–1.8 (–8.1 to 4.6)
Standard therapy vs. DCLLfxZ			
Modified intention-to-treat population	96/119 (80.7)	93/118 (78.8)	–1.9 (–12.1 to 8.4)
Per-protocol population	71/74 (95.9)	82/96 (85.4)	–10.5 (–18.9 to –2.2)
Standard therapy vs. DCMZ			
Modified intention-to-treat population	96/119 (80.7)	89/107 (83.2)	2.5 (–7.5 to 12.5)
Per-protocol population	71/74 (95.9)	82/96 (85.4)	–10.5 (–18.9 to –2.2)

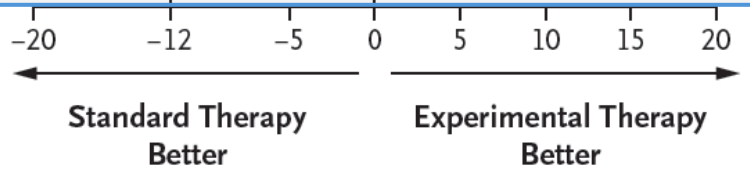


Figure 2. Primary Efficacy Analysis at Week 73.

N Engl J Med. 2025 Jan 30;392(5):468-482.

Clinical Implications

- The **endTB trial** found that three regimens (**BLMZ, BCLLfxZ**, **BDLLfxZ**) were non-inferior to standard 18–24 month therapy for treating fluoroquinolone-susceptible RR-TB, achieving >85% favorable outcomes
- Multiple effective options allow for individualized treatment based on patient characteristics
- **Bedaquiline-containing** regimens performed better than bedaquiline-sparing regimens

- Adverse events were common but manageable, mainly **hepatotoxicity** (6.3–18.3% vs 7.1% standard), hematologic toxicity, and QT prolongation (DCMZ [4.2%], BCLLfxZ [3.3%])

N Engl J Med. 2025 Jan 30;392(5):468-482.

Contents

1. Tuberculosis (TB)

- Diagnosis
- Treatment
- MDR/RR-TB
- **Prevention of TB exposure**

VQUIN MDR Trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Levofloxacin for the Prevention of Multidrug-Resistant Tuberculosis in Vietnam

Greg J. Fox, Ph.D., Nguyen Viet Nhung, Ph.D., Nguyen Cam Binh, Ph.D., Nguyen Binh Hoa, Ph.D., Frances L. Garden, Ph.D., Andrea Benedetti, Ph.D., Pham Ngoc Yen, M.Sc., Nguyen Kim Cuong, Ph.D., Emily L. MacLean, Ph.D., H. Manisha Yapa, Ph.D., David W. Dowdy, Ph.D., Nguyen Huu Lan, M.D., Elyse Guevara-Rattray, M.I.P.H., Pham Duc Cuong, B.A., Ori Solomon, Ph.D., Marcel A. Behr, M.D., Ben J. Marais, Ph.D., Steven M. Graham, Ph.D., Dick Menzies, M.D., Nguyen Thu Anh, Ph.D., and Guy B. Marks, Ph.D.

TB-CHAMP Trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Levofloxacin Preventive Treatment in Children Exposed to MDR Tuberculosis

A.C. Hesseling, S.E. Purchase, N.A. Martinson, L. Fairlie, H.S. Schaaf, J. Brigden, S. Staples, D.M. Gibb, A. Garcia-Prats, F. Conradie, C. McGowan, C. Layton, E. Batist, A.-M. Demers, S. Nyamathe, L. Frigati, R. Turner, T. Duong, and J.A. Seddon

N Engl J Med. 2024 Dec 19;391(24):2304-2314.
N Engl J Med. 2024 Dec 19;391(24):2315-2326.

Background

- **Fluoroquinolones** are part of standard MDR-TB treatment, but their role in preventing MDR-TB among exposed individuals is uncertain.
- Children in close contact with MDR-TB patients have a high risk of infection, but preventive treatment options remain unclear.
- Some observational studies suggested levofloxacin might prevent TB, but no randomized controlled trials had confirmed its effectiveness.

Question of this study

- Can a **6-month levofloxacin regimen** effectively prevent active TB disease among household contacts of persons with **MDR-TB**?
- Can a **6-month levofloxacin regimen** effectively prevent MDR-TB in children exposed to MDR-TB, and is it safe and well-tolerated?

N Engl J Med. 2024 Dec 19;391(24):2304-2314.
N Engl J Med. 2024 Dec 19;391(24):2315-2326.

VQUIN MDR Trial

Key findings

- Double-blind, randomized, controlled trial
- Household contacts of persons with bacteriologically confirmed MDR/RR-TB in Vietnam.

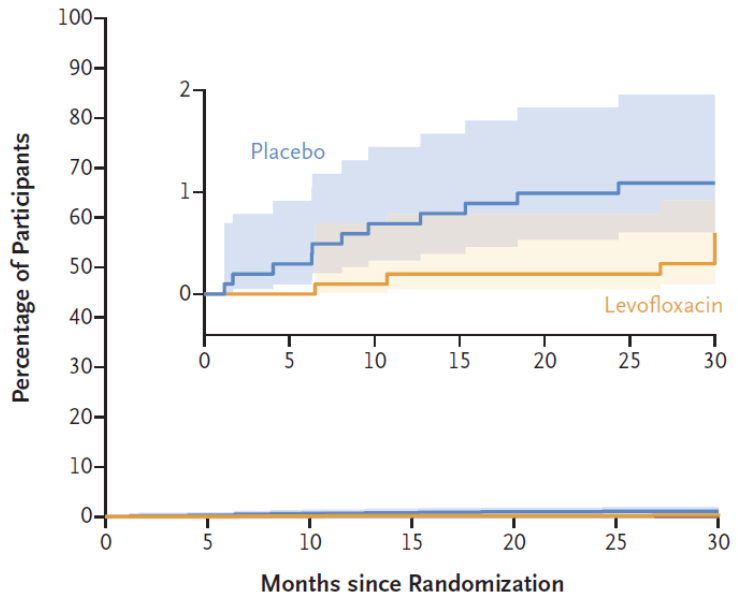


Figure 2. Kaplan–Meier Plot of Incident Bacteriologically Confirmed Tuberculosis over Time.

Table 3. Adverse Events.*

Variable	Levofloxacin	Placebo	Risk Difference (95% CI)	P Value
			percentage points	
Participants taking at least one dose of levofloxacin or placebo — no./total no. (%)†	960/1023 (93.8)	962/1018 (94.5)	–0.7 (–3.5 to 2.2)	0.65
Participants with one or more adverse events — no./total no. (%)‡				
Any grade	306/960 (31.9)	125/962 (13.0)	18.9 (14.2 to 23.6)	<0.001
Grade 1 or 2	290/960 (30.2)	111/962 (11.5)	18.7 (14.0 to 23.3)	<0.001
Grade 3 or 4	29/960 (3.0)	19/962 (2.0)	1.0 (–0.3 to 2.4)	0.14

N Engl J Med. 2024 Dec 19;391(24):2304-2314.

TB-CHAMP Trial

Key findings

- Community-based, multisite, double-blind, cluster-randomized, placebo controlled trial in South Africa
- Children <5 years (regardless of IGRA result or HIV status), 5-17 years (IGRA (+) or HIV infection)

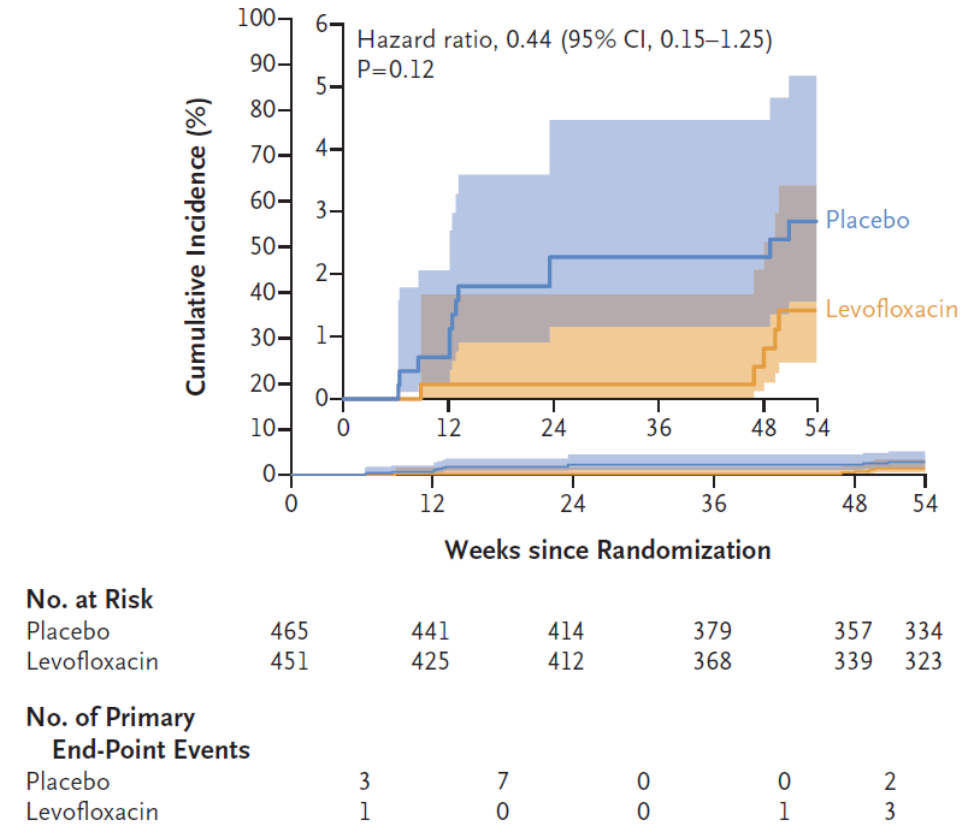


Figure 2. Incident Tuberculosis by Week 48 According to Trial Group.

Table 2. Safety End Points.*

End Point	Levofloxacin (N=452)	Placebo (N=469)	Hazard Ratio (95% CI)	P Value
	no. of participants (%)			
Grade ≥3 adverse event during treatment period at least possibly related to trial regimen	4 (0.9)	8 (1.7)	0.52 (0.16–1.71)	0.29
Any grade ≥3 adverse event†	14 (3.1)	24 (5.1)	0.64 (0.32–1.28)	0.21
Serious adverse event	9 (2.0)	8 (1.7)	1.22 (0.45–3.34)	0.69
Adverse event that led to permanent discontinuation of trial regimen	6 (1.3)	1 (0.2)	5.00 (0.61–41.32)	0.14
Prespecified adverse events‡				
Arthritis, arthralgia, or tendinopathy of any grade, alone or in combination	6 (1.3)	4 (0.9)	1.32 (0.35–4.98)	0.69
Central nervous system disorders	7 (1.5)	11 (2.3)	0.59 (0.21–1.62)	0.30
Severe rash or cutaneous reaction	1 (0.2)	0	—	—

N Engl J Med. 2024 Dec 19;391(24):2315-2326.

Clinical Implications

- The **VQUIN MDR trial** found that 6-month levofloxacin reduced MDR-TB incidence, but was not statistically significant (IRR: 0.55, 95% CI: 0.19–1.62).
- Adverse events were more frequent(31.9% *vs.* 13.0%), but serious events were rare and manageable.
- The **TB-CHAMP trial** found that 6-month levofloxacin reduced MDR-TB incidence in exposed children, but was not statistically significant(HR: 0.44, 95% CI: 0.15–1.25).
- Adverse events were similar, with no major safety concern, therefore further research is needed to confirm efficacy.

N Engl J Med. 2024 Dec 19;391(24):2304-2314.
N Engl J Med. 2024 Dec 19;391(24):2315-2326.

Contents

2. Nontuberculous Mycobacteria (NTM)

- **Epidemiology**
- Diagnosis
- Treatment

Original Article

trd Tuberculosis & Respiratory Diseases

Epidemiological Characteristics of Nontuberculous Mycobacterial Pulmonary Disease in South Korea: A Meta-analysis of Individual Participant Data

https://doi.org/10.4046/trd.2023.0193
ISSN: 1738-3536(Print)/
2005-6184(Online)
Tuberc Respir Dis 2024;87:386-397

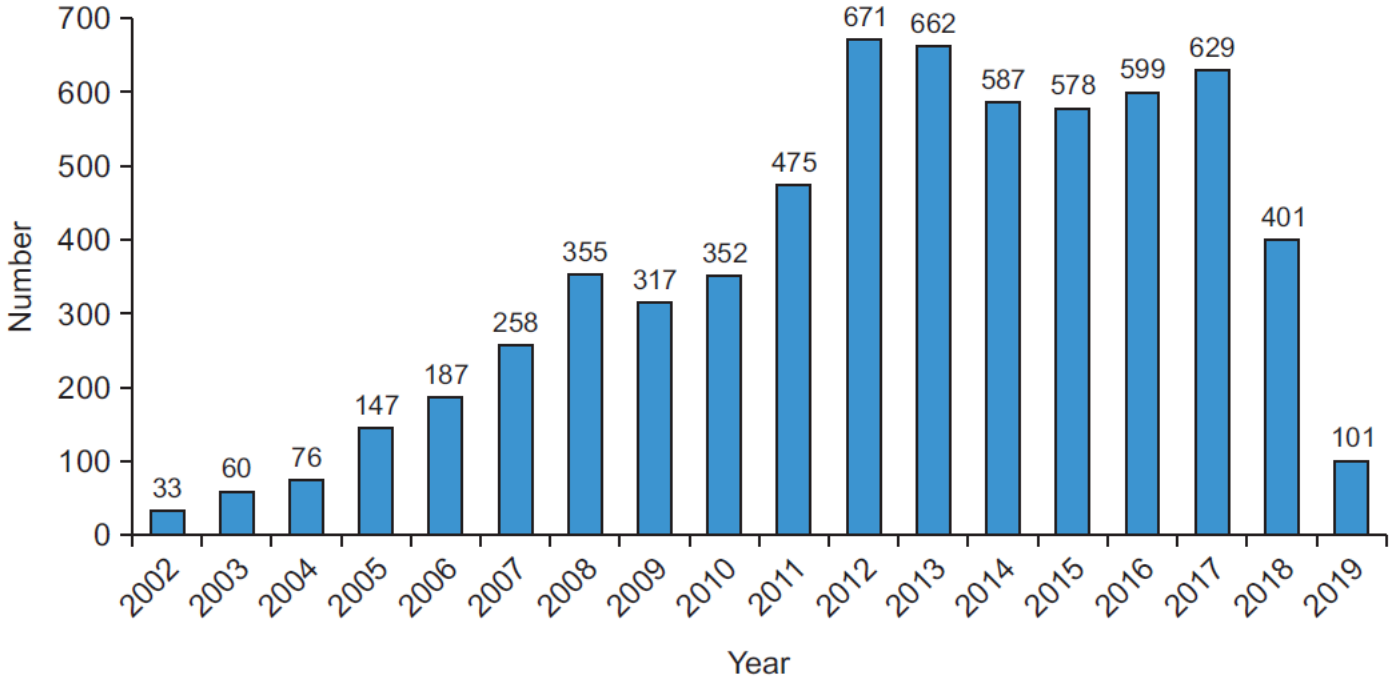
Background

- NTM-PD incidence and prevalence increasing worldwide
- Geographical variations exist in clinical characteristics
- In South Korea: prevalence increased from 11.4 to 56.7 cases/100,000 population (2010-2021)
- Limited data on comprehensive epidemiology with species, radiologic findings, and disease severity
- Treatment outcomes suboptimal: 60% success for MAC-PD, 45.6% for *M. abscessus* PD

Question of this study

- What are the clinical characteristics and epidemiological patterns of NTM-PD in South Korea?
- Are there significant differences in disease characteristics according to age and sex?
- Has the distribution of causative species or radiologic presentations changed over time?

Figure 2. Reported numbers of patients with nontuberculous mycobacterial pulmonary disease by diagnosis year.



Tuberc Respir Dis (Seoul). 2024 Jul;87(3):386-397.

Figure 3. Proportions of causative species of nontuberculous mycobacterial pulmonary disease by year of diagnosis. Cochrane-Armitage trend test was used, p for trend >0.05.

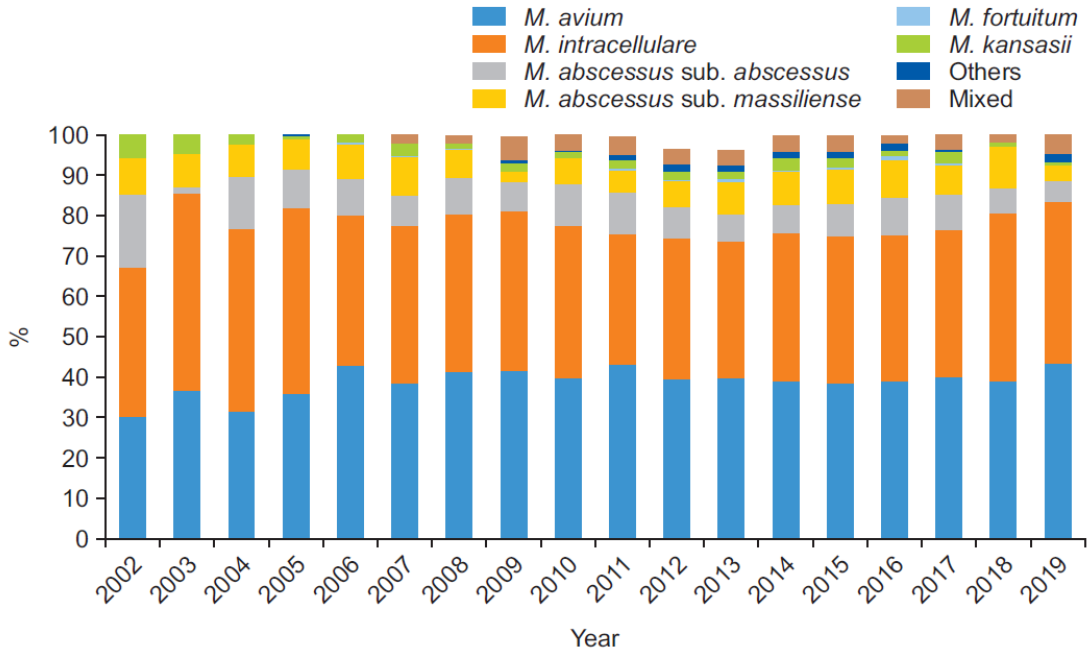
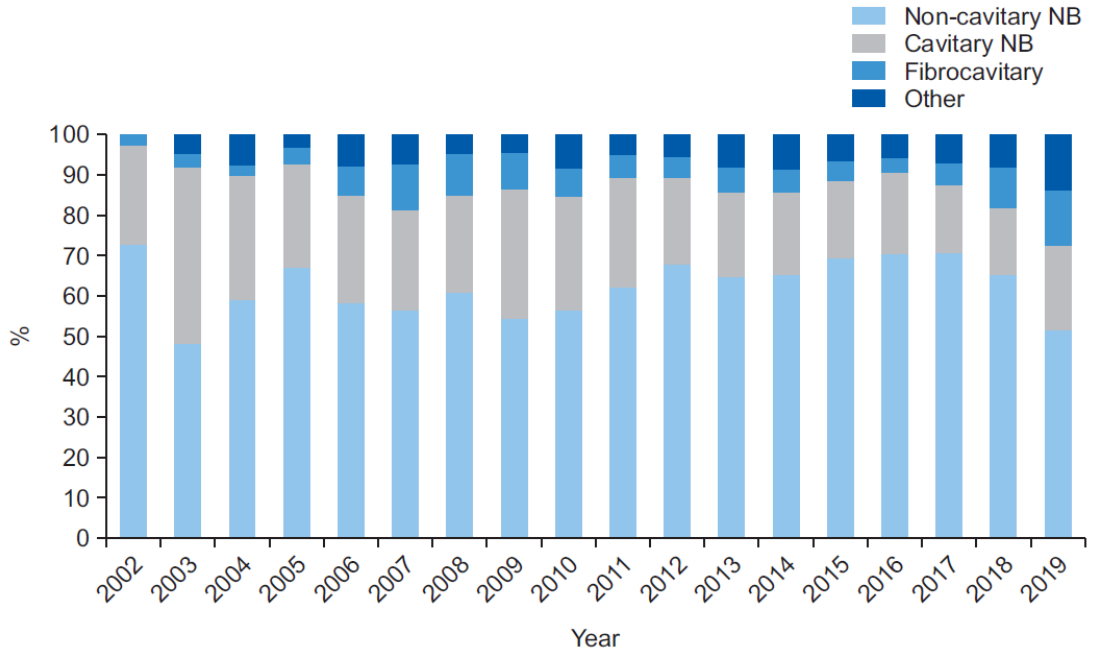


Figure 4. Proportions of radiologic types of nontuberculous mycobacterial pulmonary disease by year diagnosis. Cochrane-Armitage trend test was used, p for trend >0.05. NB: nodular bronchiectatic.



Key findings

- ***M. avium* (41.4%)** and ***M. intracellulare* (38.4%)** most common species,
  M. abscessus subspecies *abscessus* (8.6%) and *M. abscessus* subspecies *massiliense* (7.8%)
- The proportions of causative species and radiologic forms remained **similar**

Tuberc Respir Dis (Seoul). 2024 Jul;87(3):386-397.

Table 3. Clinical characteristics of patients with nontuberculous mycobacterial pulmonary disease according to age

Characteristic	Age <65 (n=3,752)	Age ≥65 (n=2,729)	p-value
Age, yr (NA=8)	53.7±8.1	72.4±5.4	<0.001
Sex, women (NA=3)	2,439 (65.0)	1,304 (47.8)	<0.001
Height, cm (NA=108)	161.4±7.7	160.8±8.5	0.003
Weight, kg (NA=103)	54.3±9.2	53.2±10.1	<0.001
BMI, kg/m^2 (NA=109)	20.8±2.8	20.5±3.2	0.002
BMI <18.5 kg/m^2 (NA=109)	668 (18.6)	735 (27.4)	<0.001
Ever smoker (NA=101)	761 (20.6)	1,064 (39.6)	<0.001
History of tuberculosis (NA=22)	1,385 (37.0)	1,114 (40.8)	0.001
History of NTM treatment (NA=4)	443 (11.8)	321 (11.8)	0.982
Radiologic type (NA=1)			<0.001
Non-cavitary NB	2,491 (66.4)	1,692 (62.0)	<0.001
Cavitary NB	835 (22.3)	595 (21.8)	<0.001
Fibrocavitary	199 (5.3)	220 (8.1)	<0.001
Others[†]	227 (6.1)	221 (8.1)	<0.001
BACS score[‡] (NA=117)			<0.001
0	1,628 (44.1)	0	
1	1,280 (34.7)	727 (27.1)	
2	638 (17.3)	1,159 (43.2)	
3	145 (3.9)	618 (23.1)	
4	0	177 (6.6)	

Tuberc Respir Dis (Seoul). 2024 Jul;87(3):386-397.

Clinical Implications

- Age- and sex-related differences in disease-specific severity identified
- Men and elderly patients showed more severe disease patterns and higher BACS scores
- Understanding these patterns may help develop targeted management strategies and improve outcomes

Tuberc Respir Dis (Seoul). 2024 Jul;87(3):386-397.

Contents

2. Nontuberculous Mycobacteria (NTM)

- Epidemiology
- **Diagnosis**
- Treatment

ORIGINAL ARTICLE

Serum Cell-Free DNA-based Detection of *Mycobacterium avium* Complex Infection

Lin Li[1,2], Emily Henkle[4], Brady M. Youngquist[2], Seungyeon Seo[6], Kamal Hamed[7], David Melnick[7], Christopher J. Lyon[2], Li Jiang[1], Adrian M. Zelazny[6], Tony Y. Hu[2,3], Kevin L. Winthrop[5*], and Bo Ning[2*]

Am J Respir Crit Care Med Vol 209, Iss 10, pp 1246–1254, May 15, 2024

Background

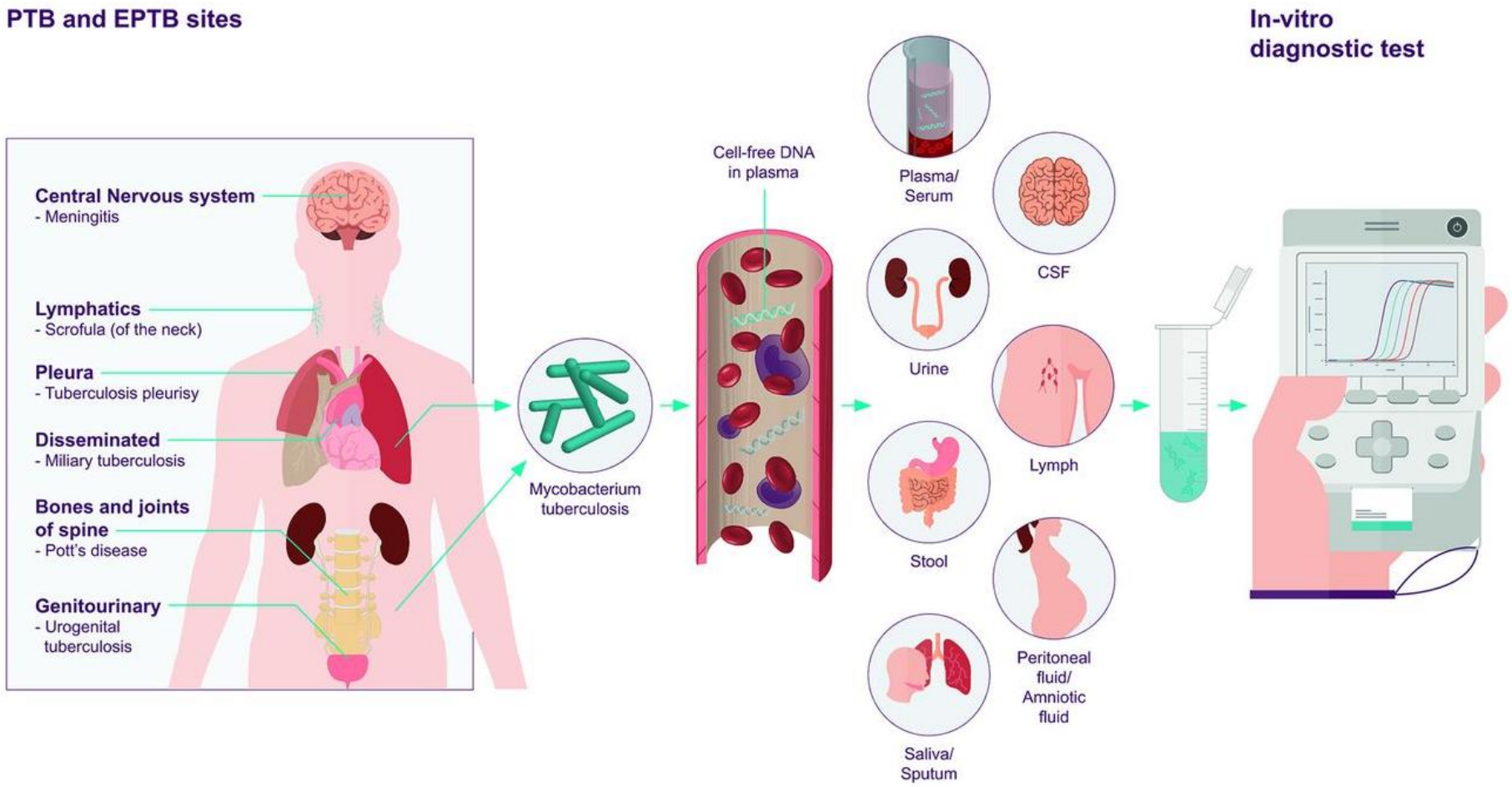
- MAC (*M. avium* complex) is the most common cause of NTM pulmonary disease (85-90% of cases)
- Current diagnostic methods require sputum culture (12-16 days)
- Diagnostic challenges: sample quality variations, slow results

Question of this study

- Can a CRISPR-based assay detecting MAC cell-free DNA (cfDNA) in serum:
  - Rapidly detect MAC infection?
  - Monitor treatment response?

Am J Respir Crit Care Med. 2024 May 15;209(10):1246-1254.

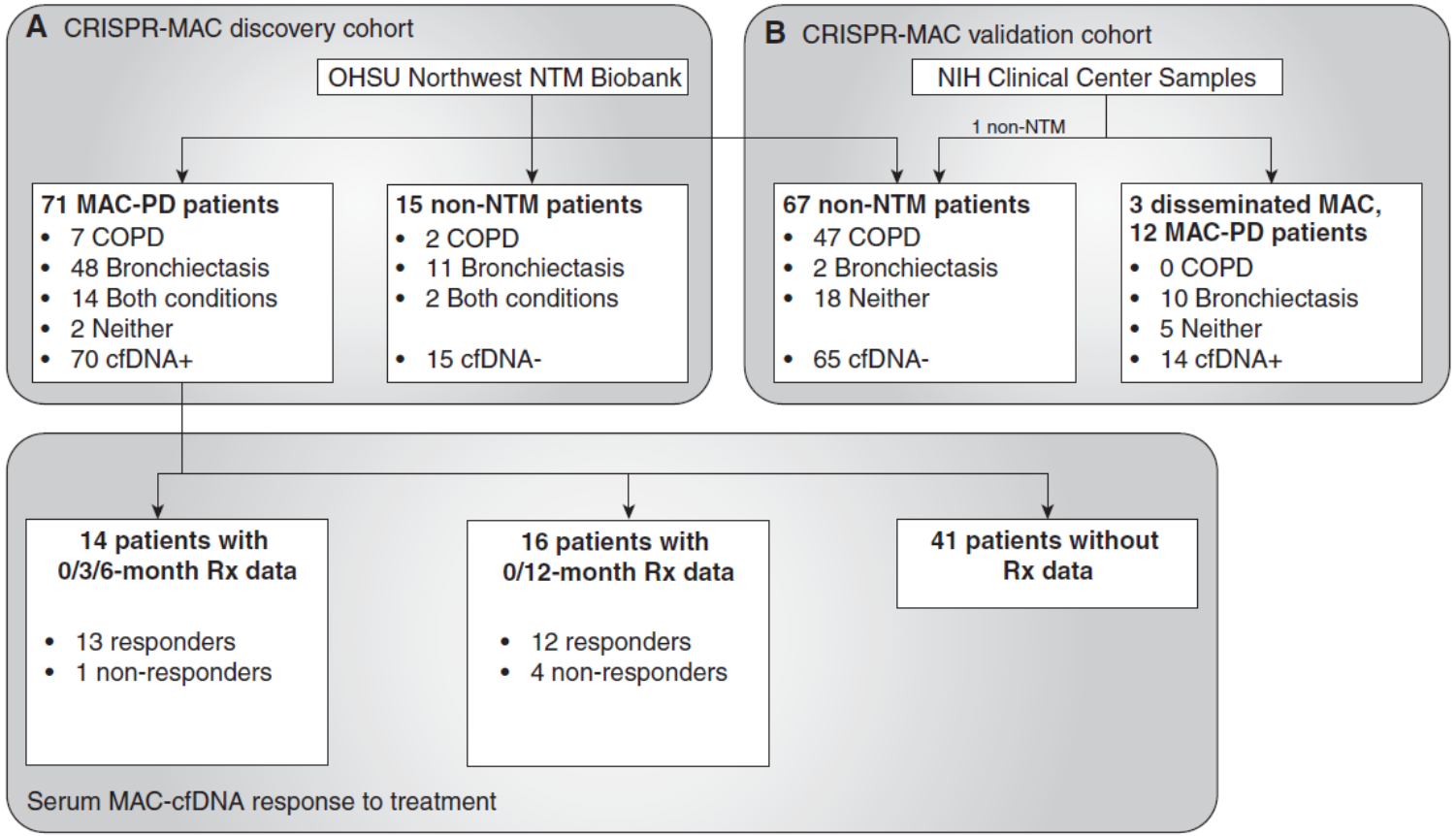
- **Cell-free DNA(cfDNA)-based *in vitro* diagnostic test** for infectious diseases



J Clin Microbiol. 2019 Mar 28;57(4):e01234-18.

- Blood-based CRISPR(*Clustered Regularly Interspaced Short Palindromic Repeats) MAC Assay

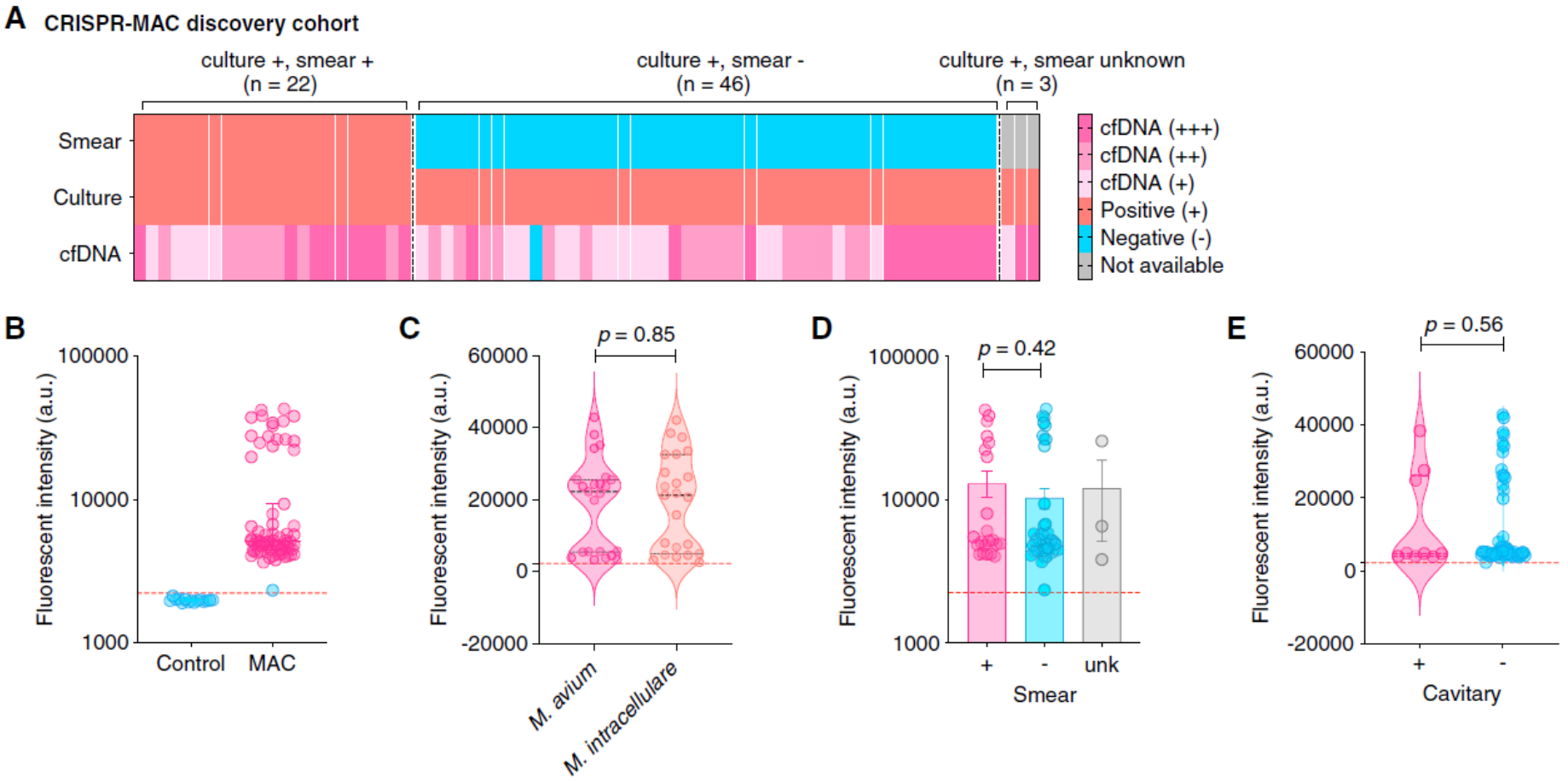
  ✓ cfDNA extraction → PCR amplification → CRISPR MAC assay → Fluorescence signal detection



Am J Respir Crit Care Med. 2024 May 15;209(10):1246-1254.

Key findings

- Diagnostic Performance - sensitivity: 97.6%, specificity: 97.6%
- Limit of detection: 0.125 copies/μl



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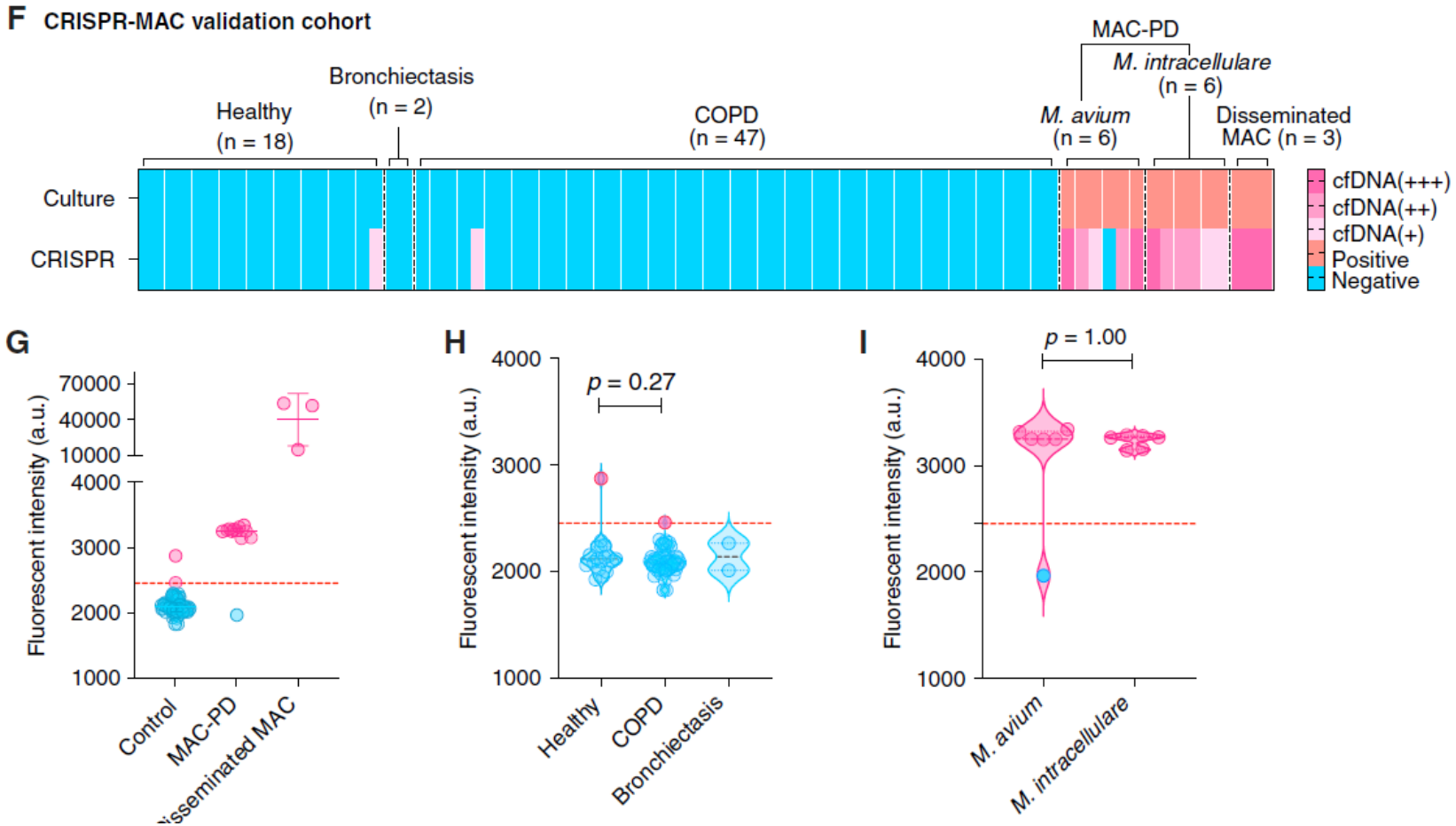
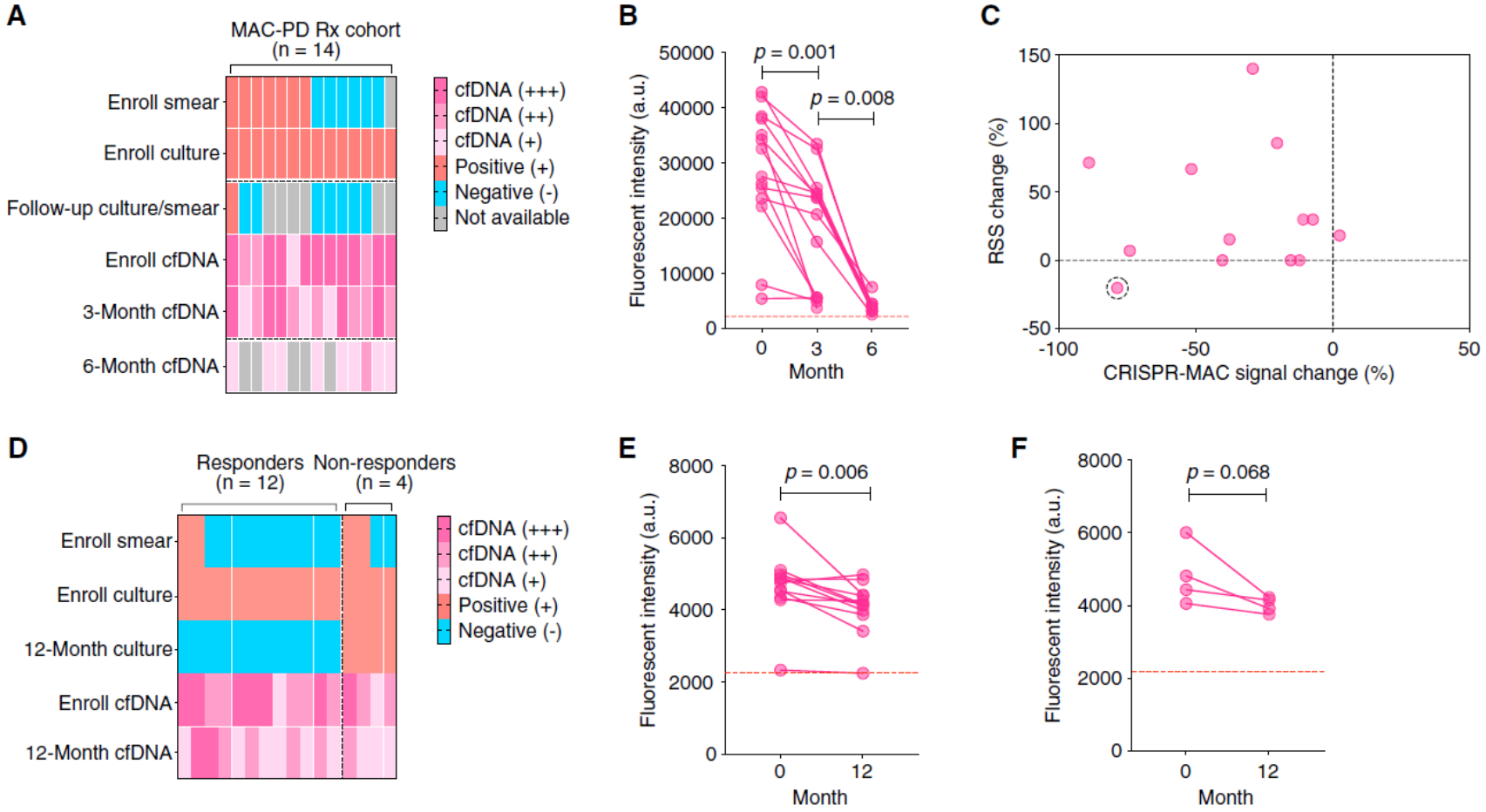


Am J Respir Crit Care Med. 2024 May 15;209(10):1246-1254.

Key findings

- Treatment Monitoring
  - ✓ Significant cfDNA decrease at 3, 6 months in responders
  - ✓ cfDNA concentrations in responders approached threshold by 6 months



Am J Respir Crit Care Med. 2024 May 15;209(10):1246-1254.

Clinical Implications

- This study provides preliminary evidence for the utility of a **serum-based CRISPR MAC assay** to **rapidly** detect MAC infection and monitor the response to treatment
- cfDNA detection is independent of sputum smear results and the presence of lung cavities and cfDNA is not detected in non-NTM patients (bronchiectasis, COPD) → High specificity (97.6%)
- The decrease in cfDNA can serve as an important biomarker reflecting the treatment response in MAC-PD, correlating with culture conversion
- Compared to culture tests (12-16 days), it provides a faster (20 minutes) and more consistent assessment of treatment response
- cfDNA detection method has the potential to be a valuable clinical tool for tracking MAC treatment efficacy and identifying disease recurrence

Am J Respir Crit Care Med. 2024 May 15;209(10):1246-1254.

Contents

2. Nontuberculous Mycobacteria (NTM)

- Epidemiology
- Diagnosis
- **Treatment**

J Antimicrob Chemother 2024; **79**: 211–240
https://doi.org/10.1093/jac/dkad372 Advance Access publication 22 December 2023

Journal of Antimicrobial Chemotherapy

Bedaquiline for treatment of non-tuberculous mycobacteria (NTM): a systematic review and meta-analysis

Shatha Omar [1]*, Michael G. Whitfield [2], Margaret B. Nolan[1], Justice T. Ngom[1], Nabila Ismail[1], Rob M. Warren[1] and Marisa Klopper[1]

Background

- In 2012, Bedaquiline is FDA-approved for MDR-TB
- A limited number of studies have investigated the susceptibility of NTM species to bedaquiline

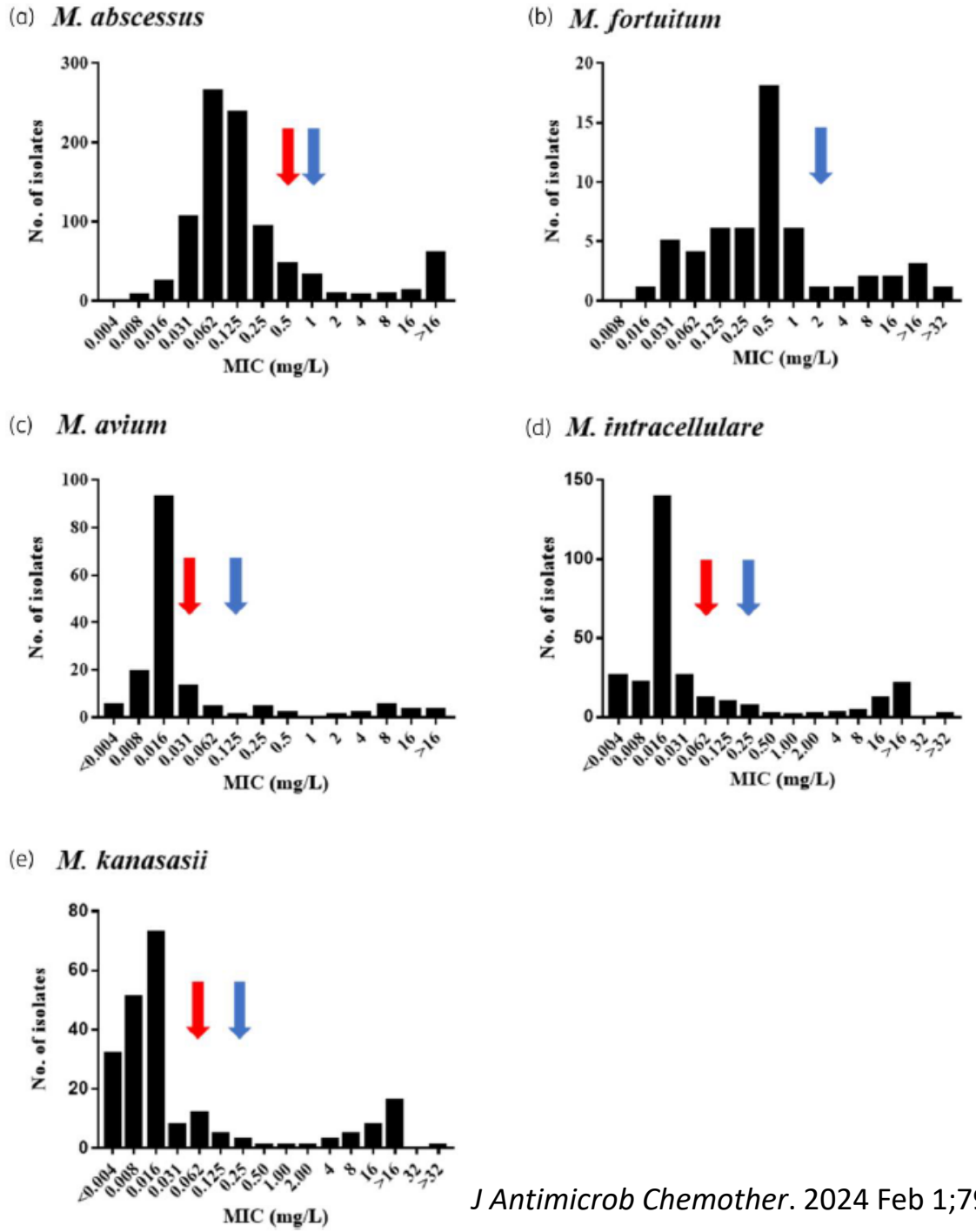
Question of this study

- Is bedaquiline effective against NTM species *in vitro* and *in vivo*?
- What is the **efficacy** of bedaquiline for treating NTM infections?

J Antimicrob Chemother. 2024 Feb 1;79(2):211-240.

Key findings

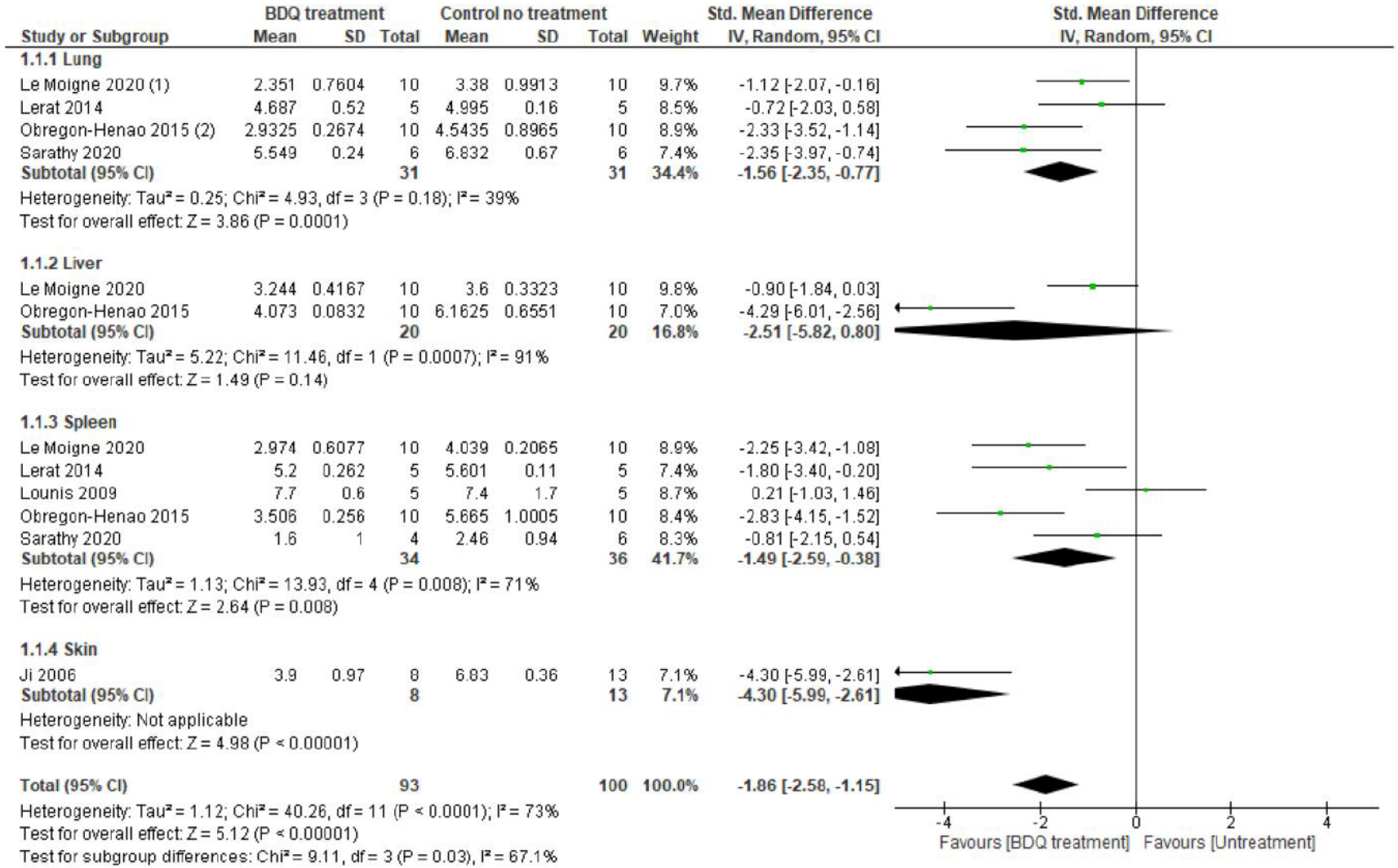
- *In vitro* studies (n=33)
  - ✓ Bedaquiline showed potent in vitro activity against most NTM species
  - ✓ But, *M. abscessus* and *M. fortuitum* have relatively **high MIC** distributions, suggesting low susceptibility and high resistance to bedaquiline



J Antimicrob Chemother. 2024 Feb 1;79(2):211-240.

Key findings

- Animal *(in vivo)* studies (n=9)
  - ✓ Bedaquiline reduced bacterial load significantly
  - ✓ More effective in **lung** and **spleen** than liver

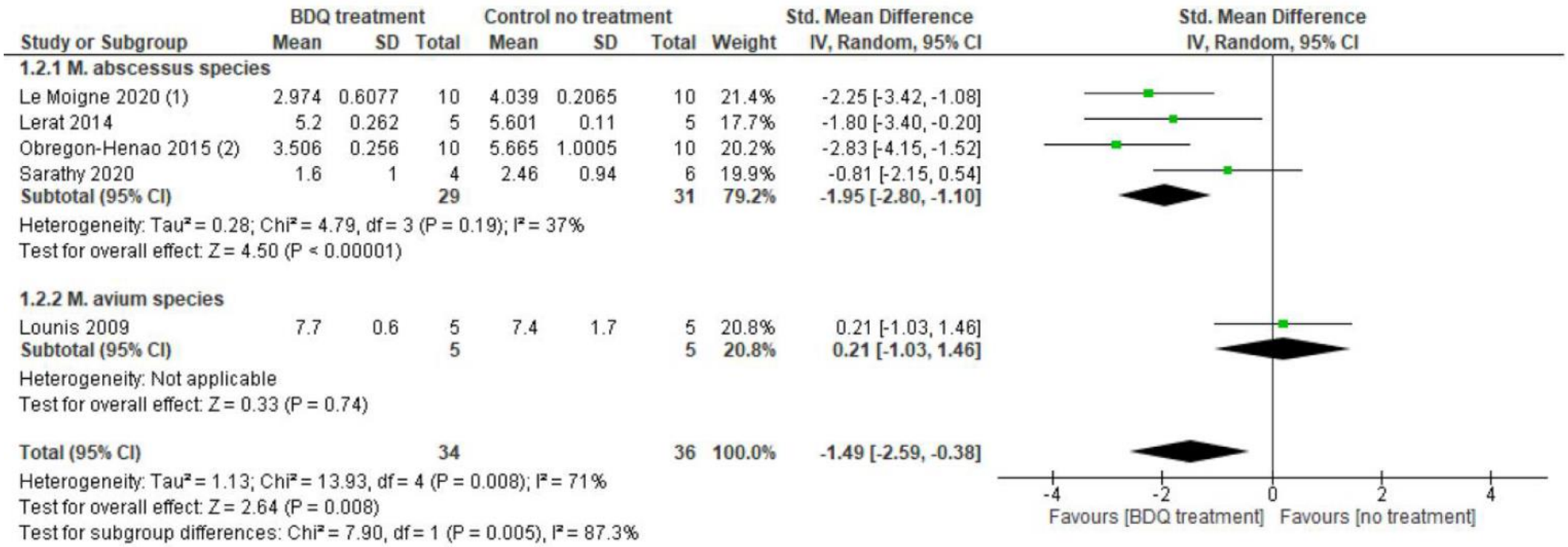


J Antimicrob Chemother. 2024 Feb 1;79(2):211-240.

Key findings

- Animal *(in vivo)* studies (n=9)

  ✓ Effective against *M. avium* > *M. abscessus*, *M. ulcerans* (skin)



Study or Subgroup	BDQ treatment Mean	SD	Total	Control no treatment Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.2.1 M. abscessus species								
Le Moigne 2020 (1)	2.974	0.6077	10	4.039	0.2065	10	21.4%	-2.25 [-3.42, -1.08]
Lerat 2014	5.2	0.262	5	5.601	0.11	5	17.7%	-1.80 [-3.40, -0.20]
Obregon-Henao 2015 (2)	3.506	0.256	10	5.665	1.0005	10	20.2%	-2.83 [-4.15, -1.52]
Sarathy 2020	1.6	1	4	2.46	0.94	6	19.9%	-0.81 [-2.15, 0.54]
Subtotal (95% CI)			**29**			**31**	**79.2%**	**-1.95 [-2.80, -1.10]**
Heterogeneity: Tau² = 0.28; Chi² = 4.79, df = 3 (P = 0.19); I² = 37%								
Test for overall effect: Z = 4.50 (P < 0.00001)								
1.2.2 M. avium species								
Lounis 2009	7.7	0.6	5	7.4	1.7	5	20.8%	0.21 [-1.03, 1.46]
Subtotal (95% CI)			**5**			**5**	**20.8%**	**0.21 [-1.03, 1.46]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.33 (P = 0.74)								
Total (95% CI)			**34**			**36**	**100.0%**	**-1.49 [-2.59, -0.38]**
Heterogeneity: Tau² = 1.13; Chi² = 13.93, df = 4 (P = 0.008); I² = 71%								
Test for overall effect: Z = 2.64 (P = 0.008)								
Test for subgroup differences: Chi² = 7.90, df = 1 (P = 0.005), I² = 87.3%								

J Antimicrob Chemother. 2024 Feb 1;79(2):211-240.

Key findings

- Human Studies (8 studies)
  - ✓ Successful treatment of extrapulmonary NTM infections (6/6 cases cured)
  - ✓ Variable results in pulmonary NTM disease
  - ✓ Resistance emergence in 3-8 months (2-8× MIC increase)

Table 5. Summary of findings: human studies treatment outcome

Study	Disease	Species	Treatment duration (months) with BDQ	Treatment outcome			
				Culture conversion	Cure	Relapse	Symptom improvement
Alexander *et al.* (2017)[62]	Pulmonary	*M. avium* complex and *M. intracellulare*	≥6	0/3	0/3	3/3	0/3
Chan *et al.* (2021)[63]	Extrapulmonary	*M. abscessus*	8	1/1	1/1	0/1	1/1
Erber *et al.* (2020)[64]	Extrapulmonary	*M. fortuitum* complex	3.5	1/1	1/1	0/1	1/1
Gil *et al.* (2021)[65]	Extrapulmonary disease	*M. abscessus* and *M. avium*	21,14	2/2	2/2	0/2	2/2
Meybeck *et al.* (2021)[66]	A mix between extrapulmonary and pulmonary	*M. marinum*	12	1/1	1/1	0/1	1/1
Pearson *et al.* (2020)[67]	Extrapulmonary	*M. abscessus*	> 3.5	1/1	1/1	0/1	1/1
Philley *et al.* (2015)[11]	Pulmonary	*M. avium* complex and *M. intracellulare*	6	0/10	0/10	4/10	4/10
Zweijpfenning *et al.* (2019)[68]	Pulmonary	*M. avium* complex	≥6	0/1	0/1	N/A	0/1

J Antimicrob Chemother. 2024 Feb 1;79(2):211-240.

Key findings

Table 6. Summary of findings: effective bedaquiline-including regimens

In animal model studies		In human studies	
Regimen	*Mycobacterium* species	Regimen	Species
RIF or RFP and/or Q203 or CLF	*M. ulcerans*	BDQ + LVX	*M. fortuitum*
CLR and/or AMK	*M. avium*	BDQ + OMC or CLF	*M. abscessus*
BDQ combined with either IPM or CLF	*M. abscessus*	BDQ + MFX	*M. marinum*
		BDQ + TDZ and CLF	*M. avium*

RIF, rifampicin; AMK, amikacin; BDQ, bedaquiline; CLF, clofazimine; CLR, clarithromycin; IPM, imipenem; RFP, rifapentine; Q203, telacebec; MFX, moxifloxacin; OMC, omadacycline; TDZ, tedizolid; LVX, levofloxacin.

J Antimicrob Chemother. 2024 Feb 1;79(2):211-240.

Clinical Implications

- **Bedaquiline** demonstrates potent *in vitro* activity against most NTM species
- Treatment efficacy varies by infection site and species:
  - ✓ More promising for extrapulmonary disease
  - ✓ Variable results for pulmonary disease
  - ✓ Resistance development during treatment is a concern
- Limitations: Limited standardization of in vitro testing methods, small sample size for animal and human studies, and lack of randomized clinical trials

J Antimicrob Chemother. 2024 Feb 1;79(2):211-240.

Thanks for attention

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