Tuberculosis/NTM

원자력병원 김혜련

BURDEN

9.6 million people fell ill with TB in 2014

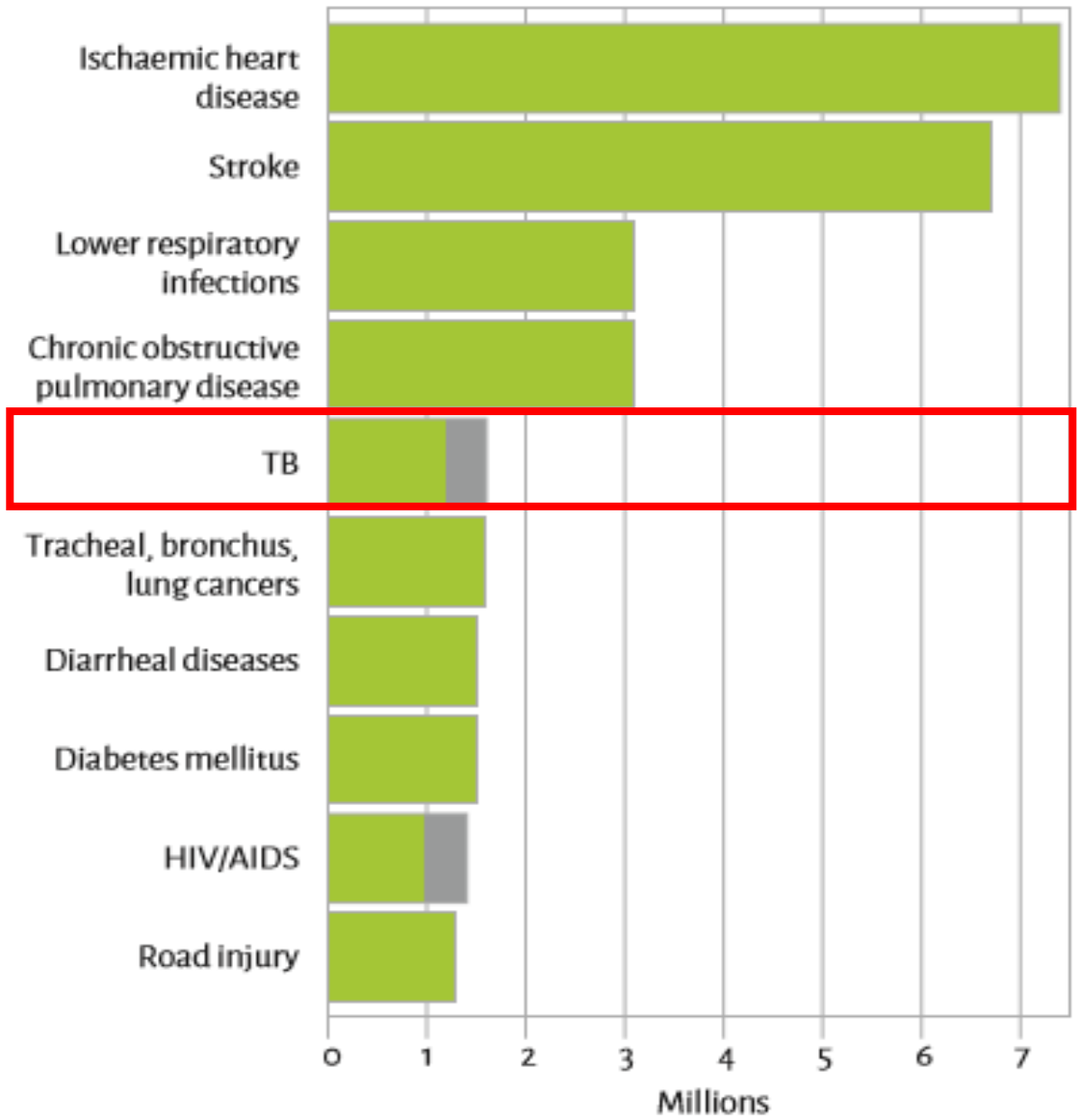
1.5 million men, women and children died from TB in 2014

1.2 million people living with HIV developed TB, with 0.4 million associated deaths in 2014

480 000 people developed MDR-TB (multidrug-resistant TB) in 2014, with 190 000 associated deaths

WHO | The End TB Strategy

Top causes of death worldwide in 2012.[a,b] Deaths from TB among HIV-positive people are shown in grey.[c]



WHO | Global tuberculosis report 2015

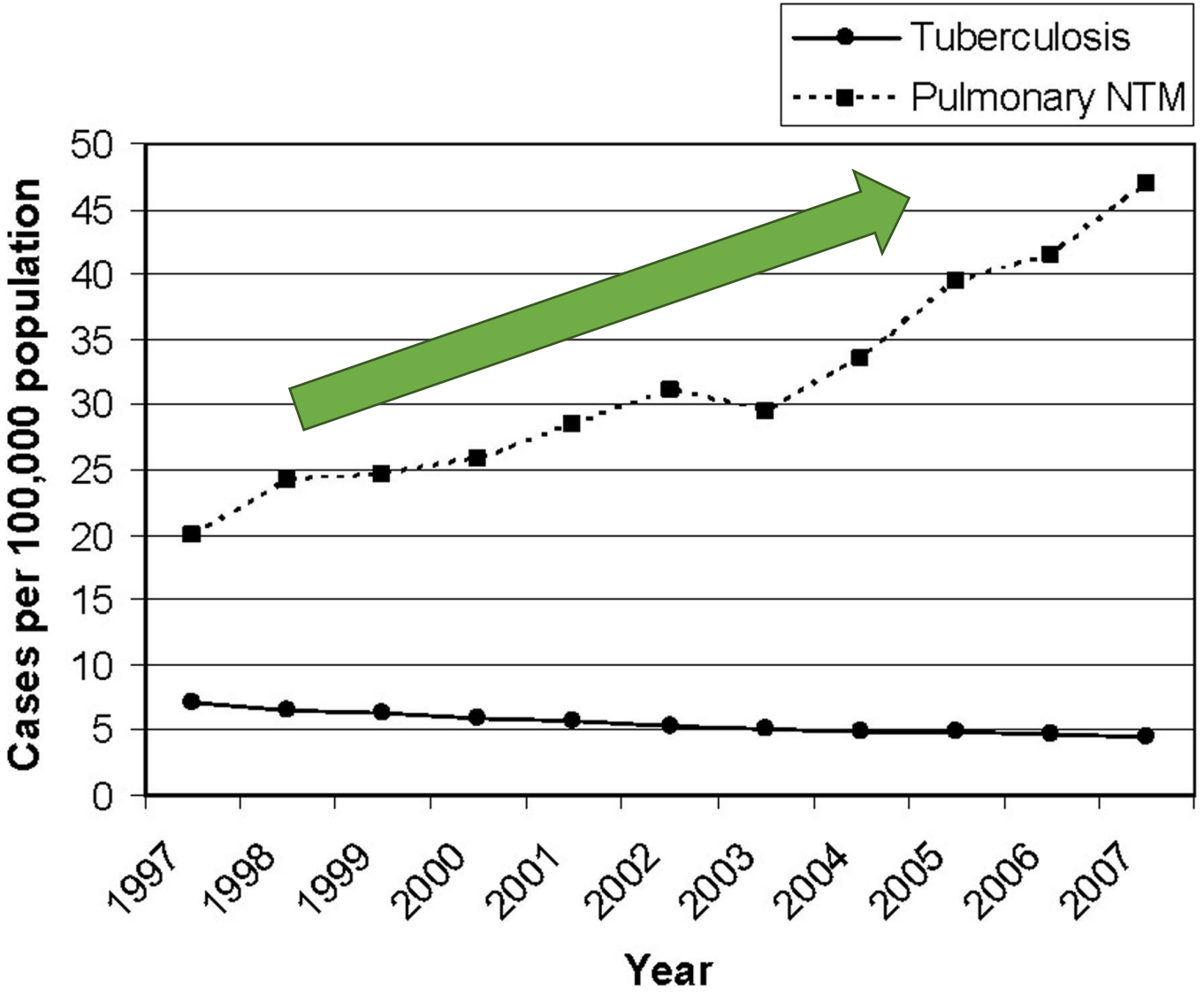
THE END TB STRATEGY

World Health Organization

Table 1. Key global indicators, milestones and targets for the post-2015 tuberculosis strategy

Indicators with baseline values for 2015	Milestones			Targets
	2020	2025	2030	2035
Percentage reduction in deaths due to tuberculosis (projected 2015 baseline: 1.3 million deaths)	35%	75%	90%	95%
Percentage and absolute reduction in tuberculosis incidence rate (projected 2015 baseline 110/100 000)	20% (<85/100 000)	50% (<55/100 000)	80% (<20/100 000)	90% (<10/100 000)
Percentage of affected families facing catastrophic costs due to tuberculosis (projected 2015 baseline: not yet available)	Zero	Zero	Zero	Zero

Changing prevalence of pulmonary NTM and tuberculosis in the USA

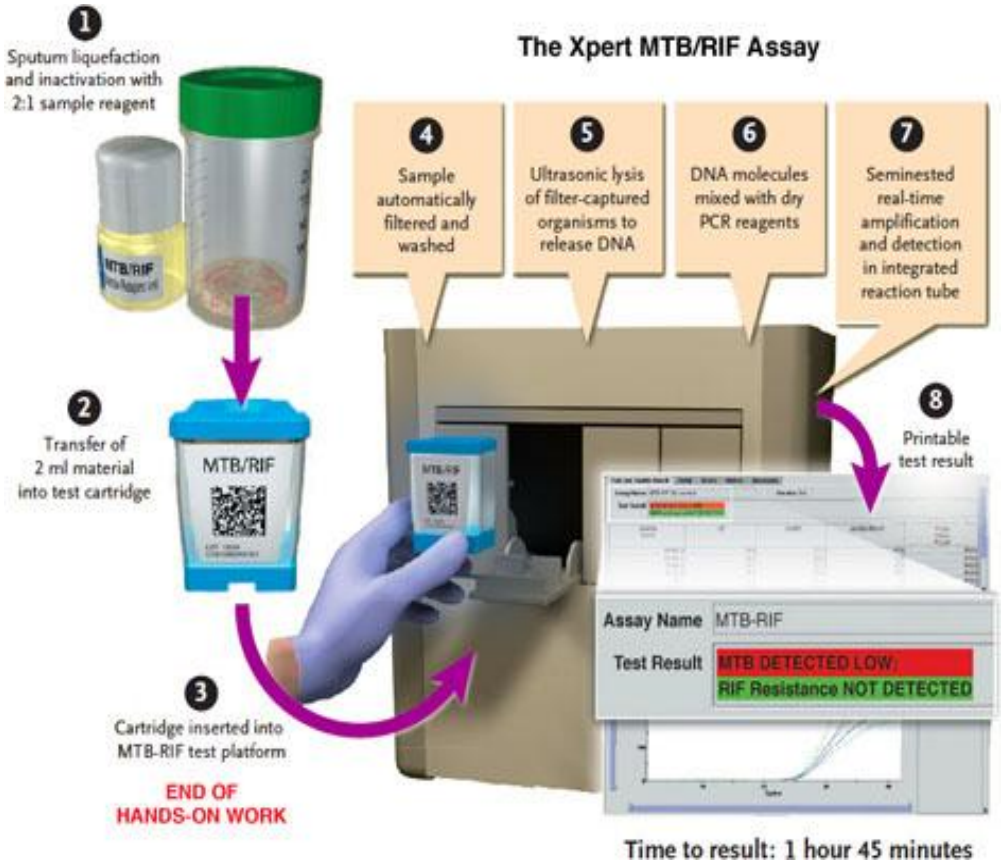


QJM 2013;106:307-315

Contents

Contents

01 Diagnosis of TB



WHO | Global tuberculosis report 2015

Expert MTB/RIF Results in Patients With Previous Tuberculosis: Can We Distinguish True From False Positive Results?

Objectives

- To examine
  - the frequency of Xpert false positivity in retreatment patients
  - distinguishable factors from true positivies
- laboratory-based substudy
  - to ascertain whether Xpert can detect DNA from lysed nonviable cells

Clin Infect Dis. 2016 Feb 16

Expert MTB/RIF Results in Patients With Previous Tuberculosis: Can We Distinguish True From False Positive Results?

Methods

- clinical study
  - in Cape Town, South Africa
  - data from 3166 patients who had symptoms suggestive of TB
  - false positive (FP) : Xpert (+), culture (-)
  - true positive (TP) : Xpert (+), culture(+)
- laboratory-based substudy
  - viable bacilli vs nonviable bacilli (heat- and mechanically-lysed)

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Table 2. Factors Associated With Xpert False Positivity in New and Retreatment Cases

	Univariate Analysis				Multivariate Logistic Regression	
★ New TB Patients (n = 461)	True-Positive Xpert (n = 421)	False-Positive Xpert (n = 40)	OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Demographic variables						
Age, y, median (IQR)	33 (27–43)	32 (25–44)	1.00 (.97–1.02)	.780	. . .	. . .
Female, No. (%)	187/414 (45)	25/40 (63)	2.02 (1.04–3.95)	.039	. . .	. . .
Smoker, No. (%)	125/347 (36)	13/30 (43)	1.36 (.64–2.89)	.427	. . .	. . .
Clinical variables						
HIV-infected, No. (%)	162/404 (58)	21/39 (50)	1.74 (.90–3.37)	.099	. . .	. . .
Xpert information						
TB-specific C_T values, median (IQR)	21.50 (17.72–26.10)	28.03 (21.20–32.23)	1.14 (1.07–1.21)	<.001	1.14 (1.08–1.21)	<.001
★ Retreatment Patients (n = 321)	True-Positive Xpert (n = 276)	False-Positive Xpert (n = 45)	OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Demographic variables						
Age, y, median (IQR)	37 (30–45)	41 (21–48)	1.03 (1–1.07)	.030	. . .	. . .
Female, No. (%)	108/274 (39)	15/42 (36)	1.17 (.60–2.30)	.647	. . .	. . .
Smoker, No. (%)	100/229 (44)	18/32 (56)	1.66 (.79–3.50)	.184	. . .	. . .
Clinical variables						
HIV-infected, No. (%)	122/273 (45)	20/43 (47)	1.08 (.57–2.05)	.823	. . .	. . .
Previous TB treatment not completed, No. (%)	55/239 (23)	26/39 (26)	1.15 (.53–2.51)	.719	. . .	. . .
Years since previous TB treatment stopped or completed, median (IQR)	2 (0–5)	1 (0–1)	0.92 (.85–.99)	.033	0.91 (.84–.99)	.048
Xpert information						
TB-specific C_T values, median (IQR)	20.30 (16.71–25.05)	29.28 (26.18–30.60)	1.27 (1.18–1.37)	<.001	1.25 (1.15–1.35)	<.001

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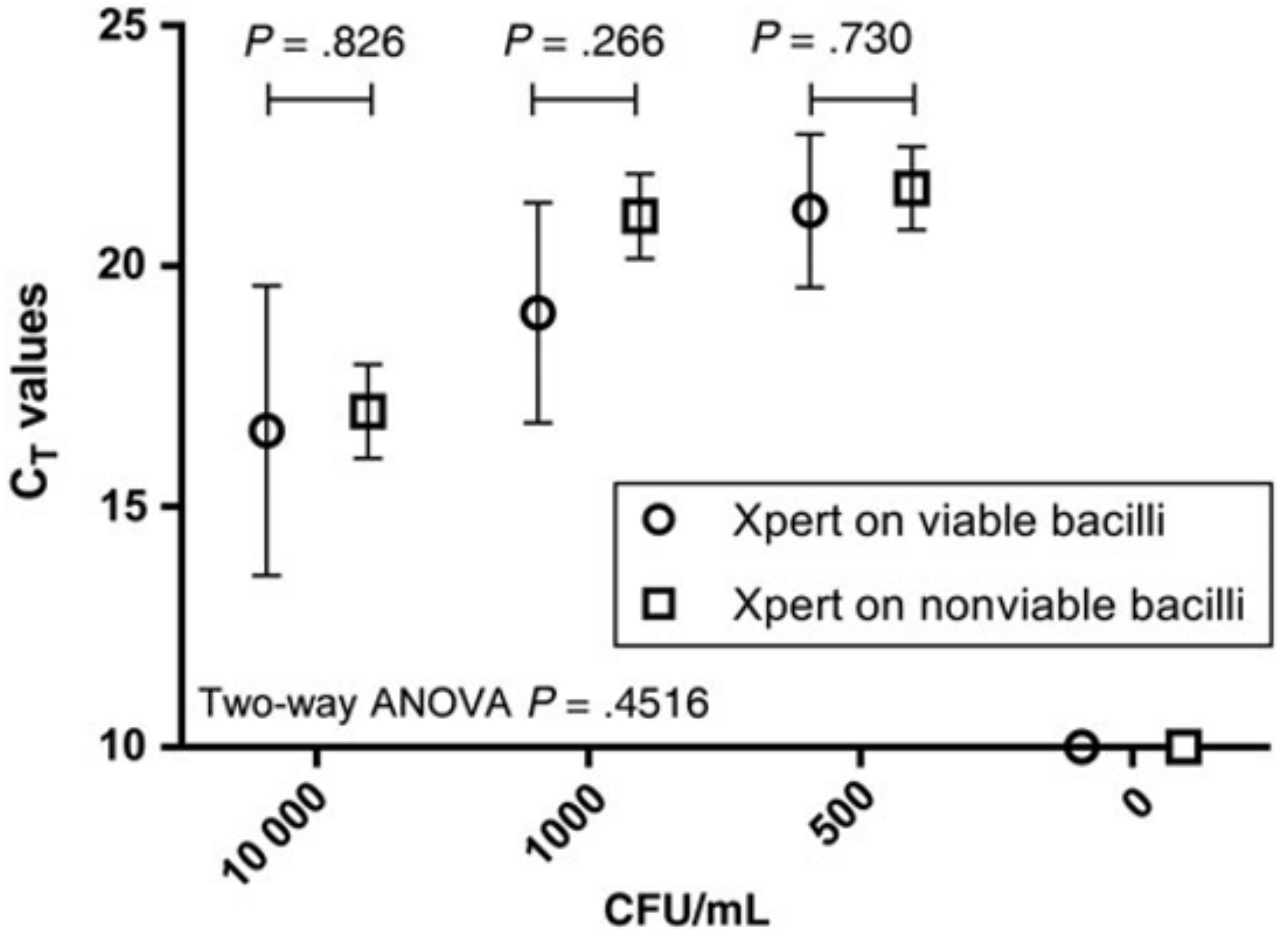

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Expert MTB/RIF Results in Patients With Previous Tuberculosis: Can We Distinguish True From False Positive Results?

Conclusions

- FP Xpert
  - previous TB (more recently)
  - low mycobacterial DNA load (measured by C_T)
  - CXR not compatible with active TB
- about 1 in 7 Xpert (+) results in retreatment patients will be FP
- Xpert detects DNA from nonviable cells

Clin Infect Dis. 2016 Feb 16

Genome-wide expression for diagnosis of pulmonary tuberculosis: a multicohort analysis

Objectives

- To derive a diagnostic gene set in the peripheral blood of patients with active TB

Lancet Respir Med. 2016 Feb 19

Genome-wide expression for diagnosis of pulmonary tuberculosis: a multicohort analysis

Methods

- from two public gene expression microarray repositories
- datasets that examined clinical cohorts of active pulmonary TB in whole blood
- compared gene expression in patients with either latent TB or other ds. *vs.* active TB

Lancet Respir Med. 2016 Feb 19

01 Diagnosis of TB

	Year	Reference	Platform	Use	Country	Age	HIV status	Active tuberculosis culture or smear	Healthy controls	Latent tuberculosis	Other disease	Active tuberculosis	Treatment	Total
GSE19491	2010	Berry[8]	GPL6947	Discovery	South Africa, UK, USA	Adults	Negative	Positive	86	69	193	31	..	409
GSE25534	2010	Maertzdorf[30]	GPL1708	Validation	South Africa	Adults	Negative	Positive	6	19	..	19	..	44
GSE28623	2011	Maertzdorf[22]	GPL4133/ GPL6480	Validation	The Gambia	Adults	Negative	Positive	37	25	..	46	..	108
Cliff Combined Dataset	2013	Cliff[13]	GPL570	Validation	South Africa	Adults	Negative	Positive	..	..	..	36	117	153
GSE34608	2012	Maertzdorf[24]	GPL4133/ GPL6480	Validation	Germany	Adults	Negative	Positive	18	..	18	8	..	44
GSE37250	2014	Kaforou[7]	GPL10558	Discovery	Malawi, South Africa	Adults	Positive and negative	Positive	..	167	175	195	..	537
GSE39939	2014	Anderson[6]	GPL10558	Validation	Kenya	Child-ren	Positive and negative	Positive and negative	..	14	64	44 negative, 35 positive	..	157
GSE39940		Anderson[6]		Validation	Malawi, South Africa	Child-ren	Positive and negative	Positive	..	54	169	111	..	334
GSE40553	2012	Bloom[9]	GPL10558	Validation	South Africa, UK	Adults	Negative	Positive	..	..	..	36	130	166
GSE41055	2013	Verhagen[10]	GPL5175	Validation	Venezuela	Child-ren	Negative	Positive and negative	9	9	..	7 negative; 2 positive	..	27
GSE42834	2014	Bloom[9]	GPL10558	Discovery	UK, France	Adults	Negative	Positive	118	..	123	40	..	281
GSE56153	2012	Ottenhoff[23]	GPL6883	Validation	Indonesia	Adults	Negative	Positive	18	..	..	18	35	71
GSE62147	2015	Tientcheu[29]	GPL6480	Validation	The Gambia	Adults	Negative	Positive	..	..	..	26	26	52
GSE74092	2015	Maertzdor[212]	RT-PCR array GPL21040	Validation	India	Adults	Negative	Positive	76	..	..	113	..	189

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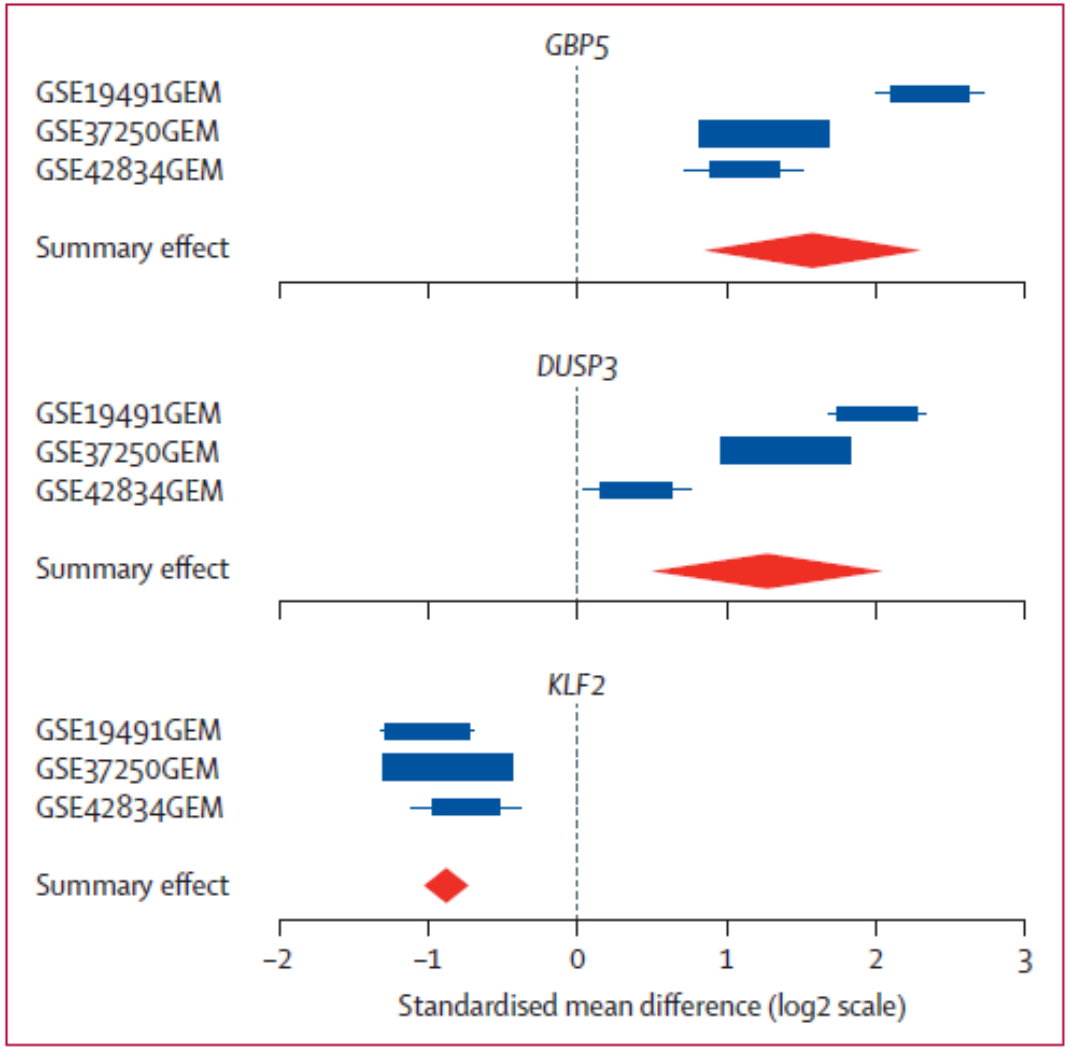

Figure 2: **Forest plots for each of the three genes derived in the forward search**

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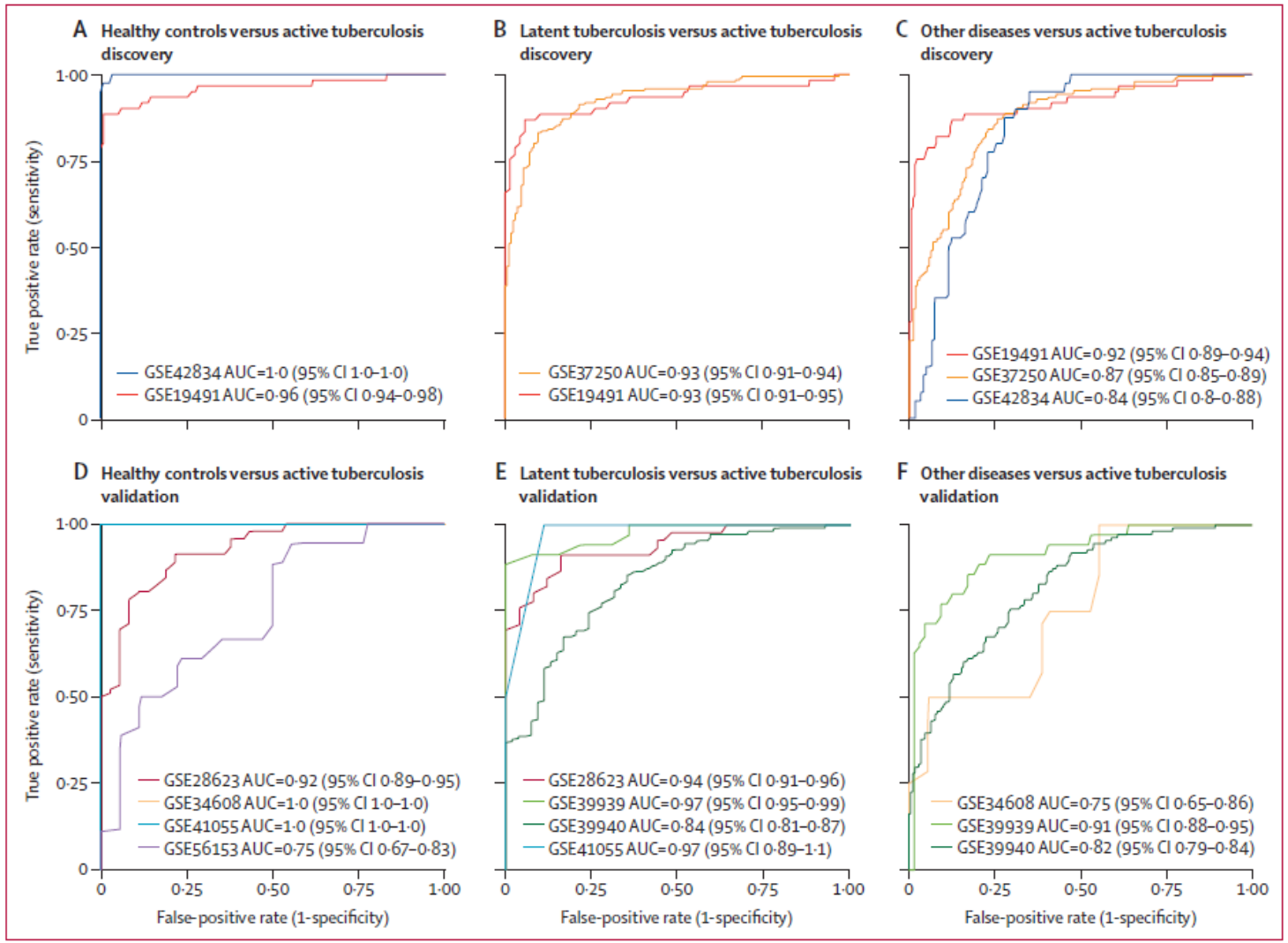

Figure 3: **Performance of the three-gene set in the discovery datasets**

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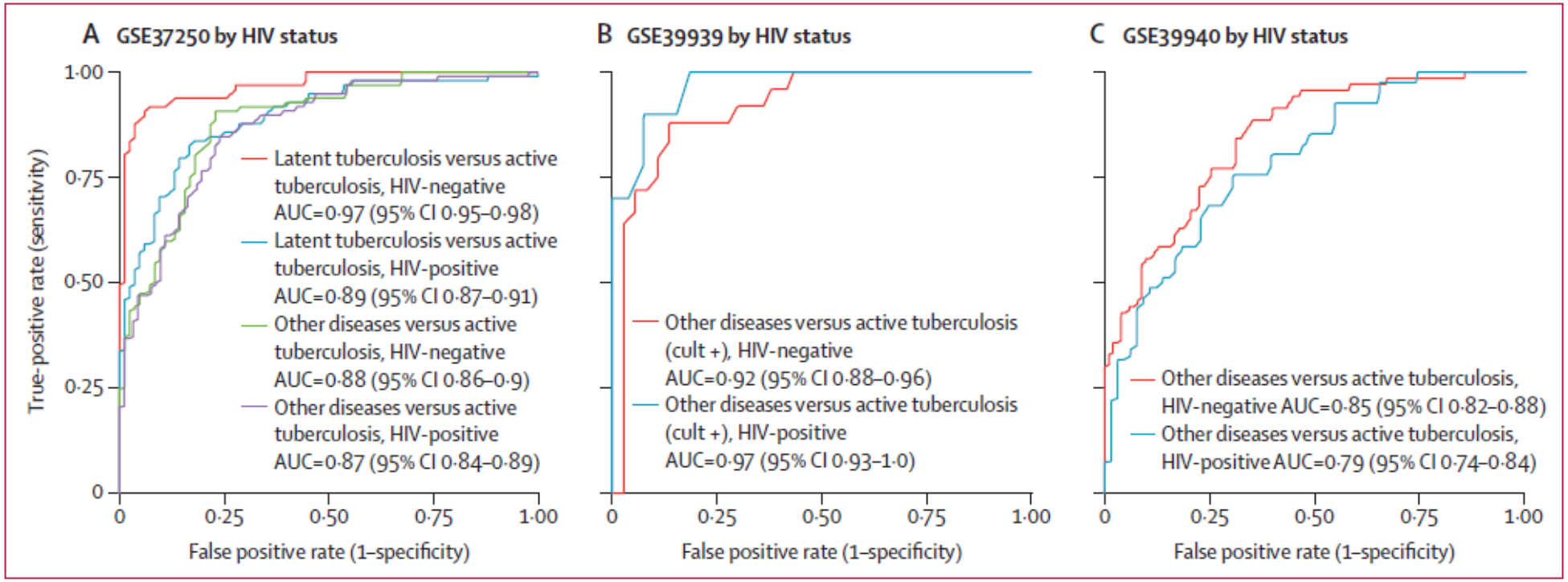

Figure 5: **Effect of HIV co-infection on the diagnostic power of the tuberculosis score**

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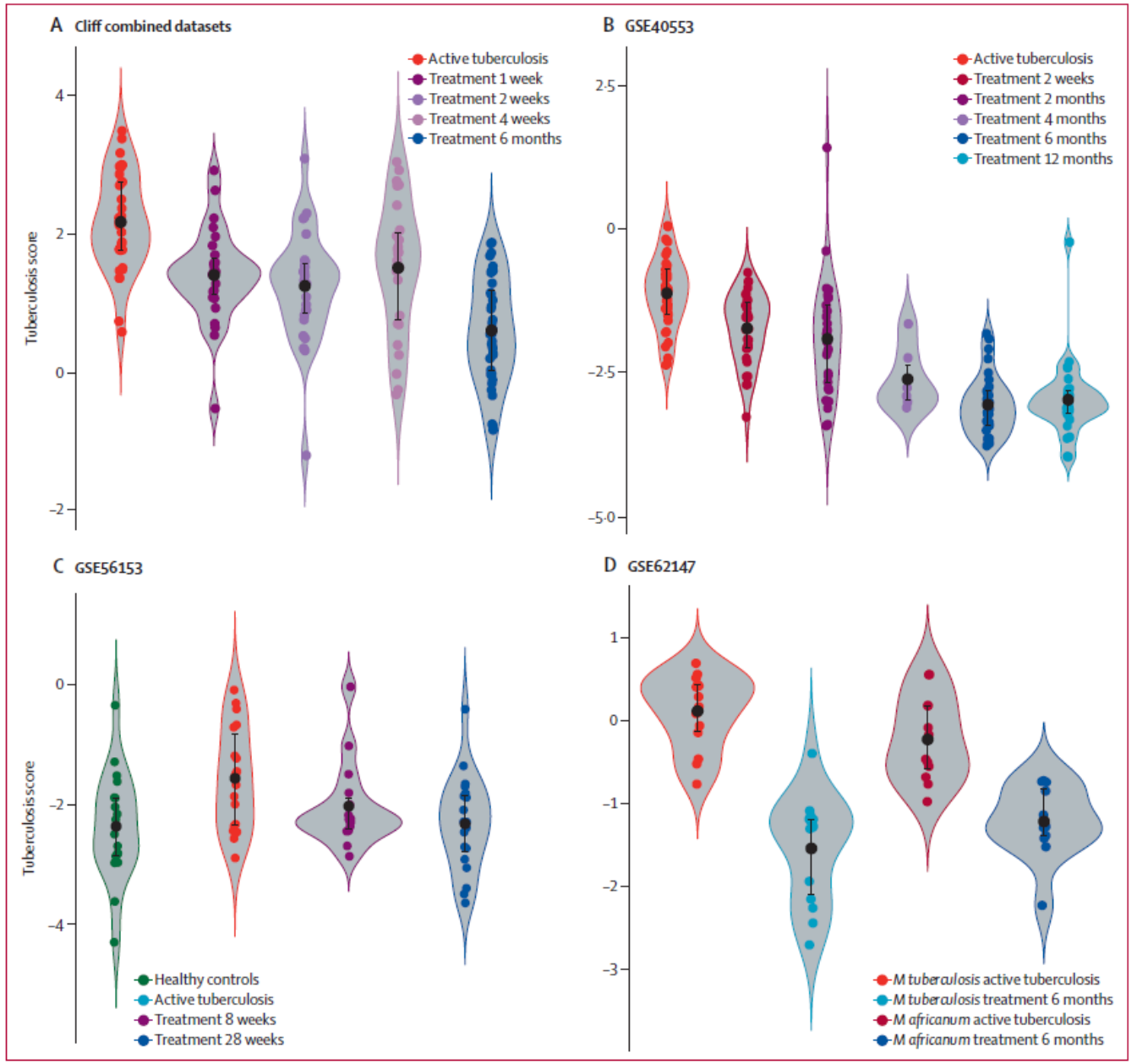

Figure 6: **Violin plots showing the performance of the three-gene set in longitudinal validation datasets**

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Genome-wide expression for diagnosis of pulmonary tuberculosis: a multicohort analysis

Conclusions

- three-gene set for active TB
  - potential clinical application for diagnosis and monitoring treatment response

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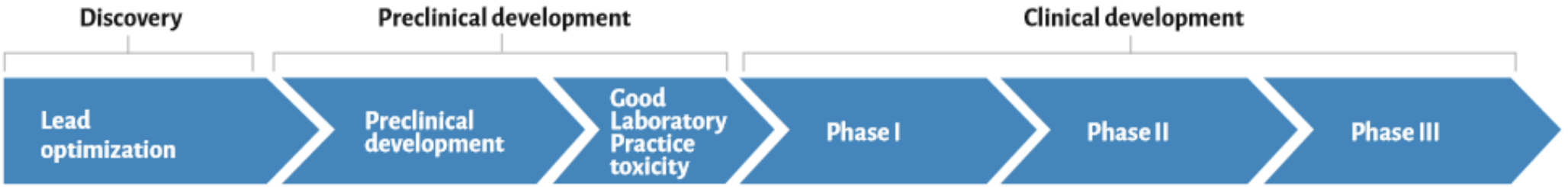
Contents

The development pipeline for new TB drugs, August 2015[a]



Lead optimization	Preclinical development	Good Laboratory Practice toxicity	Phase I	Phase II	Phase III
Cyclopeptides	TBI-166	PBTZ169	TBA-354	Sutezolid (PNU-100480)	Bedaquiline (TMC-207) with OBR[b] for MDR-TB
Diarylquinolines	CPZEN-45	Q203		SQ109	Delamanid (OPC-67683) with OBR[b] for MDR-TB
DprE Inhibitors	SQ609			Rifapentine for DS-TB	Rifapentine for LTBI
InhA Inhibitor, Indazoles	SQ641			AZD5847	Pretomanid-Moxifloxacin-Pyrazinamide Regimen
LeuRS Inhibitors, Ureas	DC-159a			Bedaquiline-Pretomanid-Pyrazinamide Regimen	
Macrolides, Azaindoles					
Mycobacterial Gyrase Inhibitors					
Pyrazinamide Analogs					
Ruthenium(II) Complexes					
Spectinamides SPR-113					
Translocase-1 Inhibitors					

Chemical classes: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone

[a] Details for projects listed can be found at http://www.newtbdrugs.org/pipeline.php and ongoing projects without a lead compound series identified can be viewed at http://www.newtbdrugs.org/pipeline-discovery.php

[b] OBR = Optimized Background Regimen

Source: Working Group on New TB Drugs, 2015 – www.newtbdrugs.org

WHO | Global tuberculosis report 2015

A dose-ranging trial to optimize the dose of rifampin in the treatment of tuberculosis

Objectives

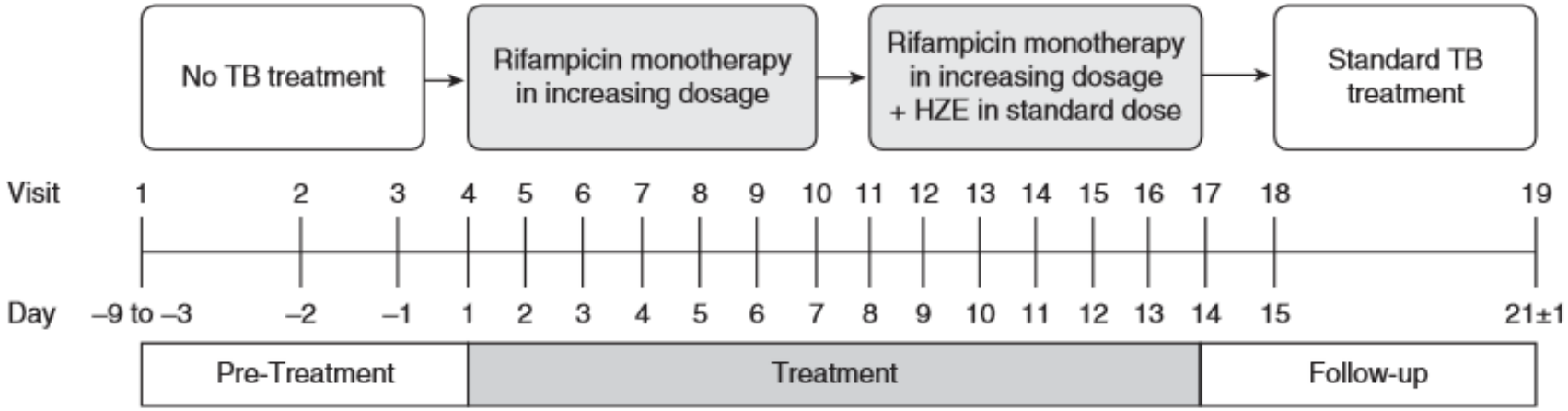
- To evaluate the safety and tolerability, the pharmacokinetics, and the extended early bactericidal activity of increasing doses of rifampin

Am J Respir Crit Care Med. 2015;191(9):1058-65

A dose-ranging trial to optimize the dose of rifampin in the treatment of tuberculosis

Methods

- 68 culture-positive patients with pulmonary TB
- 10 mg/kg (8), 20 mg/kg (15), 25 mg/kg (15), 30 mg/kg (15), 35 mg/kg (15)



Am J Respir Crit Care Med. 2015;191(9):1058-65

Table 2. Possibly Related and Definitely Related Adverse Events per Grade and per Dose Group

Group	Total	Grade 1		Grade 2		Grade 3*	
		Possibly Related	Related	Possibly Related	Related	Possibly Related	Related
10 mg/kg RIF (control)	7	0	0	0	0	0	0
20 mg/kg RIF	39	21	1	4	0	2	0
25 mg/kg RIF	24	11	2	2	0	0	0
30 mg/kg RIF	39	21	3	4	0	1	0
35 mg/kg RIF	54	27	2	9	0	0	0
Total	163	80	8	19	0	3	0

Table 3. Steady-State Pharmacokinetics of Rifampin (Day 14)

Group	AUC_{0-24h} (h · mg/L)	C_{max} (mg/L)*
10 mg/kg (control)	26.3 (21.3–40.9)	7.4 (6.1–9.9)
20 mg/kg	113 (77.5–162)	21.6 (16.0–31.9)
25 mg/kg	135 (91.5–228)	25.1 (16.3–34.6)
30 mg/kg	190 (84.7–436)	33.1 (17.6–55.8)
35 mg/kg	235 (166–321)	35.2 (28.6 –44.2)

Am J Respir Crit Care Med. 2015;191(9):1058-65

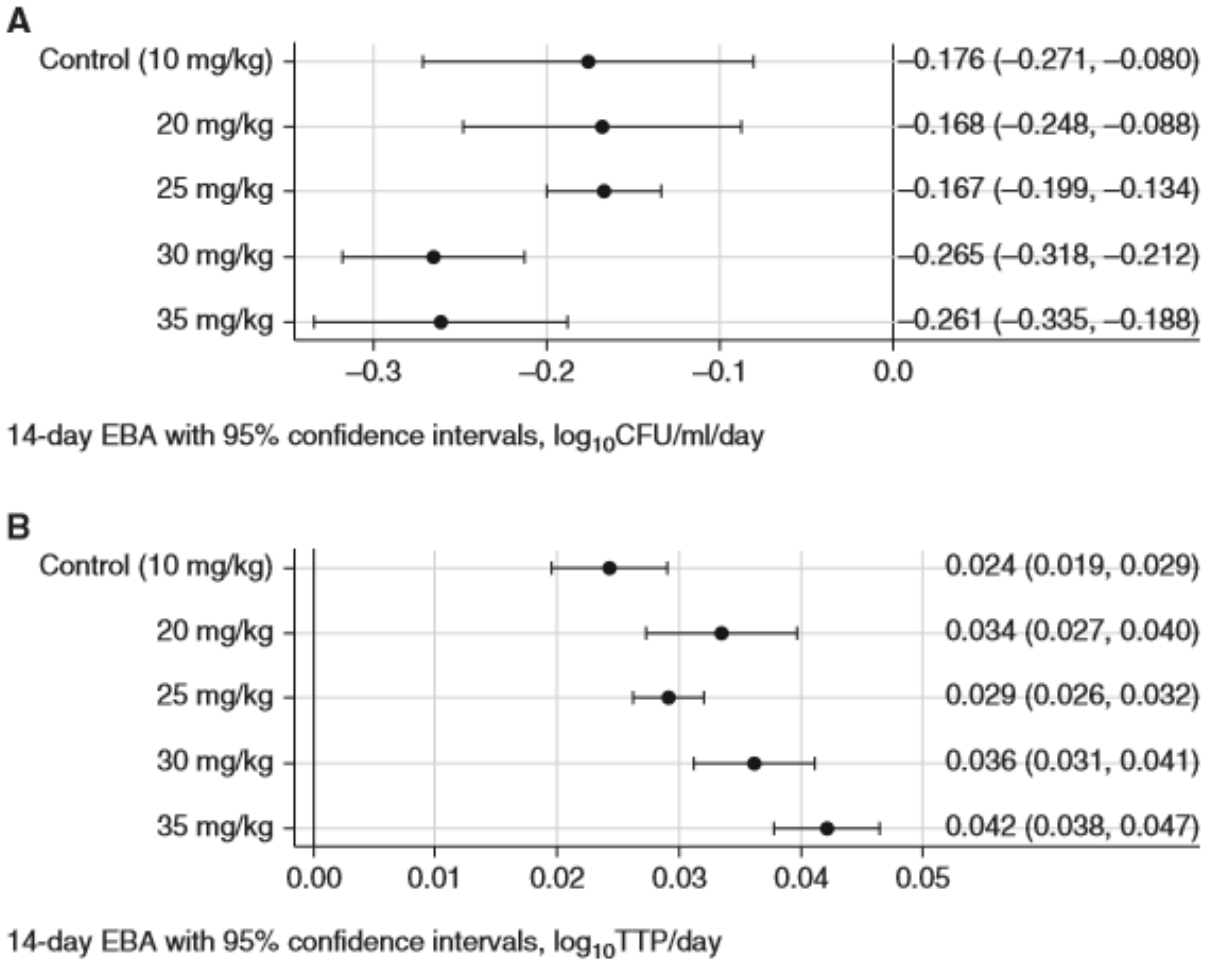


Figure 4. Early bactericidal activity (EBA) of rifampin based on CFU (*A*) and TTP (*B*) per day. CFU = colony-forming units; TTP = time to positivity.

Am J Respir Crit Care Med. 2015;191(9):1058-65

A dose-ranging trial to optimize the dose of rifampin in the treatment of tuberculosis

Conclusions

- Two weeks of rifampin up to 35 mg/kg was safe and well tolerated.
- There was a nonlinear increase in exposure to rifampin without an apparent ceiling effect and a greater estimated fall in bacterial load in the higher dosing groups.

Am J Respir Crit Care Med. 2015;191(9):1058-65

Daily rifapentine for treatment of pulmonary tuberculosis. A randomized, dose-ranging trial

Objectives

- To determine safety, tolerability and antimicrobial activity of daily rifapentine
- To determine the optimal dose of daily rifapentine during the first 8 weeks (intensive phase) of combination treatment for pulmonary TB

Am J Respir Crit Care Med. 2015;191(3):333-43

Daily rifapentine for treatment of pulmonary tuberculosis. A randomized, dose- ranging trial

Methods

- randomized, multicenter, partially blinded phase 2 trial
  - 18 sites (9 in North America, 4 in Africa, 2 in South America, 2 in Asia, 1 in Europe)
- pulmonary TB with AFB smear (+)

Am J Respir Crit Care Med. 2015;191(3):333-43

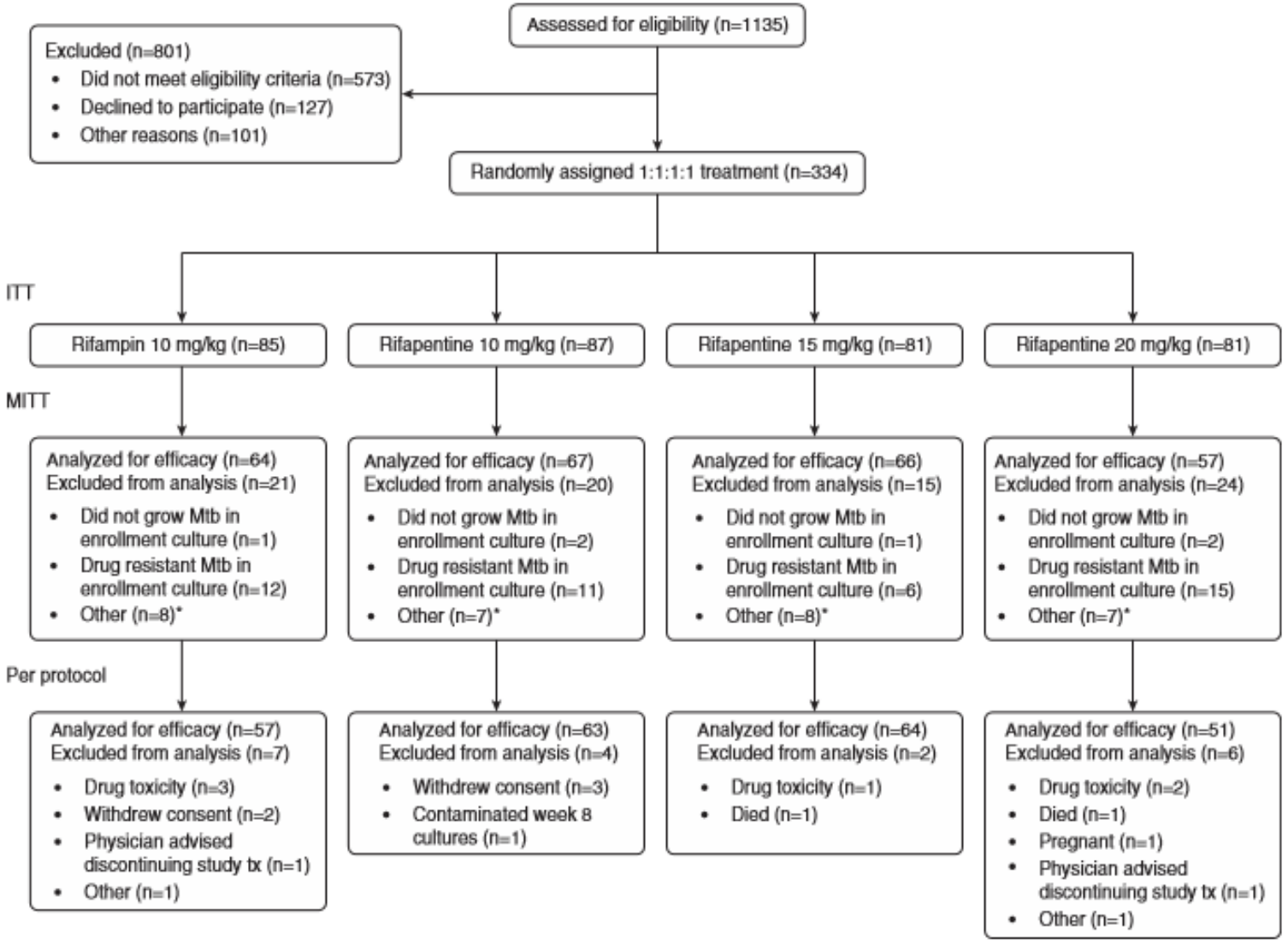


Figure 1. Enrollment and disposition of study participants. ITT = intention-to-treat; MITT = modified intention-to-treat; Mtb = *Mycobacterium tuberculosis*.

Am J Respir Crit Care Med. 2015;191(3):333-43

Table 1. Baseline Characteristics of Participants in the Intention-to-Treat Analysis Population

Characteristic	Overall (*n* = 334)	Rifampin (*n* = 85)	Rifapentine 10 mg/kg (*n* = 87)	Rifapentine 15 mg/kg (*n* = 81)	Rifapentine 20 mg/kg (*n* = 81)
Enrolled at African site, n (%)	190 (56.9)	45 (52.9)	49 (56.3)	48 (59.3)	48 (59.3)
Cavitation on chest radiograph at enrollment, n (%)	257 (77.0)	69 (81.2)	67 (77.0)	61 (75.3)	60 (74.1)
Median (range) age, yr	31 (18–78)	33 (19–78)	29 (19–66)	31 (18–69)	31 (19–70)
Male, n (%)	230 (68.9)	55 (64.7)	63 (72.4)	58 (71.6)	54 (66.7)
History of smoking cigarettes, n (%)	142 (42.5)	45 (52.9)	32 (36.8)	30 (37.0)	35 (43.2)
HIV-positive, n (%)	26 (7.8)	5 (5.9)	6 (6.9)	4 (4.9)	11 (13.6)
Median (IQR) CD4 count for HIV-positive participants, cells/μl	321 (196–429)	277 (257–400)	428 (415–434)	353 (134–474)	283 (156–414)
Median (IQR) # days of prestudy TB treatment	2 (0–3)	2 (0–4)	2 (0–4)	2 (0–3)	1 (0–3)
Median (IQR) body mass index, kg/m^2	19.4 (17.8–21.4)	19.2 (17.5–21.2)	19.1 (17.6–21.1)	19.5 (17.9–21.5)	19.7 (18.1–22.0)
Serum or plasma ALT > ULN, n (%)	35 (10.5)	9 (10.6)	7 (8.1)	11 (13.6)	8 (9.9)
High sputum smear grade, n (%)	186 (56.0)	50 (59.5)	47 (54.0)	39 (48.2)	50 (62.5)
Median (IQR) days to detection in MGIT culture	6.6 (5.0–9.0)	6.9 (5.5–8.5)	7.0 (5.1–10.5)	7.0 (4.8–9.3)	6.4 (4.7–8.6)
Rifapentine dose in mg, n (%)					
450 mg	—	—	49 (56.3)	0 (0)	0 (0)
600 mg	—	—	37 (42.5)	38 (46.9)	0 (0)
900 mg	—	—	1 (1.2)	39 (48.2)	44 (54.3)
1,200 mg	—	—	0 (0)	4 (4.9)	33 (40.7)
1,500 mg	—	—	0 (0)	0 (0)	4 (4.9)

Am J Respir Crit Care Med. 2015;191(3):333-43

Table 2. Discontinuations during the Intensive Phase of Tuberculosis Treatment, and Adverse Events within the First 70 Days after the Initial Dose of Study Drugs

	Rifampin (*n* = 85)	Rifapentine 10 mg/kg (*n* = 87)	Rifapentine 15 mg/kg (*n* = 81)	Rifapentine 20 mg/kg (*n* = 81)
Regimen permanently discontinued, n (%; upper bound of 90% one-sided CI)	11 (12.9; 19.0)	5 (5.7; 10.5)	5 (6.2; 11.3)	9 (11.1; 17.1)
Based on microbiologic findings*, n (% of group n)	4 (4.7)	2 (2.2)	3 (3.7)	3 (3.7)
Based on reasons other than microbiologic findings, n (% of group n)	7 (8.2)	3 (3.4)	2 (2.5)	6 (7.4)
Death, n	0	0	1†	1‡
Toxicity other than death, n	3§	0	1‖	2¶
Withdrawal of consent, n	2	3	0	0
Other, n	2	0	0	3
Any SAE, n (%)	3 (3.5)	3 (3.4)	3 (3.7)	8 (9.9)
SAE attributed to study treatment, n	2**	1††	0	1‡‡
SAE not attributed to study treatment, n	1§§	2‖‖	3¶¶	7***
Any adverse event, n (%)	20 (23.5)	29 (33.3)	25 (30.9)	26 (32.1)
Hepatitis, n	2	1	3	2
Absolute neutrophil count < 1,000 cells/mm^3, n	2	2	1	3
Pruritis and/or rash, n	3	1	1	1

Am J Respir Crit Care Med. 2015;191(3):333-43

Table 3. Percentages of Participants with Negative Cultures at Completion of Intensive Phase Treatment, by Treatment Assignment, for the Modified Intention-to-Treat Analysis Group

	Rifampin	Rifapentine 10 mg/kg	Rifapentine 15 mg/kg	Rifapentine 20 mg/kg
Solid culture medium				
% (n/n) with negative cultures	81.3 (52/64)	92.5 (62/67)	89.4 (59/66)	94.7 (54/57)
% difference vs. rifampin (95% CI)		11.3 (−1.7 to 24.3)	8.1 (−5.5 to 21.8)	13.5 (0.6 to 26.3)
P value		0.097	0.29	0.049
Liquid culture medium				
% (n/n) with negative cultures	56.3 (36/64)	74.6 (50/67)	69.7 (46/66)	82.5 (47/57)
% difference vs. rifampin (95% CI)		18.4 (0.8 to 35.9)	13.4 (−4.5 to 31.4)	26.2 (8.9 to 43.5)
P value		0.042	0.16	0.004

Am J Respir Crit Care Med. 2015;191(3):333-43

Daily rifapentine for treatment of pulmonary tuberculosis. A randomized, dose- ranging trial

Conclusions

- Daily rifapentine was well-tolerated and safe.
- High rifapentine exposures were associated with high levels of sputum sterilization at completion of intensive phase.

Am J Respir Crit Care Med. 2015;191(3):333-43

Bedaquiline in the treatment of multidrug- and extensively drug-resistant tuberculosis

Objectives

- To evaluate the safety, tolerability and efficacy of bedaquiline for the treatment of patients with drug-resistant-TB, including pre-XDR and XDR-TB

Eur Respir J. 2016;47(2):564-74

Bedaquiline in the treatment of multidrug- and extensively drug-resistant tuberculosis

Methods

- multicenter, open-label, single-arm, phase 2 trial
- 31 sites in 11 countries
  - Asia (China, South Korea, Philippines, Thailand), Eastern Europe (Estonia, Latvia, Russia, Turkey, Ukraine), Peru and South Africa
- .Participants
  - age ⩾18 years with pulmonary MDR-TB
  - 400 mg bedaquiline once daily for 2 weeks -> 200 mg 3 times a week for a further 22 weeks in combination with a BR of drugs
  - After bedaquiline treatment, participants were followed for a further 96 weeks during which BR was completed

Eur Respir J. 2016;47(2):564-74

TABLE 1 Baseline patient demographic and clinical characteristics

	Safety (ITT) population N=233	Efficacy (mITT) population N=205
Male	150 (64.4)	132 (64.4)
Age years	32 (18–68)	32 (18–68)
Race		
American Indian[#]	8 (3.4)	6 (2.9)
Asian	89 (38.2)	84 (41.0)
Black or African American	75 (32.2)	67 (32.7)
White	61 (26.2)	48 (23.4)
Bodyweight kg	57 (30–113)	57 (30–113)
Body mass index kg·m^{-2}	19.9 (13–37)	19.8 (13–37)
Lung cavitations		
None or <2 cm	85 (36.5)	70 (34.1)
Cavitations ⩾2 cm in one lung only	120 (51.5)	108 (52.7)
Cavitations ⩾2 cm in both lungs	28 (12.0)	27 (13.2)
Extent of resistance of *M. tuberculosis* strain		
Drug-susceptible TB	3 (1.3)	0
MDR-TB[¶]	148 (63.5)	124 (60.5)
Pre-XDR-TB	44 (18.9)	44 (21.5)
Pre-XDR-TB fluoroquinolone resistant	31 (13.3)	31 (15.1)
Pre-XDR-TB injectable resistant	13 (5.6)	13 (6.3)
XDR-TB	38 (16.3)	37 (18.0)
Previous TB medications		
No previous anti-TB treatment	12 (5.2)	12 (5.9)
Previous use of second-line TB drugs	203 (87.1)	177 (86.3)
Previous treatment with		
Aminoglycosides	156 (67.0)	139 (67.8)
Fluoroquinolones	193 (82.8)	167 (81.5)
Macrolides	33 (14.2)	33 (16.1)

espir J. 2016;47(2):564-74

TABLE 3 Incidence of treatment-emergent adverse events (AEs) and grade ⩾3 laboratory abnormalities (safety (intent-to-treat) population)

AE category	24 weeks of bedaquiline treatment N=233	Overall 120 weeks of treatment N=233
Any AE	212 (91.0)	219 (94.0)
Any serious AE	15 (6.4)	47 (20.2)
Any AE related to TB	47 (20.2)	77 (33.0)
Any grade 4 AE	5 (2.1)	24 (10.3)
Any AE possibly related to bedaquiline	77 (33.0)	77 (33.0)
Any serious AE possibly related to bedaquiline	1 (0.4)	1 (0.4)
Any AE leading to bedaquiline discontinuation	6 (2.6)[#]	6 (2.6)[#]
Any AE leading to background regimen discontinuation	49 (21.0)	73 (31.3)
AEs regardless of causality with >10% incidence		
Hyperuricaemia	49 (21.0)	56 (24.0)
Nausea	27 (11.6)	35 (15.0)
Arthralgia	29 (12.4)	35 (15.0)
Headache	21 (9.0)	31 (13.3)
Diarrhoea	18 (7.7)	27 (11.6)
Vomiting	21 (9.0)	27 (11.6)
AEs of special interest[¶]		
Hepatic disorders	27 (11.6)	42 (18.0)
Increased AST	9 (3.9)	14 (6.0)
Increased ALT	5 (2.1)	12 (5.2)
QT prolongation[+]	6 (2.6)	10 (4.3)
Severe cutaneous AEs	8 (3.4)	9 (3.9)[§]
Acute pancreatitis[f]	3 (1.3)	7 (3.0)
Laboratory abnormalities grade ⩾3 with >3% incidence during 120 weeks[##]	**N=229**	**N=230**

spir J. 2016;47(2):564-74

TABLE 4 Summary of deaths (safety (intent-to-treat) population)

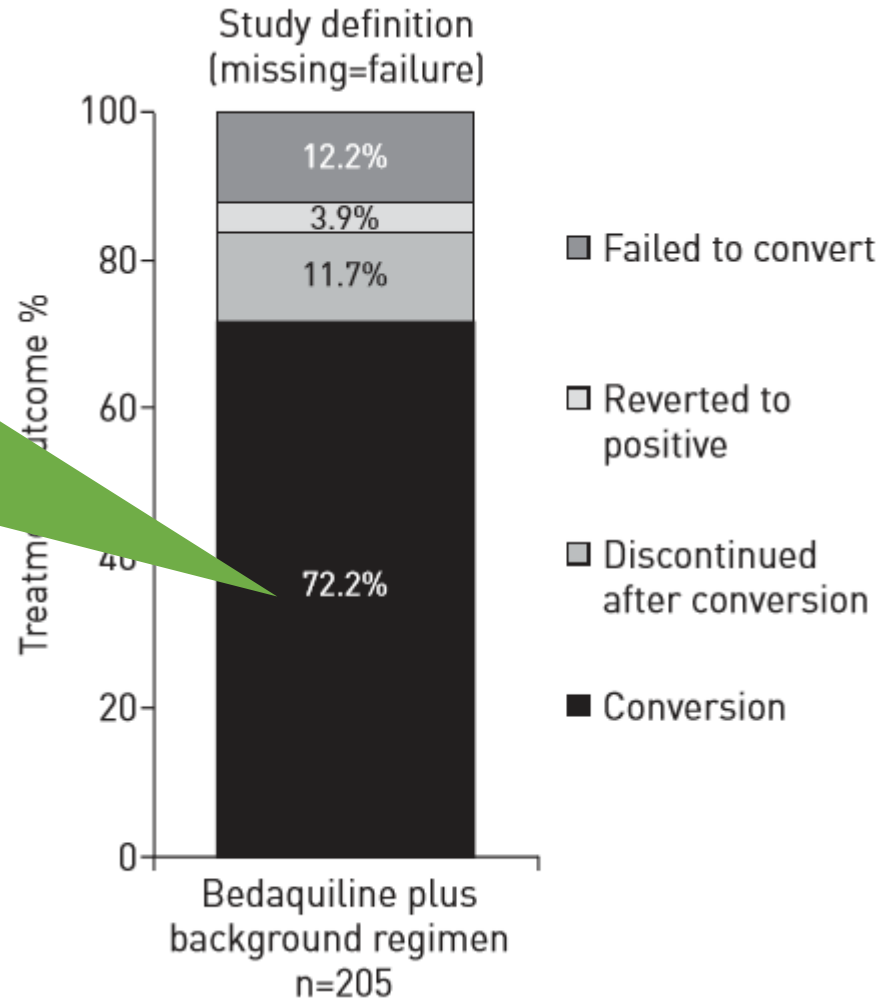
	While on 120-week study N=233	During survival follow-up of premature discontinuations N=20
Deaths n[#]	12	4
Microbiology response	7 nonconverters; 4 converters; 1 reverted to positive[¶]	3 nonconverters; 0 converters; 1 reverted to positive[¶]
Investigator-reported causes of death	TB-related illness (n=5); haemoptysis (n=1); renal impairment (n=1); lung infection (n=1); pneumonia (n=1); respiratory failure (n=1); congestive cardiac failure (n=1); hypertension (n=1)	TB-related illness (n=4)
Completed 24 weeks of bedaquiline treatment n with full exposure/n total deaths	9/12	1/4
Median time since last bedaquiline intake days	376	211
Investigator causality (related to bedaquiline) n/n total deaths	12/12 not related[+], including 1 doubtfully related (renal impairment)	4/4 not related[+] including 1 doubtfully related (TB-related illness)

Eur Respir J. 2016;47(2):564-74

MDR TB
: 73.1% (95% CI 62.9–81.8%)

pre-XDR TB
: 70.5% (95% CI 54.8–83.3%)

XDR TB
: 62.2% (95% CI 44.8–77.6%)



Eur Respir J. 2016;47(2):564-74

Bedaquiline in the treatment of multidrug- and extensively drug-resistant tuberculosis

Conclusions

- Bedaquiline was well tolerated and led to good outcomes in patients with MDR-TB.

Eur Respir J. 2016;47(2):564-74

Efficacy, safety and tolerability of linezolid for the treatment of XDR-TB: a study in China

Objectives

- To evaluate the efficacy, safety and tolerability of linezolid in patients with XDR-TB

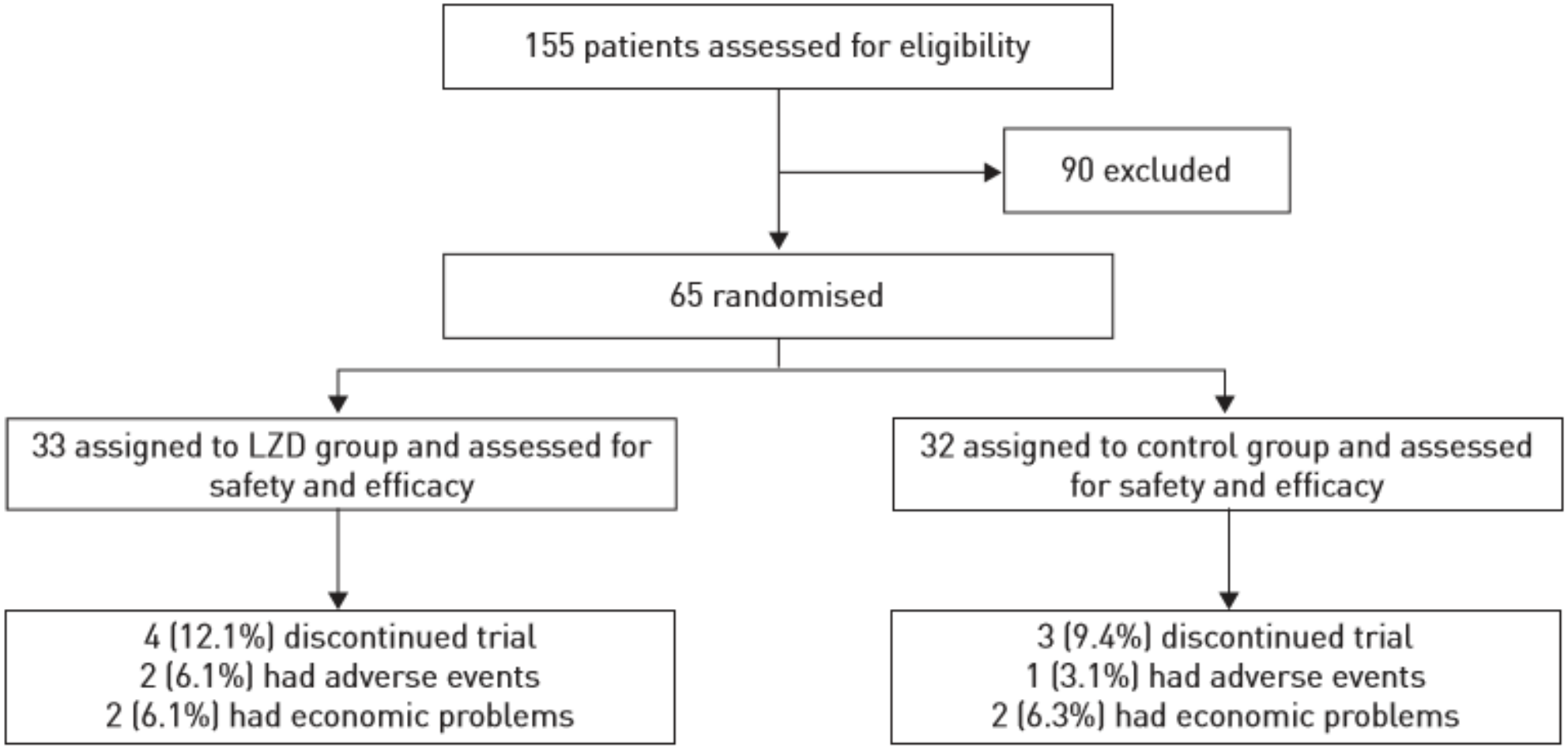
Eur Respir J. 2015;45(1):161-70

Efficacy, safety and tolerability of linezolid for the treatment of XDR-TB: a study in China

Methods

- prospective, multicenter, randomized study in China
- participants
  - age between 18 and 64 years with pulmonary XDR-TB
  - smear (+) after using available chemotherapeutic options during the previous ⩾12 months
  - 1200 mg linezolid per day for 4-6 weeks -> 300-600 mg per day until the patients provided two consecutive negative sputum cultures during a 2-month period
  - 2 years of individually based chemotherapy regimens based on medication history and drug susceptibility tests (DST)

Eur Respir J. 2015;45(1):161-70



Eur Respir J. 2015;45(1):161-70

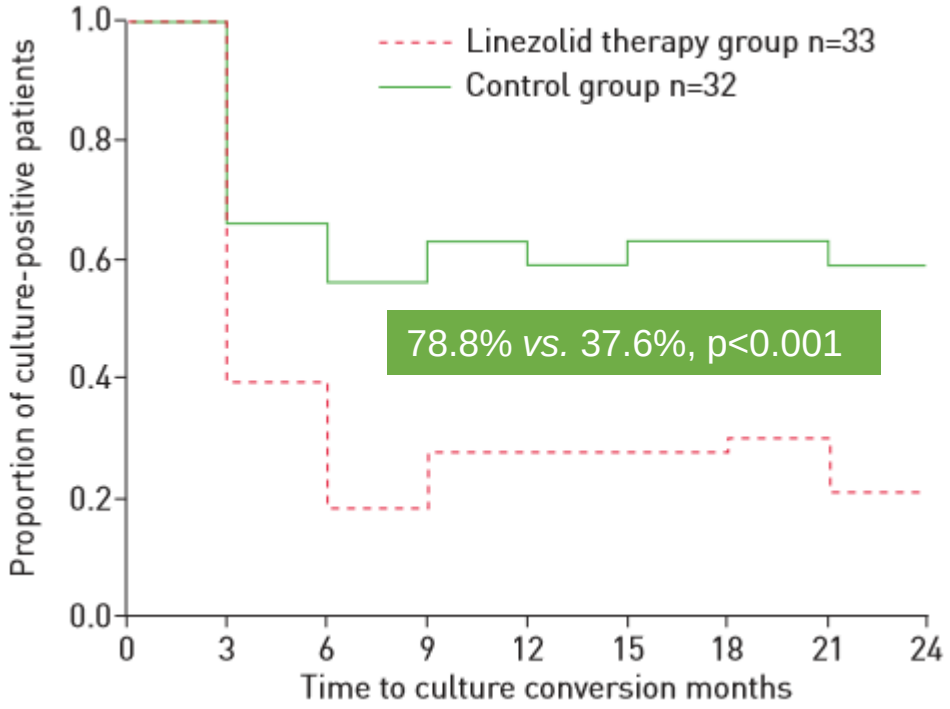


FIGURE 2 The proportion of patients with a positive sputum culture and the time taken for conversion to a negative culture in sputum.

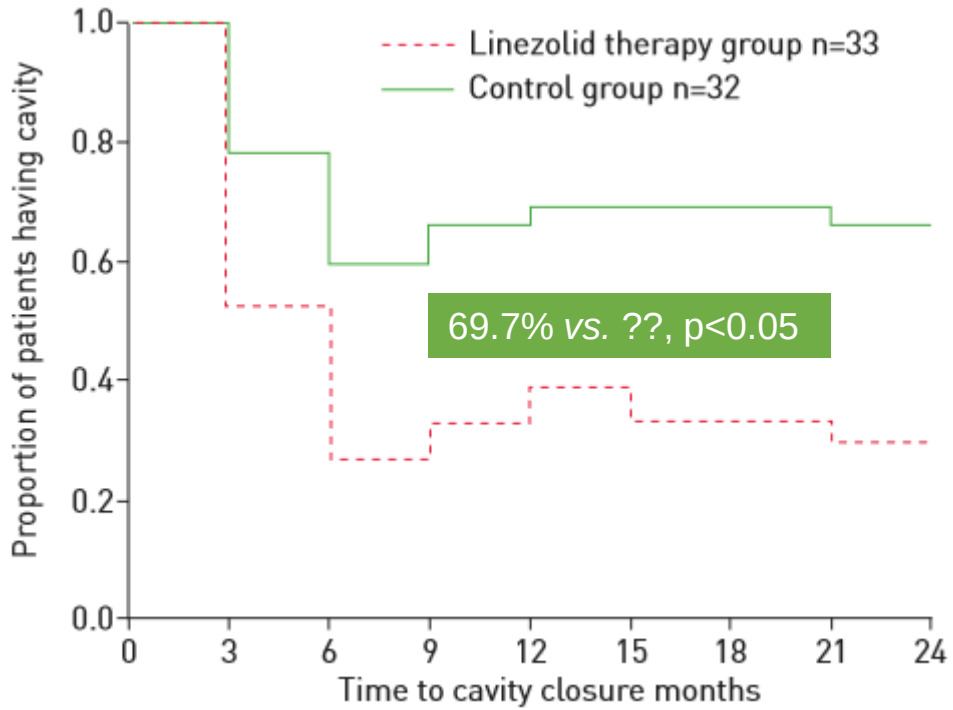


FIGURE 3 The proportion of patients having a cavity and the time to cavity closure.

Eur Respir J. 2015;45(1):161-70

TABLE 2 Treatment outcomes for the linezolid therapy group and the control group

Treatment outcomes	Linezolid group	Control group	Chi-squared	p-value
Patients n	33	32		
Treatment success	23 (69.7)	11 (34.4)	8.125	0.004
Cure	17 (51.5)	7 (21.9)	6.128	0.013
Treatment completion	6 (18.2)	4 (12.5)	0.403	0.526
Poor treatment outcomes	10 (30.3)	21 (65.6)	8.125	0.004
Death	2 (6.1)	3 (9.4)	0.247	0.619
Failure	4 (12.1)	15 (46.9)	9.486	0.002
Default	4 (12.1)	3 (9.1)	0.126	0.723

Eur Respir J. 2015;45(1):161-70

TABLE 3 Adverse events of the linezolid therapy group and the control group

	Linezolid group	Control group	Chi-squared	p-value
Patients n	33	32		
Anaemia	17 (51.5)	2 (6.3)	16.091	0.000
Thrombocytopenia	4 (12.1)	1 (3.1)	0.801	0.371
Leukopenia	5 (15.2)	2 (6.3)	0.573	0.449
Nausea/vomiting	16 (48.5)	3 (9.4)	12.013	0.001
Peripheral neuropathy	8 (24.2)	1 (3.1)	4.432	0.035
Optic neuropathy	6 (18.2)	0 (0)	4.424	0.035
Liver injury	6 (18.2)	7 (21.9)	0.138	0.710
Tinnitus or hearing loss	4 (12.1)	5 (15.6)	0.167	0.683
Rash or pruritus	3 (9.1)	3 (9.4)	0.002	0.968
Arrhythmia	3 (9.1)	2 (6.3)	0.185	0.667
Hypokalaemia	2 (6.1)	2 (6.3)	0.000	1

Eur Respir J. 2015;45(1):161-70

Efficacy, safety and tolerability of linezolid for the treatment of XDR-TB: a study in China

Conclusions

- Linezolid may significantly promote cavity closure, increase sputum culture-conversion rate and improve treatment success rate in patients with XDR-TB .

Eur Respir J. 2015;45(1):161-70

Clofazimine for the treatment of multidrug-resistant tuberculosis: prospective, multicenter, randomized controlled study in China

Objectives

- To evaluate the clinical efficacy and tolerability of Cfz in treating patients with MDR-TB

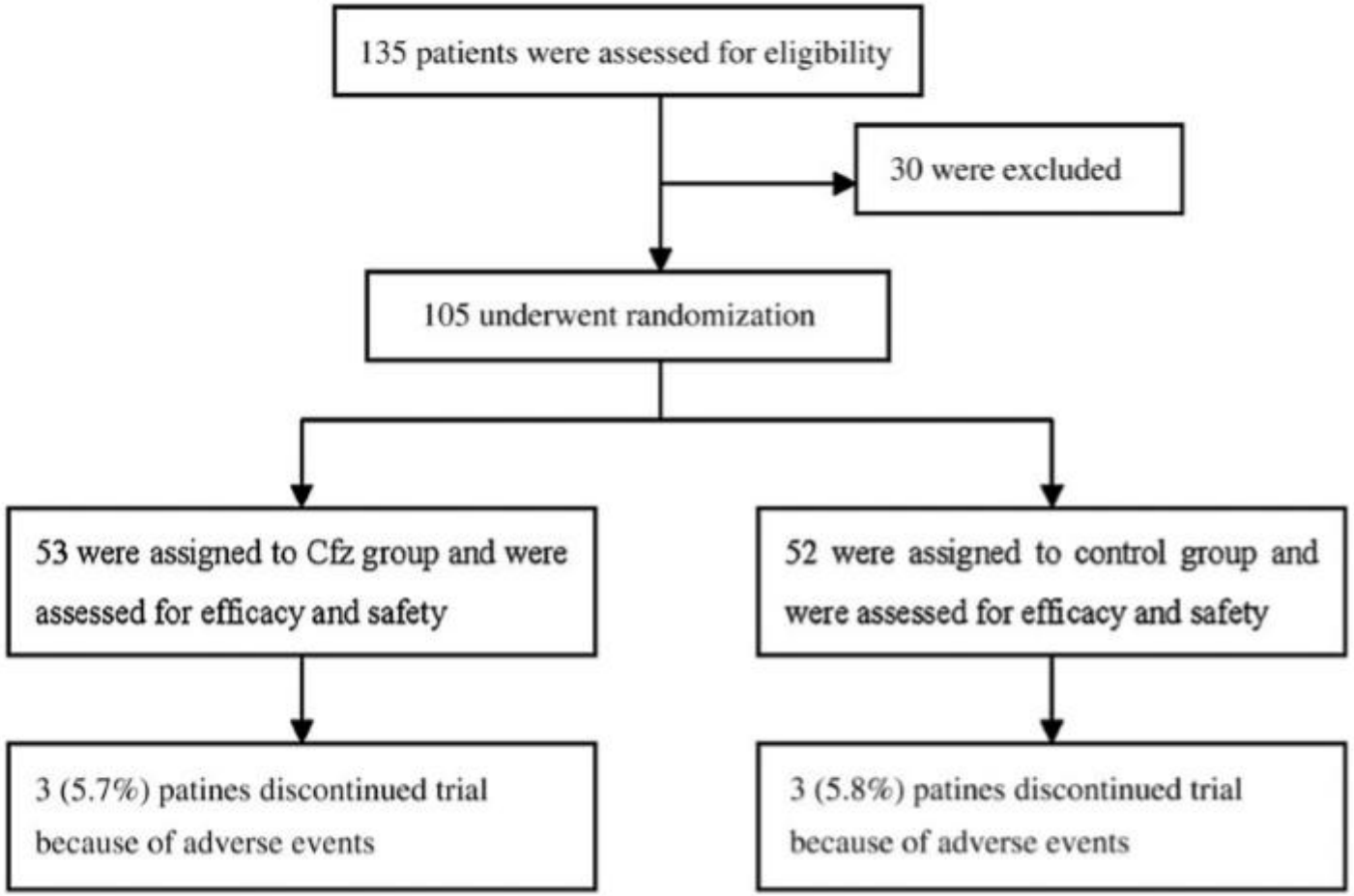
Clin Infect Dis. 2015;60(9):1361-7

Clofazimine for the treatment of multidrug-resistant tuberculosis: prospective, multicenter, randomized controlled study in China

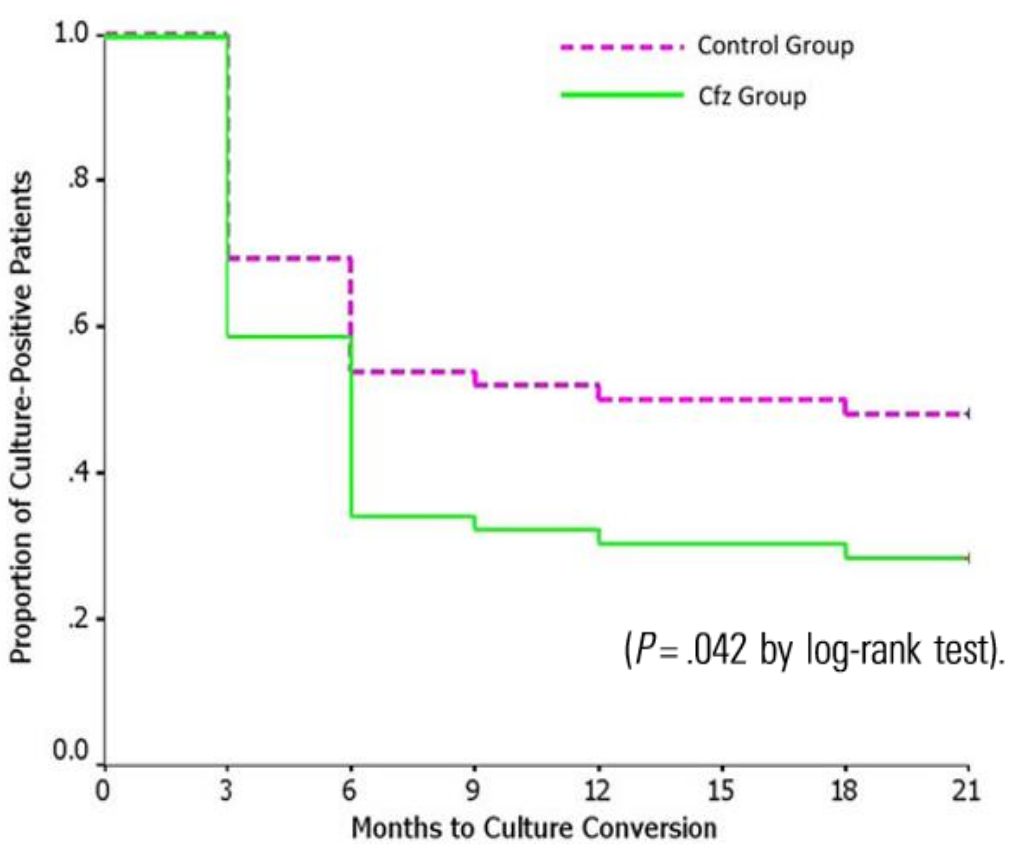
Methods

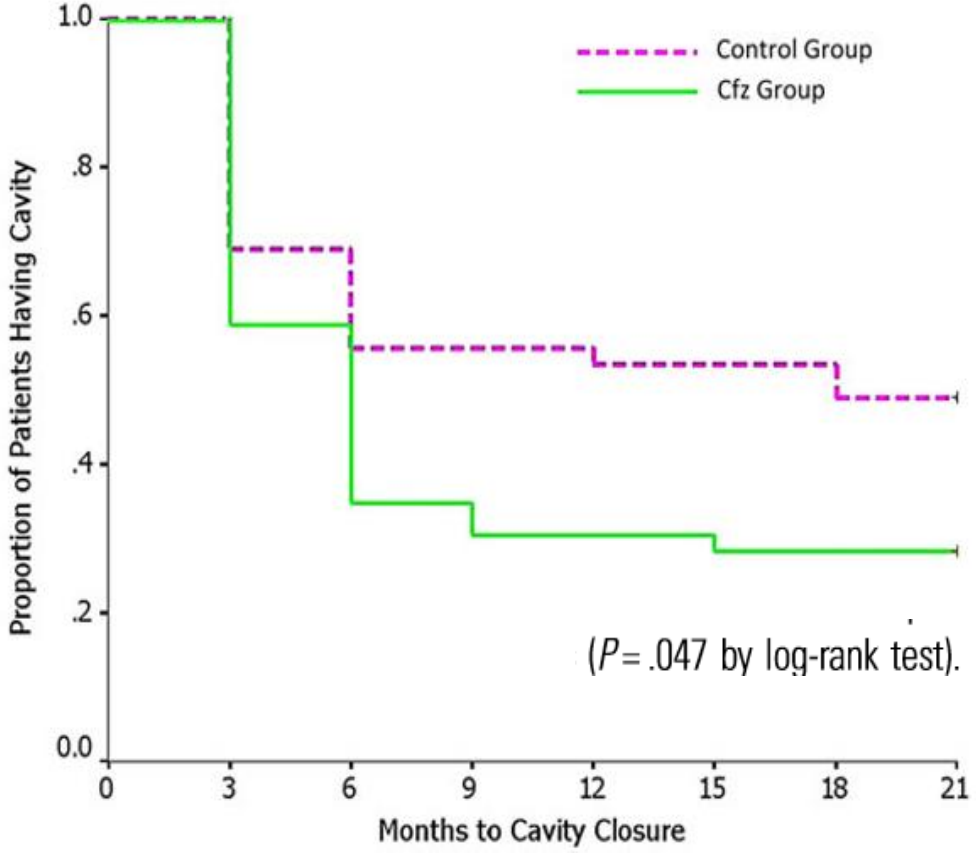
- prospective, multicenter, randomized study in China
- participants
  - age between 18 and 64 years with pulmonary MDR-TB
  - unsatisfactory response to available chemotherapeutic option during the previous ≥6 months
  - 100 mg clofazimine per day for 21 months
  - 21 months of individually based chemotherapy regimens based on medication history and drug susceptibility tests (DST)

Clin Infect Dis. 2015;60(9):1361-7



Clin Infect Dis. 2015;60(9):1361-7





Clin Infect Dis. 2015;60(9):1361-7

Table 2. Treatment Outcomes

Treatment Outcomes	Cfz Group (n = 53), No. (%)	Control Group (n = 52), No. (%)	*P* Value
Treatment success	39 (73.6)	28 (53.8)	.04
Cure	27 (50.9)	20 (38.5)	.20
Treatment completion	12 (22.6)	8 (15.4)	.34
Poor treatment outcomes	14 (26.4)	24 (46.2)	.04
Death	4 (7.5)	4 (7.7)	1
Failure	6 (11.3)	15 (28.8)	.03
Default	4 (7.5)	5 (9.6)	.74

Clin Infect Dis. 2015;60(9):1361-7

Table 3. Adverse Events

Adverse Events	Cfz Group (n = 53), No. (%)	Control Group (n = 52), No. (%)	*P* Value
Anemia	1 (1.9)	1 (1.9)	1
Thrombocytopenia	2 (3.8)	2 (3.8)	1
Leukopenia	4 (7.5)	5 (9.6)	1
Nausea/vomiting	6 (11.3)	5 (9.6)	1
Peripheral neuropathy	2 (3.8)	1 (1.9)	1
Optic neuropathy	1 (1.9)	1 (1.9)	1
Liver injury	6 (11.3)	5 (9.6)	1
Tinnitus or hearing loss	2 (3.8)	3 (5.8)	.68
Rash or pruritus	2 (3.8)	2 (3.8)	1
Arrhythmia	3 (5.7)	3 (5.8)	1
Hypokalemia	3 (5.7)	4 (7.7)	.72
Pink to brownish-black discoloration of skin	50 (94.3)	0 (0)	0
Ichthyosis	25 (47.2)	0 (0)	0

Clin Infect Dis. 2015;60(9):1361-7

Clofazimine for the treatment of multidrug-resistant tuberculosis: prospective, multicenter, randomized controlled study in China

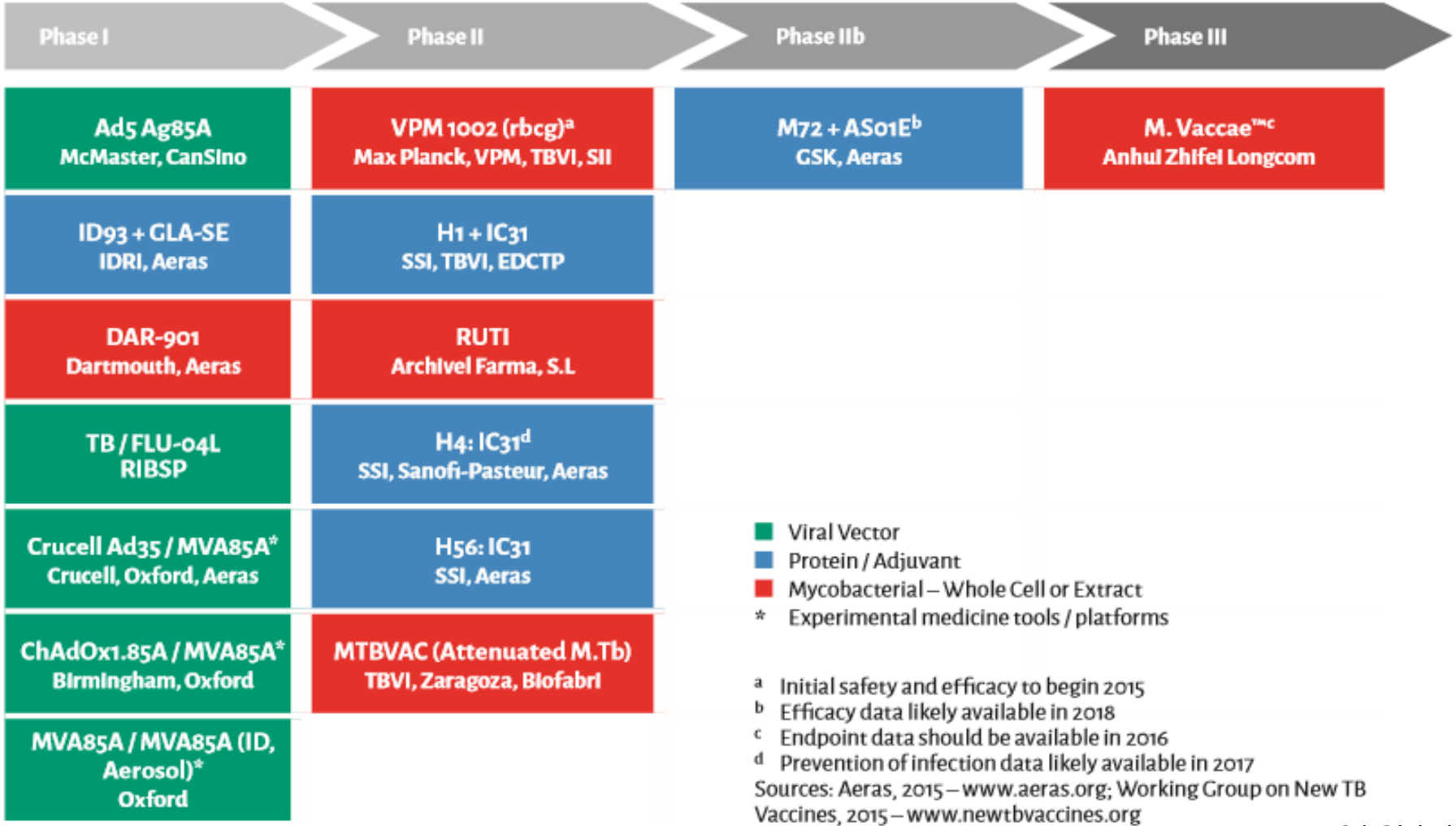
Conclusions

- Using clofazimine to treat MDR tuberculosis promotes cavity closure, accelerates sputum culture conversion, and improves treatment success rates.

Clin Infect Dis. 2015;60(9):1361-7

Contents

The development pipeline for new TB vaccines, August 2015



WHO | Global tuberculosis report 2015

Duration of BCG protection against tuberculosis and change in effectiveness with time since vaccination in Norway: a retrospective population-based cohort study

Objectives

- To assesse the long-term vaccine effectiveness of BCG

Lancet Infect Dis. 2016;16(2):219-26

Duration of BCG protection against tuberculosis and change in effectiveness with time since vaccination in Norway: a retrospective population-based cohort study

Methods

- retrospective population-based cohort study
- the tuberculosis screening and BCG vaccination programme in Norway
- participants
  - age between 12 and 50
  - preserved information of TST and BCG status (between 1962 and1975)

Lancet Infect Dis. 2016;16(2):219-26

Table 1: Baseline characteristics	Vaccinated (n=297 905)	Unvaccinated (n=83 421)
Sex		
Female	163 634 (55%)	54 340 (65%)
Male	134 271 (45%)	29 081 (35%)
Age at entry (years)		
12–15	145 366 (49%)	3171 (4%)
16–20	67 990 (23%)	6251 (7%)
21–30	29 989 (10%)	5943 (7%)
31–40	27 217 (9%)	21 315 (26%)
≥41	27 343 (9%)	46 741 (56%)
Birth cohort (year of birth)		
1910–19	5026 (2%)	38 771 (46%)
1920–29	30 566 (10%)	26 813 (32%)
1930–39	25 371 (9%)	7272 (9%)
1940–49	67 809 (23%)	5930 (7%)
≥1950	169 133 (57%)	4635 (6%)
Marital status		
Married	78 321 (26%)	63 932 (77%)
Single or other	216 162 (73%)	18 455 (22%)
Missing	3422 (1%)	1034 (1%)

ect Dis. 2016;16(2):219-26

Missing	421 (<1%)	169 (<1%)
Occupation of head of household		
Manufacture, construction, or mining and blasting	119232 (40%)	34571 (41%)
Technical, scientific, or humanities and arts	24814 (8%)	4653 (6%)
Administration and management, sales, or services	38234 (13%)	11475 (14%)
Agriculture, forestry, or fishing	54497 (18%)	17025 (20%)
Trade, transport, or communication	49356 (17%)	13178 (16%)
Military, other	10136 (3%)	1438 (2%)
Missing	1636 (1%)	1081 (1%)
5 year average annual tuberculosis notification rate for 1961–65 per 100 000 person-years		
<20	127961 (43%)	41976 (50%)
20–25	78637 (26%)	17310 (21%)
≥26	91300 (31%)	24135 (29%)
Missing	7 (<1%)	0
Follow-up		
Median (years)	44 (41–46)	41 (32–49)
Total (person-years)	12425273	3131918
Number of first tuberculosis episodes (rate per 100 000 person-years)		
All tuberculosis	157 (1·3)	103 (3·3)
Pulmonary tuberculosis	121 (1·0)	78 (2·5)

Lancet Infect Dis. 2016;16(2):219-26

	Number of tuberculosis cases/ person-years	Crude rate (per 100 000 person-years)	Crude HR*	Crude VE*	p value	Adjusted HR†	Adjusted VE (%)†	p value
Overall								
Unvaccinated	103/3 131 917	3·3 (2·7 to 4·0)	..	..	..	..	..	..
Vaccinated	157/12 425 272	1·3 (1·1 to 1·5)	0·36 (0·27 to 0·48)	64% (52 to 73)	<0·0001	0·51 (0·35 to 0·74)	49% (26 to 65)	<0·0001
0–9 years (including tuberculosis events in first 2 years after screening)								
Unvaccinated	29/812 004	3·6 (2·5 to 5·1)	..	..	..	..	..	..
Vaccinated	46/2 920 797	1·6 (1·2 to 2·1)	0·45 (0·25 to 0·80)	55% (20 to 75)	0·006	0·49 (0·26 to 0·93)	51% (7 to 74)	0·03
0–9 years (excluding tuberculosis events in first 2 years after screening)								
Unvaccinated	27/812 000	3·3 (2·3 to 4·8)	..	..	..	..	..	..
Vaccinated	36/2 920 781	1·2 (0·9 to 1·7)	0·41 (0·23 to 0·76)	59% (24 to 77)	0·005	0·39 (0·20 to 0·76)	61% (24 to 80)	0·006
10–19 years								
Unvaccinated	44/784 840	5·6 (4·2 to 7·5)	..	..	..	..	..	..
Vaccinated	45/2 874 574	1·6 (1·2 to 2·1)	0·35 (0·21 to 0·58)	65% (42 to 79)	<0·0001	0·42 (0·24 to 0·73)	58% (27 to 76)	0·002
20–29 years								
Unvaccinated	15/704 774	2·1 (1·3 to 3·5)	..	..	..	..	..	..
Vaccinated	29/2 794 374	1·0 (0·7 to 1·5)	0·72 (0·36 to 1·43)	28% (–43 to 64)	0·35	0·62 (0·29 to 1·32)	38% (–32 to 71)	0·22
30–40 years								
Unvaccinated	15/830 300	1·8 (1·1 to 3·0)	..	..	..	..	..	..
Vaccinated	37/3 835 528	1·0 (0·7 to 1·3)	0·72 (0·35 to 1·46)	28% (to 46 to 65)	0·36	0·58 (0·27 to 1·24)	42% (–24 to 73)	0·16

Data in parentheses are 95% CIs. HR=hazard ratio. VE=vaccine effectiveness. *Adjusted for present age (years; Cox model fitted on age timescale). †Fully adjusted for present age, time, and baseline characteristics (test for log-linear trend in HRs by timeband p=0·015).

Table 2: **BCG vaccine effectiveness against all tuberculosis**

Lancet Infect Dis. 2016;16(2):219-26

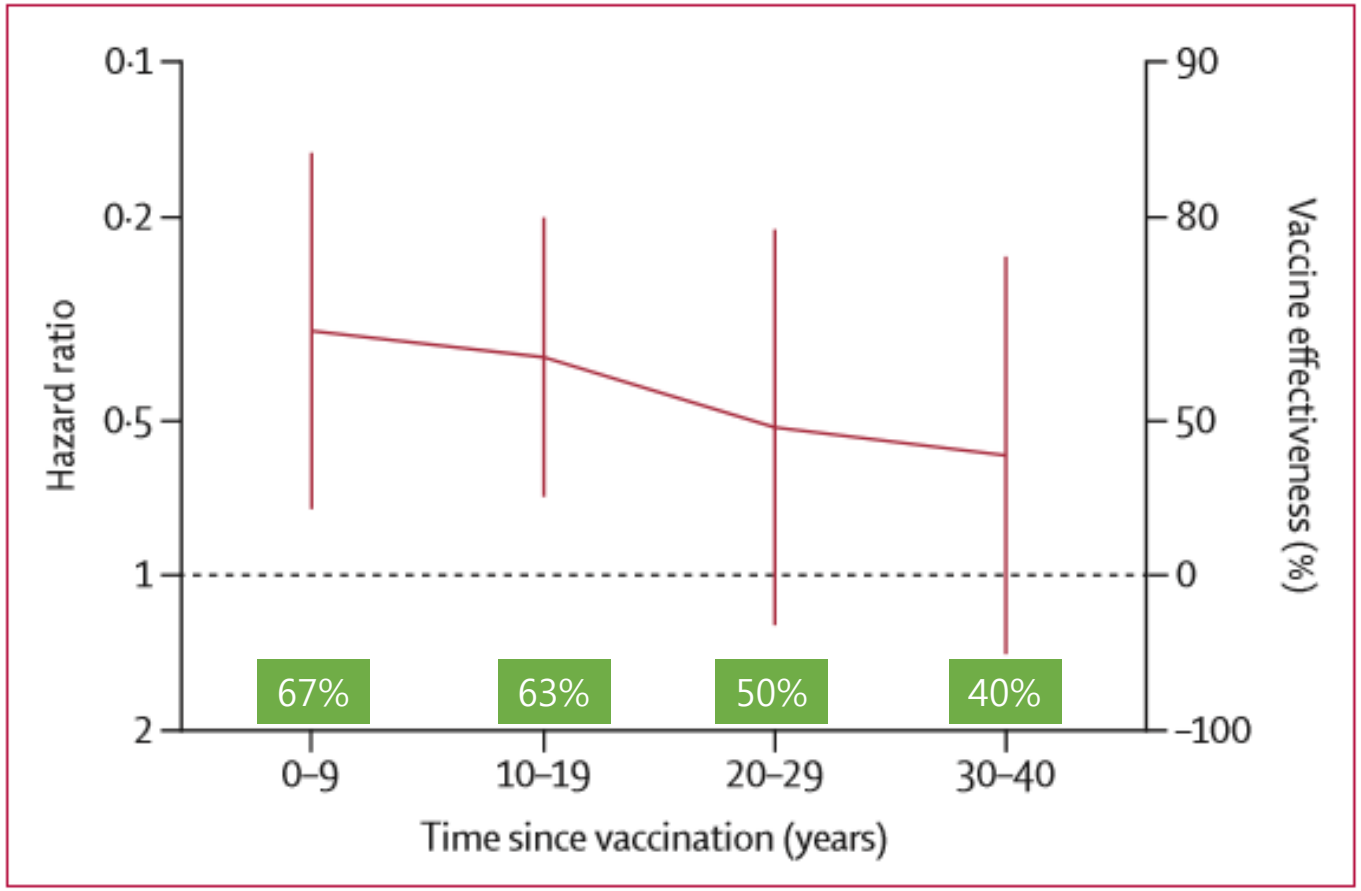


Figure 2: **BCG vaccine effectiveness against pulmonary tuberculosis by time since vaccination**

Lancet Infect Dis. 2016;16(2):219-26

Duration of BCG protection against tuberculosis and change in effectiveness with time since vaccination in Norway: a retrospective population-based cohort study

Conclusions

- long-lasting BCG protection, but waning of VE with time

Lancet Infect Dis. 2016;16(2):219-26

Safety of human immunisation with a live-attenuated Mycobacterium tuberculosis vaccine: a randomised, double-blind, controlled phase I trial

MTBVAC

- new live tuberculosis vaccine based on genetically attenuated *M. tuberculosis*

Objectives

- To compare the safety of MTBVAC with BCG in healthy adult volunteers

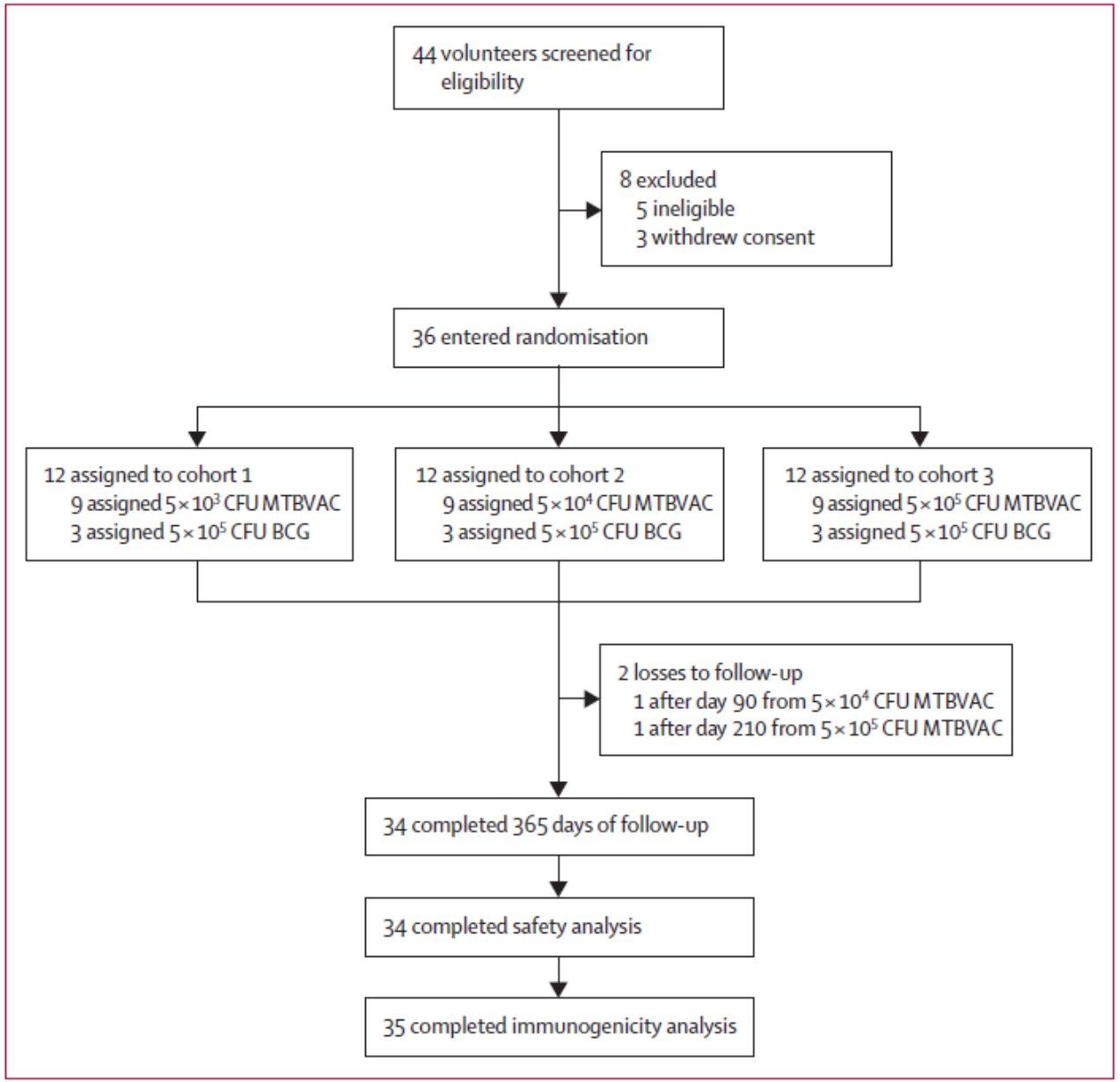
Lancet Respir Med. 2015;3(12):953-62

Safety of human immunisation with a live-attenuated Mycobacterium tuberculosis vaccine: a randomised, double-blind, controlled phase I trial

Methods

- single-center, randomized, double-blind, controlled phase 1 study
- at the Centre Hospitalier Universitaire Vaudois (CHUV; Lausanne, Switzerland)
- Volunteers
  - age 18-45 years, clinically healthy, HIV-negative and tuberculosis-negative, and had no history of active tuberculosis, chemoprophylaxis for tuberculosis, or BCG vaccination
  - randomly assigned to three cohorts in a dose-escalation manner

Lancet Respir Med. 2015;3(12):953-62



Lancet Respir Med. 2015;3(12):953-62

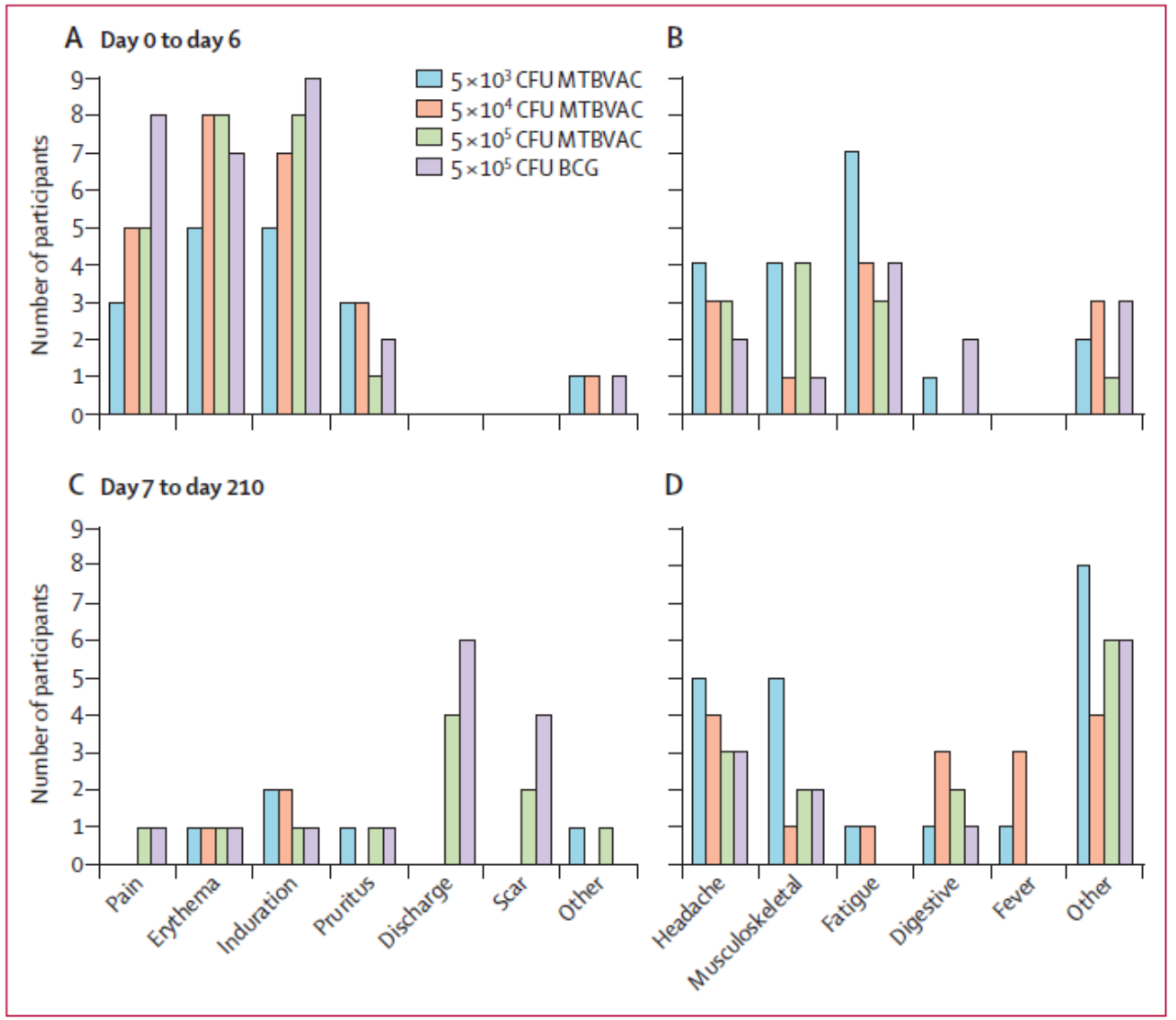


Figure 2: Adverse events

Lancet Respir Med. 2015;3(12):953-62

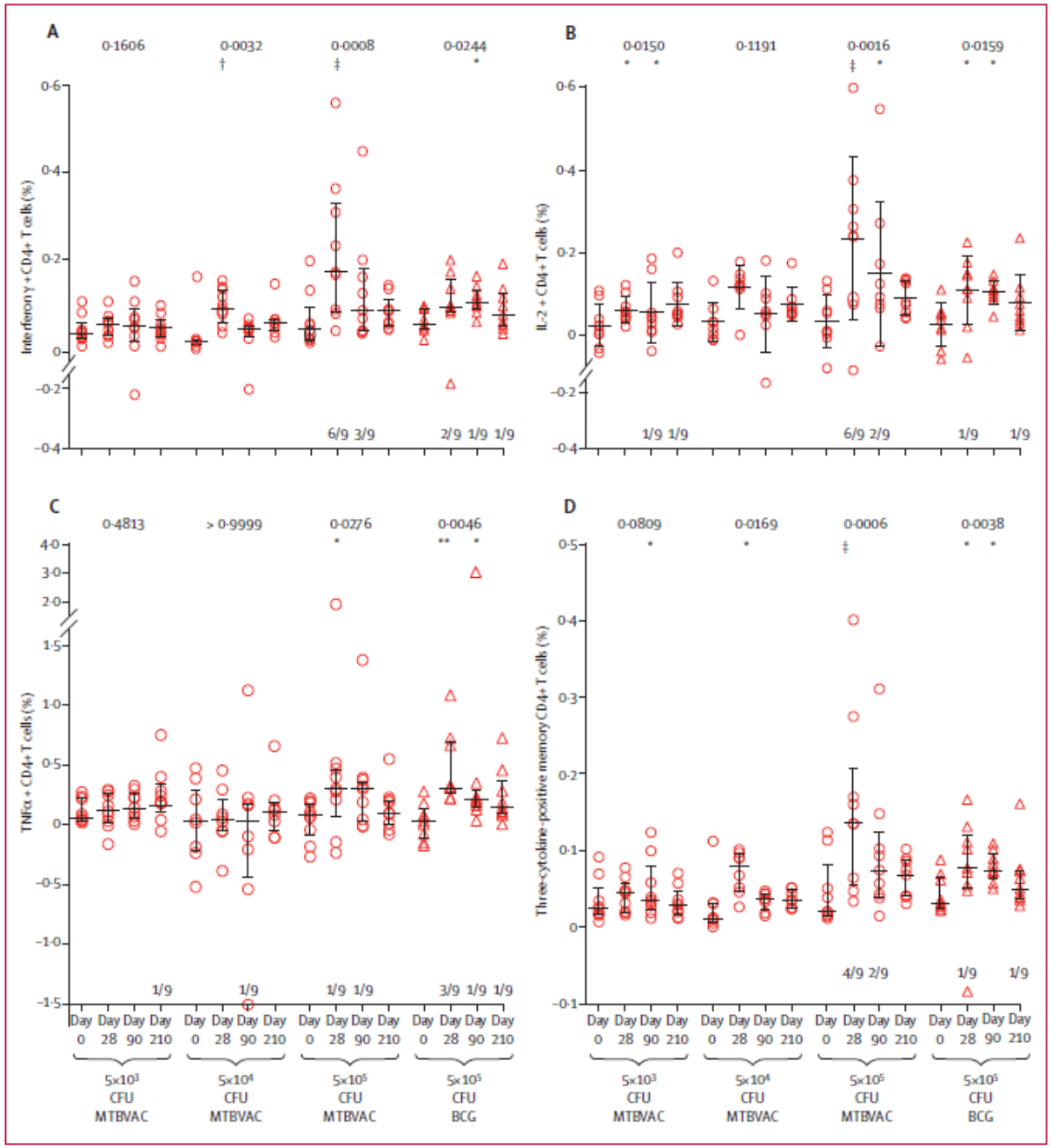


Figure 4: Intracellular cytokine staining of MTBVAC-specific CD4+ responses in whole blood assay

Lancet Respir Med. 2015;3(12):953-62

Safety of human immunisation with a live-attenuated Mycobacterium tuberculosis vaccine: a randomised, double-blind, controlled phase I trial

Conclusions

- MTBVAC is the first live-attenuated *M tuberculosis* vaccine to reach clinical assessment, showing similar safety to BCG
- MTBVAC seemed to be at least as immunogenic as BCG

Lancet Respir Med. 2015;3(12):953-62

Contents

Risk Assessment of Tuberculosis in Contacts by IFN-γ Release Assays. A Tuberculosis Network European Trials Group Study

Objectives

- To analyze IGRA results and the effect of preventive chemotherapy on TB progression rates among recent contacts

Am J Respir Crit Care Med. 2015;191(10):1176-84

Risk Assessment of Tuberculosis in Contacts by IFN-γ Release Assays. A Tuberculosis Network European Trials Group Study

Methods

- prospective study
- 26 centers in 10 European countries
- participants
  - contacts of tuberculosis index cases
  - IGRA (QFT or TSPOT)

Am J Respir Crit Care Med. 2015;191(10):1176-84

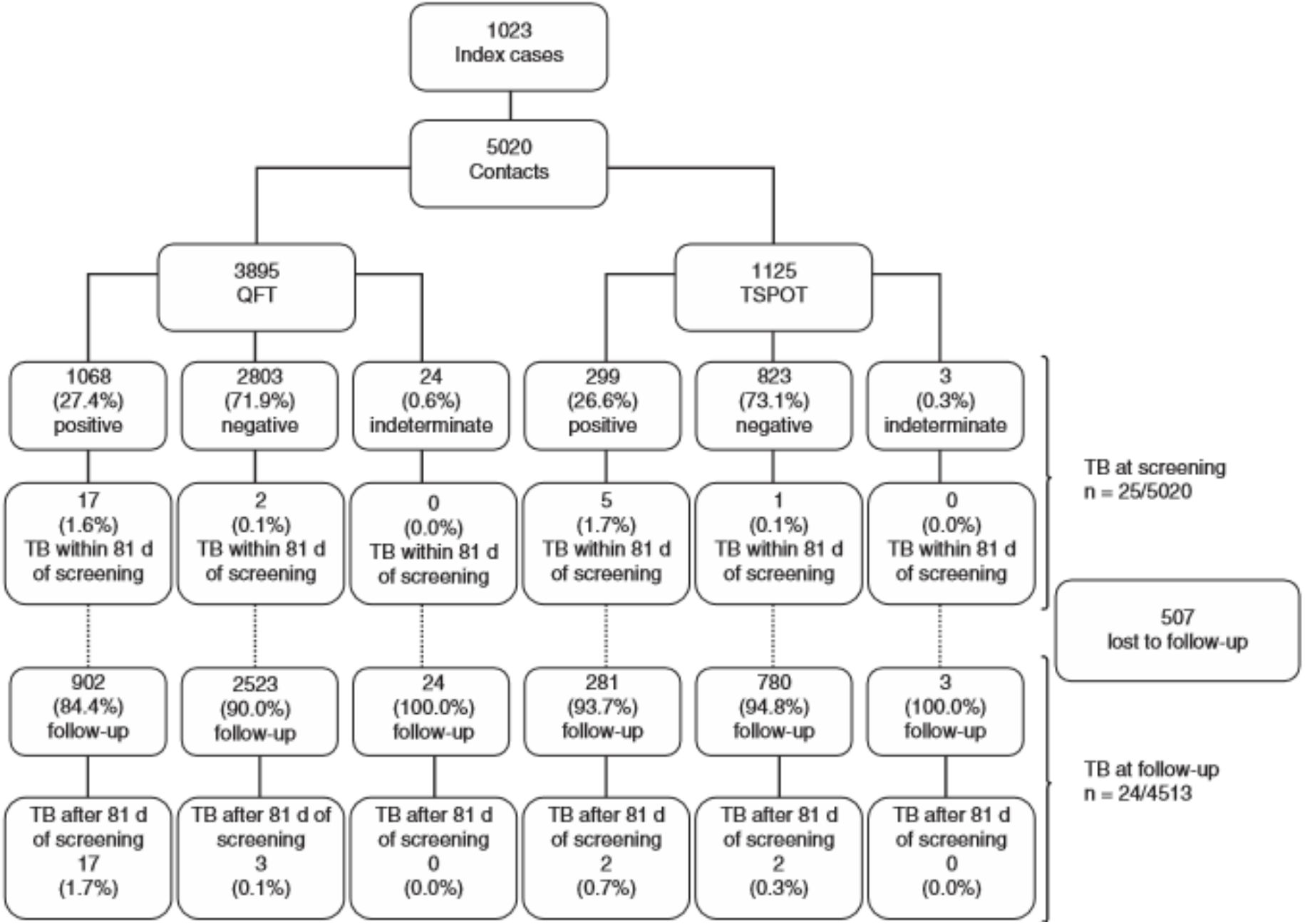

1023
Index cases
5020
Contacts
3895
QFT
1125
TSPOT
1068
(27.4%)
positive
2803
(71.9%)
negative
24
(0.6%)
indeterminate
299
(26.6%)
positive
823
(73.1%)
negative
3
(0.3%)
indeterminate
17
(1.6%)
TB within 81 d
of screening
2
(0.1%)
TB within 81 d
of screening
0
(0.0%)
TB within 81 d
of screening
5
(1.7%)
TB within 81 d
of screening
1
(0.1%)
TB within 81 d
of screening
0
(0.0%)
TB within 81 d
of screening
TB at screening
n = 25/5020
507
lost to follow-up
902
(84.4%)
follow-up
2523
(90.0%)
follow-up
24
(100.0%)
follow-up
281
(93.7%)
follow-up
780
(94.8%)
follow-up
3
(100.0%)
follow-up
TB at follow-up
n = 24/4513
TB after 81 d
of screening
17
(1.7%)
TB after 81 d of
screening
3
(0.1%)
TB after 81 d
of screening
0
(0.0%)
TB after 81 d
of screening
2
(0.7%)
TB after 81 d
of screening
2
(0.3%)
TB after 81 d
of screening
0
(0.0%)

Table 3. Development of Tuberculosis during Follow-up Depending on IGRA Test Result and Preventive Chemotherapy

	Test Result	n	Prophylaxis	TB Cases	Progression Rate (%)	Person Time (*yr*)	Incidence/100 Patient-Years	Number Needed to Treat
QFT	Negative	2,419	No	3	0.12	6,349.8	0.047	807
	Negative	104	Yes	0	0	326.4	0	
	Positive	421	No	14	3.33	1,169.1	1.198	38
	Positive	481	Yes	3	0.62	1,296.5	0.231	
TSPOT	Negative	722	No	2	0.28	1,790.1	0.112	361
	Negative	58	Yes	0	0	316.1	0	
	Positive	73	No	2	2.73	247.8	0.807	37
	Positive	208	Yes	0	0	829.7	0	

Am J Respir Crit Care Med. 2015;191(10):1176-84

Table 4. Diagnostic Performance of the QFT Test and the TSPOT Test for Active Tuberculosis in Contacts

	Value	95% CI
QFT		
Sensitivity, %	85.0	62.1–96.6
Specificity, %	74.0	72.5–75.5
Positive likelihood ratio	3.3	2.7–4.0
Negative likelihood ratio	0.2	0.1–0.6
Positive predictive value, %	1.9	1.1–3.0
Negative predictive value, %	99.9	99.7–100.0
TSPOT		
Sensitivity, %	50.0	8.3–91.7
Specificity, %	73.6	70.8–76.2
Positive likelihood ratio	1.9	0.7–5.1
Negative likelihood ratio	0.7	0.3–1.8
Positive predictive value, %	0.7	0.1–2.6
Negative predictive value, %	99.7	99.1–99.9

Am J Respir Crit Care Med. 2015;191(10):1176-84

Risk Assessment of Tuberculosis in Contacts by IFN-γ Release Assays. A Tuberculosis Network European Trials Group Study

Conclusions

- TB rarely developed among contacts.
- Preventive chemotherapy effectively reduced the TB risk among IGRA-positive contacts.
- Although the negative predictive value of IGRAs is high, the risk for the development of TB is poorly predicted by these assays.

Am J Respir Crit Care Med. 2015;191(10):1176-84

Combinatorial Immunoprofiling in Latent Tuberculosis Infection. Toward Better Risk Stratification

Objectives

- To identify potential immunomarker combinations that distinguish among unexposed subjects, untreated patients with LTBI, and treated patients with LTBI
- To differentiate risk of reactivation

Am J Respir Crit Care Med. 2015;192(5):605-17

Combinatorial Immunoprofiling in Latent Tuberculosis Infection. Toward Better Risk Stratification

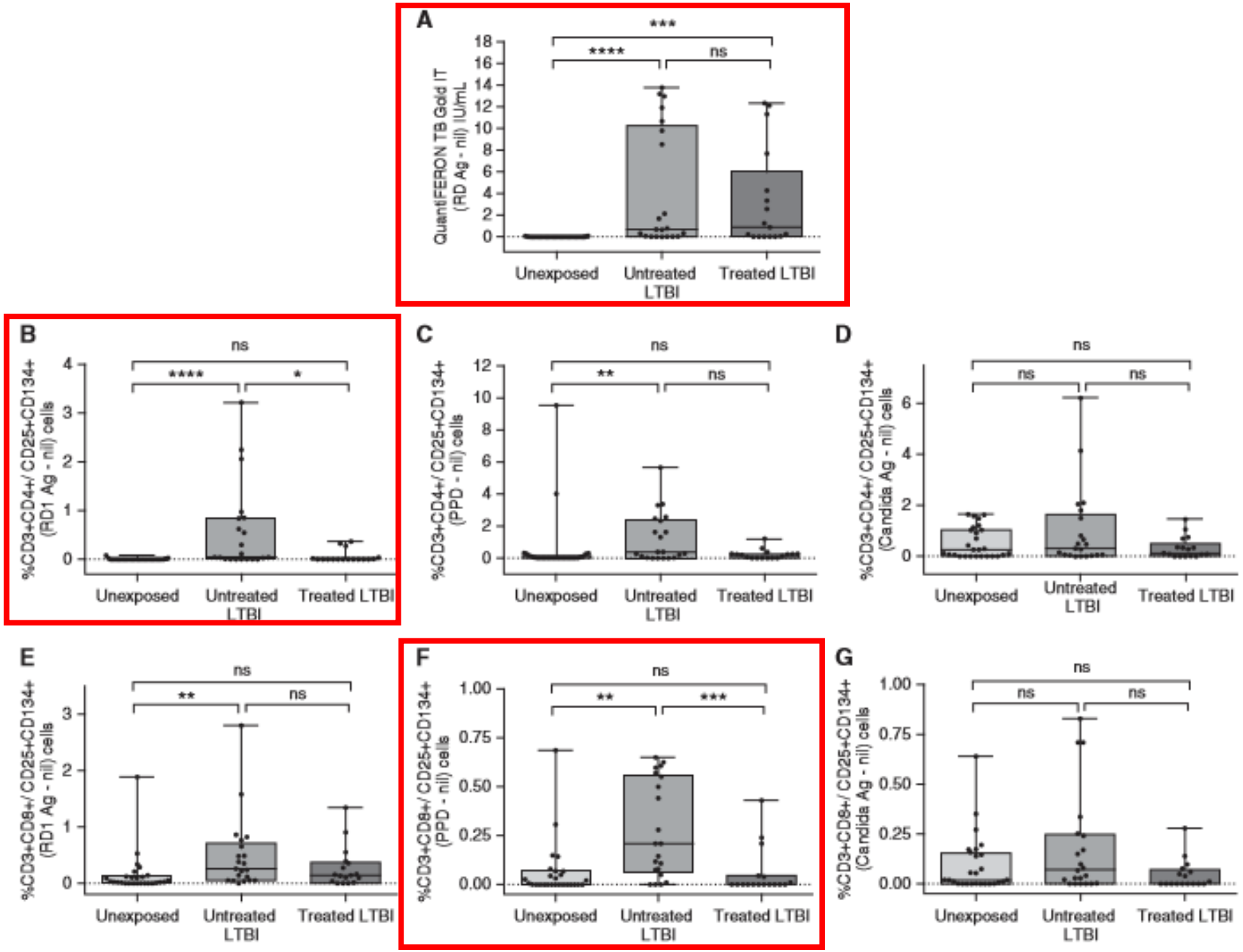
Methods

- Using peripheral blood
- Combinatorial immunoprofiling
  - IGRA
  - FC assay ($CD25^{+}CD134^{+}$ coexpression on TB antigen–stimulated T cells)

Am J Respir Crit Care Med. 2015;192(5):605-17

Table 1. Characteristics of Study Subjects

Demographics	Unexposed Control Subjects (*n* = 27)	Untreated LTBI Subjects (*n* = 21)	Treated LTBI Subjects (*n* = 17)	*P* Value*
Male, n (%)	13 (48.2)	17 (90.0)	8 (47.1)	0.042
Age, yr				
Mean ± SD	32.7 ± 13.5	51.3 ± 20.9	47.2 ± 14.2	0.476†
Range	20–74	19–91	27–68	
Ethnicity, n (%)				0.319
White	23 (85.2)	10 (47.6)	12 (70.6)	
African American	0 (0)	6 (28.5)	1 (5.9)	
Asian Pacific	2 (7.4)	3 (14.3)	3 (17.6)	
Hispanics	2 (7.4)	1 (4.8)	0 (0)	
Others	0 (0)	1 (4.8)	1 (5.9)	
Place born, n (%)‡				0.662
United States	27 (100)	9 (42.8)	10 (58.8)	
Foreign born (high TB)	0 (0)	11 (52.4)	6 (35.3)	
Foreign born (low TB)	0 (0)	1 (4.8)	1 (5.9)	
History of BCG vaccination, n (%)				0.137
Yes	0 (0)	10 (47.6)	3 (17.6)	
No	27 (100.0)	10 (47.6)	11 (64.7)	
Unknown	0 (0)	1 (4.8)	3 (17.7)	
Occupation, n (%)				0.625
HCW, direct patient contact	0 (0)	12 (57.1)	8 (47.0)	
HCW, no direct patient contact	21 (77.8)	4 (10.1)	6 (35.3)	
Other	6 (22.2)	5 (23.8)	3 (17.7)	
Likelihood of TB contact, n (%)§				0.134
Close contact or prior TB	0 (0)	2 (9.2)	0 (0)	
Probable TB contact	0 (0)	13 (61.9)	7 (41.2)	


A
QuantiFERON TB Gold IT (RD Ag - nil) IU/mL
***
****
ns
Unexposed
Untreated LTBI
Treated LTBI
B
%CD3+CD4+/ CD25+CD134+ (RD1 Ag - nil) cells
ns
****
*
C
%CD3+CD4+/ CD25+CD134+ (PPD - nil) cells
ns
**
ns
D
%CD3+CD4+/ CD25+CD134+ (Candida Ag - nil) cells
ns
ns
ns
E
%CD3+CD8+/ CD25+CD134+ (RD1 Ag - nil) cells
ns
**
ns
F
%CD3+CD8+/ CD25+CD134+ (PPD - nil) cells
ns
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***
G
%CD3+CD8+/ CD25+CD134+ (Candida Ag - nil) cells
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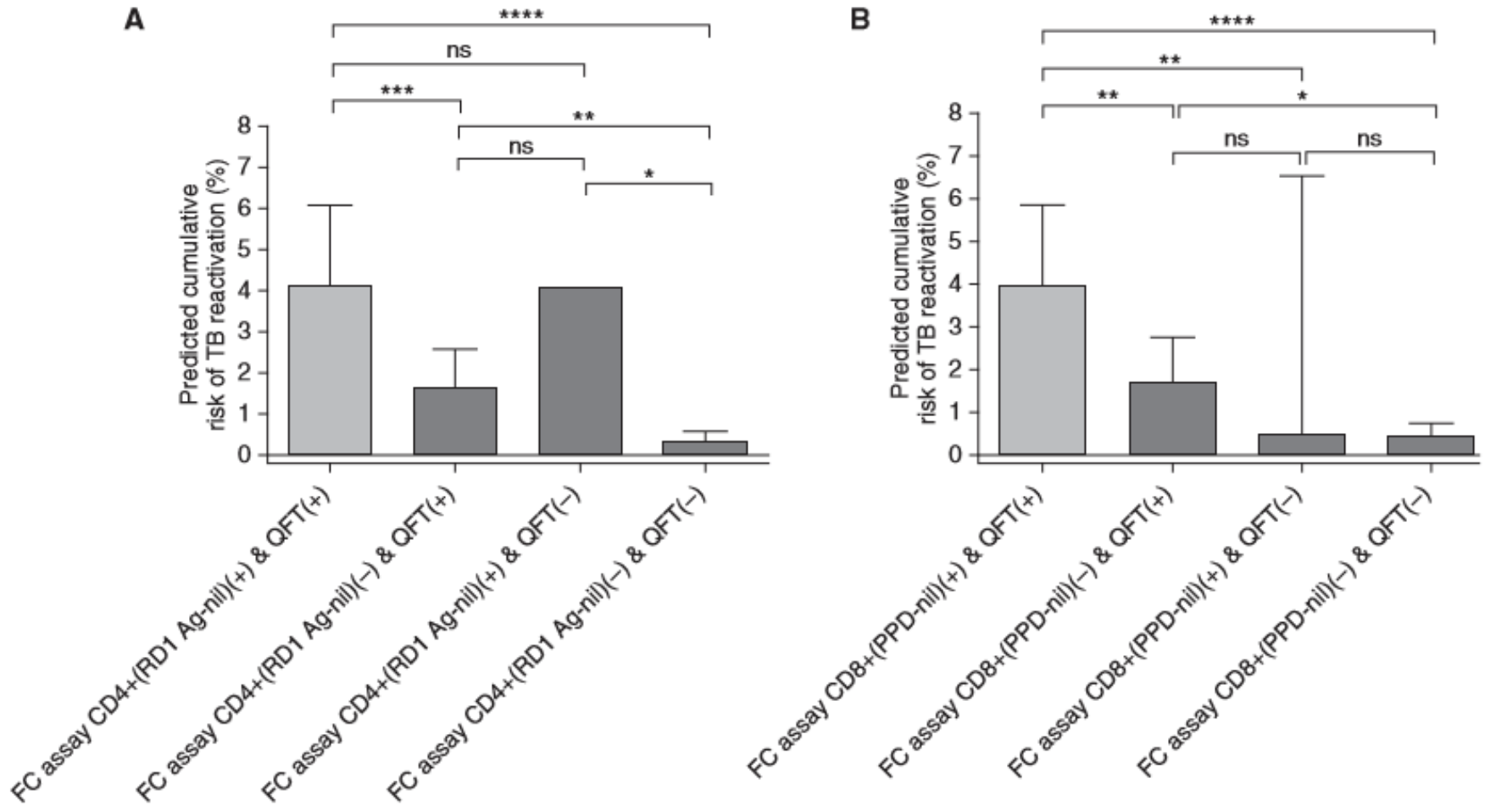
2(5):605-17



Am J Respir Crit Care Med. 2015;192(5):605-17

Combinatorial Immunoprofiling in Latent Tuberculosis Infection. Toward Better Risk Stratification

Conclusions

- Immune phenotypes defined by combinatorial assays may potentially have a role in identifying those at risk of developing TB

Am J Respir Crit Care Med. 2015;192(5):605-17

Contents

Analysis of drug treatment outcome in clarithromycin-resistant Mycobacterium avium complex lung disease

Objectives

- To reveal the effectiveness of the continuation of a macrolide and the use of a multidrug regimen in the treatment of CAM-resistant MAC lung disease.

BMC Infect Dis. 2016;16(1):31

Analysis of drug treatment outcome in clarithromycin-resistant Mycobacterium avium complex lung disease

Methods

- retrospective single center study
- at Tokyo National Hospital
- patients with diagnosed CAM-resistant MAC (MIC ≥32 μg/ml)

BMC Infect Dis. 2016;16(1):31

Table 1 Characteristics of the 33 patients

Variables	Total ($n = 33$)
Age at onset of MAC, yrs ± SD	57 ± 12
Age (when found to be resistant), yrs ± SD	67 ± 9
Female, n (%)	31 (93.9)
Body mass index, kg/m^2 ± SD	17.2 ± 5.0
Smoking history, n (%)	
Current/Former/Never	0 (0)/3 (9.1)/30 (90.9)
Pack-years ≥20, n (%)	1 (3.0)
Alcohol abuse, n (%)	1 (3.0)
Underlying respiratory disease, n (%)	
Old pulmonary tuberculosis	2 (6.1)
Bronchiectasis	2 (6.1)
Interstitial pneumonia	1 (3.0)
Underlying systematic disease, n (%)	
Old cerebral infarction	1 (3.0)
Diabetes mellitus	1 (3.0)
Radiographic features, n (%)	
NB/FC	8 (24.2)/25 (75.8)
Total lesion extent[a] 1/2/3, n (%)	2 (6.1)/24 (72.7)/7 (21.2)
Cavity at the beginning of treatment, n (%)	25 (75.8)
Laboratory	

BMC Infect Dis. 2016;16(1):31

Table 4 Analysis of the risk factors of radiological non-deterioration evaluated with chest X-ray and CT scans

Variables	Total	Non-deterioration	Worsening	Multivariate analysis
	n	(*n* = 15)	(*n* = 18)	Odds ratio
Continuation of CAM or AZM	26	12 (80)	14 (78)	3.7 (0.28–50)
Treatment with 3 or more drugs	21	10 (67)	11 (66)	1.3 (0.16–11)
Age ≥75 years	8	3 (20)	5 (28)	
Female	31	15 (100)	16 (89)	
Nonsmoker	3	1 (6.7)	2 (11)	
BMI ≧18 kg/m^2	11	6 (40)	5 (28)	
NB (radiological findings)	27	13 (87)	14 (78)	
Total lesion extent[a] 1 or 2	26	13 (87)	13 (72)	
Cavity	25	9 (60)	16 (89)	0.22 (0.018–2.7)
Albumin ≥3.5 g/dl	26	14 (93)	12 (67)	6.8 (0.28–168)
CRP <1.0 mg/dl[*]	16	12 (80)	4 (22)	12 (1.6–95)[**]

BMC Infect Dis. 2016;16(1):31

Table 5 Analysis of the risk factors of microbiological improvement evaluated with MAC cultures

Variables	Total	Sputum conversion	Sputum positive	Multivariate analysis
	n	($n = 12$)	($n = 21$)	Odds ratio
Continuation of CAM or AZM	26	10 (83)	16 (76)	1.1 (0.13–8.7)
Treatment with 3 or more drugs	21	6 (50)	15 (71)	0.57 (0.092–3.5)
Age ≥75 years*	8	6 (50)	2 (9.5)	5.7 (0.67–49)
Female	31	10 (83)	21 (100)	
Nonsmoker	30	11 (92)	19 (90)	
BMI ≧18 kg/m^2	11	5 (42)	6 (29)	
NB (radiological findings)	27	9 (75)	18 (86)	
Total lesion extent[a] 1 or 2	26	9 (75)	17 (81)	
Cavity	25	10 (83)	15 (71)	
Albumin ≥3.5 g/dl	26	11 (92)	15 (71)	3.0 (0.22–41)
CRP <1.0 mg/dl	16	5 (42)	11 (52)	0.79 (0.12–5.2)

BMC Infect Dis. 2016;16(1):31

Analysis of drug treatment outcome in clarithromycin-resistant Mycobacterium avium complex lung disease

Conclusions

- Continuation of macrolides or the addition of a new quinolone or injectable aminoglycoside to rifampicin and ethambutol would not improve clinical outcome in the treatment of CAM-resistant MAC lung disease.

BMC Infect Dis. 2016;16(1):31

Preliminary Results of Bedaquiline as Salvage Therapy for Patients With Nontuberculous Mycobacterial Lung Disease

Objectives

- To describe the treatment with bedaquiline-containing regimens of individuals with refractory Mab or MAC lung disease

Chest. 2015;148(2):499-506

Preliminary Results of Bedaquiline as Salvage Therapy for Patients With Nontuberculous Mycobacterial Lung Disease

Methods

- case series of off-label use of bedaquiline for treatment failure lung disease caused by MAC or Mab.
- at Health Science Center at Tyler (UTHSCT), Tyler, Texas
- Participants
  - ≥18 years of age, NTM lung disease
  - failed ≥ 12 months of therapy for MAC and ≥ 6 months for Mab
  - Treatment failure was defined as persistent positive sputum cultures for NTM, with progressive symptoms and radiographic abnormalities
  - All were considered to have potentially life-threatening NTM disease

Chest. 2015;148(2):499-506

TABLE 2 | Clinical and Microbiologic Characteristics of 10 Patients Treated With Bedaquiline-Containing Regimens

Patient No.	Age, y	Sex	Species Pre-Rx Culture	Macrolide Susceptibility	Radiographic Feature	Prior Drugs Used in Treatment	Companion Drugs With Bedaquiline	New Drugs Started With Bedaquiline	Duration of Prior Rx, mo	Positive AFB Cultures Prior 12 mo	Negative AFB Cultures Prior 12 mo
1	36	M	Mab species *abscessus* 4+	Resistant (*erm* gene)	Nodular	Amikacin, linezolid, tigecycline	Amikacin, linezolid, tigecycline	None	96	5	0
2	31	M	Mab species *abscessus* 1+	Resistant (*erm* gene)	Nodular	Azithromycin, tigecycline, amikacin	Azithromycin, amikacin, tigecycline, moxifloxacin	Moxifloxacin	>12	15	0
3	64	F	Mab species *abscessus* 4+	Resistant (*erm* gene)	Cavitary	Clarithromycin, moxifloxacin, azithromycin, doxycycline, amikacin	Clarithromycin, moxifloxacin, azithromycin, doxycycline, amikacin, tigecycline	Amikacin, tigecycline	43	5	1
4	65	F	Mab species *abscessus* 4+	Resistant (*erm* gene)	Nodular	Linezolid, levofloxacin, amikacin	Linezolid, levofloxacin, imipenem, amikacin	Imipenem, amikacin	27	9	0
5	58	F	MAC 4+	Resistant	Nodular	Rifabutin, ethambutol, clarithromycin, amikacin, streptomycin	Rifabutin, ethambutol, streptomycin	Streptomycin	78	4	0
6	54	M	MAC 4+	Resistant	Cavitary	Linezolid, streptomycin, ethambutol, rifabutin, amikacin, clarithromycin	Streptomycin, ethambutol, rifabutin	None	96	2	0
7	64	M	MAC 4+	Susceptible	Cavitary	Ethambutol, clarithromycin, rifampin	Ethambutol, clarithromycin, rifabutin, (streptomycin added after 2 mo)	Rifabutin	20	3	0
8	60	F	MAC 4+	Susceptible	Nodular	Ethambutol, azithromycin, amikacin (inhaled and IV)	Ethambutol, azithromycin, amikacin, rifabutin (2 wk) streptomycin	Rifabutin	25	9	0
9	65	M	MAC 4+	Resistant	Cavitary	Amikacin, moxifloxacin ethambutol, rifampin, ciprofloxacin, azithromycin, clarithromycin	Ethambutol, rifabutin, streptomycin	Streptomycin (rifampin changed to rifabutin)	13	3	0
10	73	F	MAC 30 colonies	Resistant	Cavitary	Ethambutol, amikacin, moxifloxacin, ciprofloxacin rifabutin, rifampin, azithromycin, clarithromycin	Ethambutol, rifampin, streptomycin	Ethambutol, rifampin, streptomycin	96	5	1

015;148(2):499-506

TABLE 1] Semiquantitative Monthly Sputum Cultures of 10 Patients on a Bedaquiline-Containing Regimen

Patient No.	Baseline (at the Start of Therapy)	1 mo	2 mo	3 mo	4 mo	5 mo	6 mo
1 Mab	4+	3+	1+	2+	3+	1+	2+
2 Mab	1+	3+	1+	35 colonies	37 colonies	16 colonies	3+
3 Mab	4+	28 colonies	Negative	8 colonies	Negative	Negative	32 colonies
4 Mab	4+	4+	4+	4+	4+	4+	4+
5 MAC	4+	3+	4+	4+	4+	4+	4+
6 MAC	4+	4+	Negative	Negative	2+	4+	3+
7 MAC	4+	4+	30 colonies	Negative	Negative	...[a]	...[a]
8 MAC	4+	1+	Negative	3+	4+	4+	4+
9 MAC	4+	2+	3+	1 colony	4 colonies	1+	4 colonies
10 MAC	30 colonies	8 colonies	Negative	1+	Negative	9 colonies	Negative

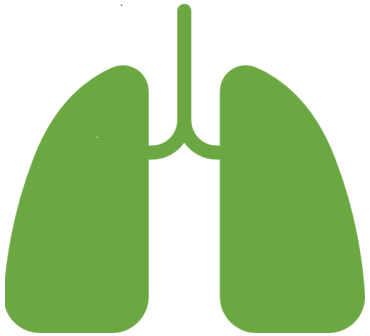
Chest. 2015;148(2):499-506

Preliminary Results of Bedaquiline as Salvage Therapy for Patients With Nontuberculous Mycobacterial Lung Disease

Conclusions

- This small preliminary report demonstrates potential clinical and microbiologic activity of bedaquiline in patients with advanced MAC or Mab lung disease

Chest. 2015;148(2):499-506



경청해 주셔서 감사합니다