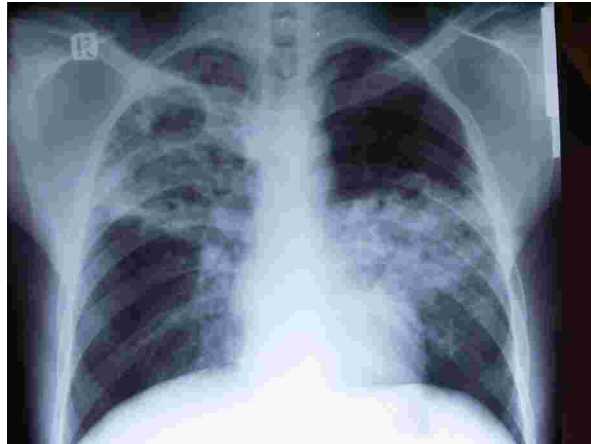


The Future of TB Treatment



Gerry Davies

Professor of Infection Pharmacology

Institutes of Infection and Global Health & Translational Medicine



RCP Update Wales, 10th May 2019

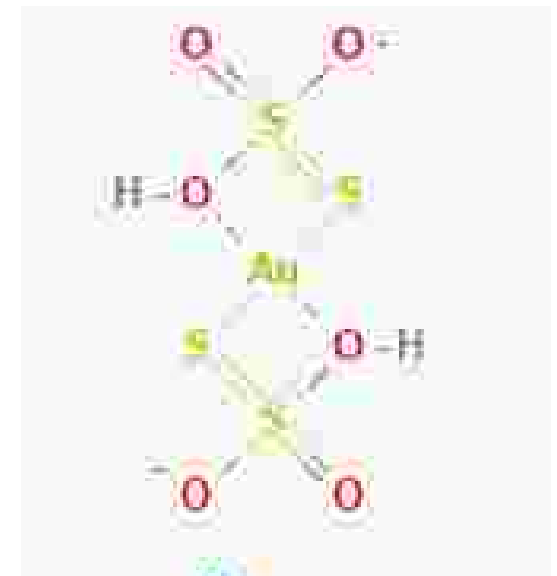
Overview

- What we're up against
- Shortening first-line treatment
- Overcoming drug resistance
- New approaches to latent infection
- What the near-future holds

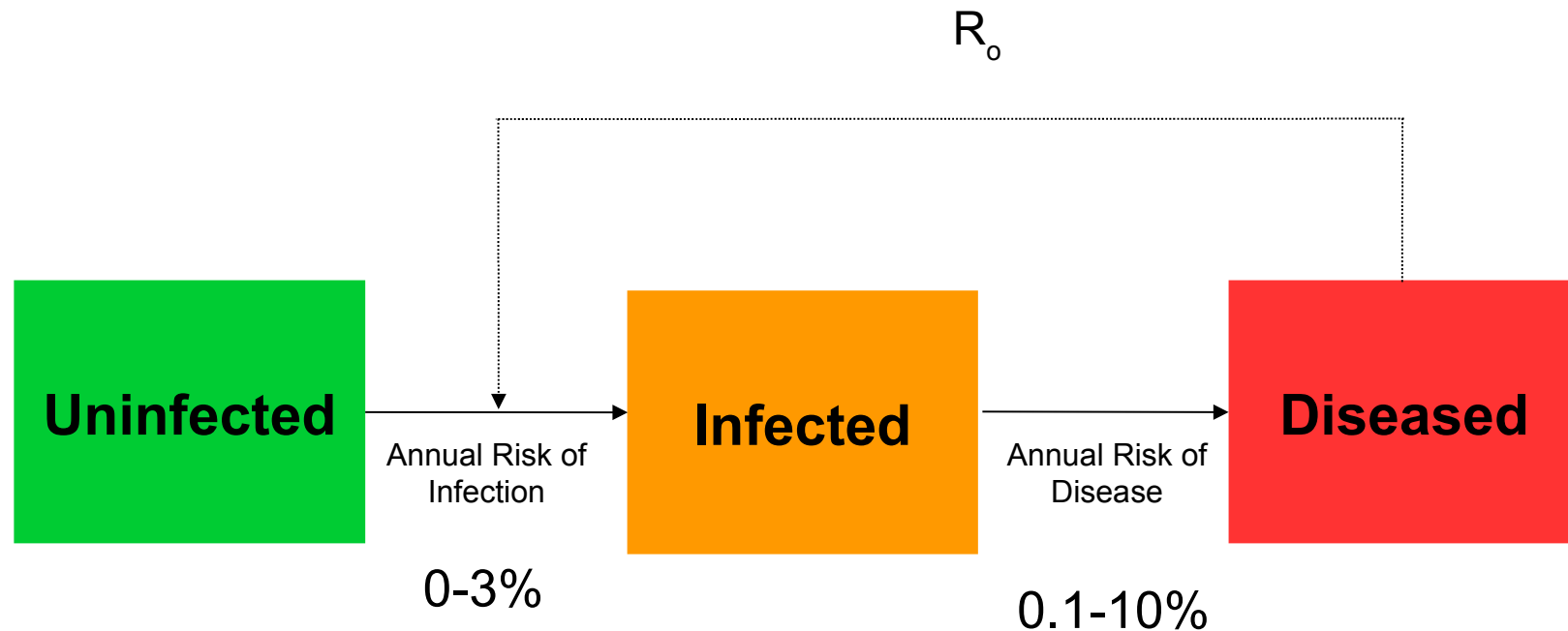


Hugh Morrison Davies 1879-1965

TB Treatment 1926



Natural History of TB



R_0 = average number of secondary infectious cases resulting from each case = <1-3

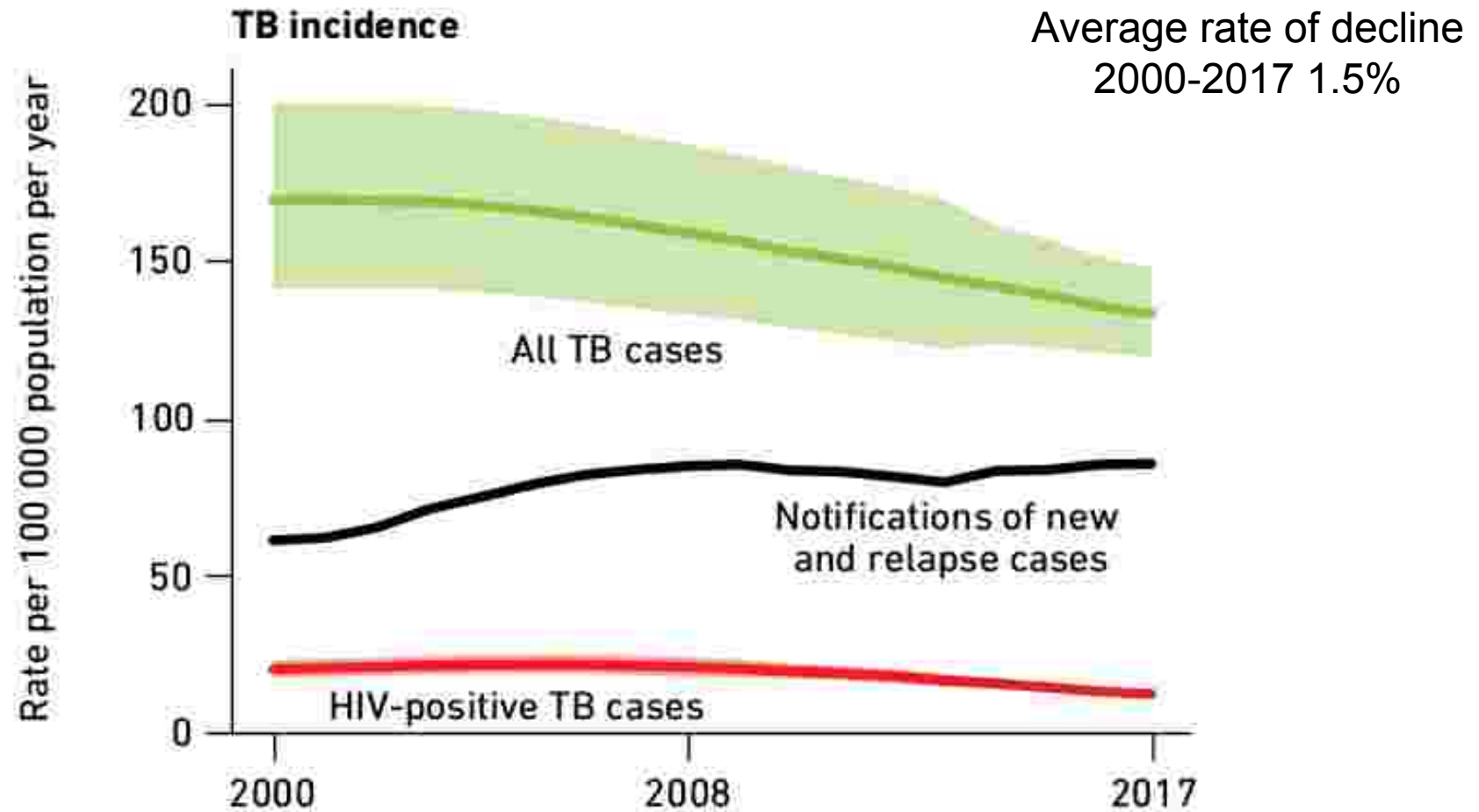
Burden of TB

**1.7 billion latent
infections**

**10 million new
cases/yr**

**1.6 million
deaths /yr**

State of the pandemic 2019

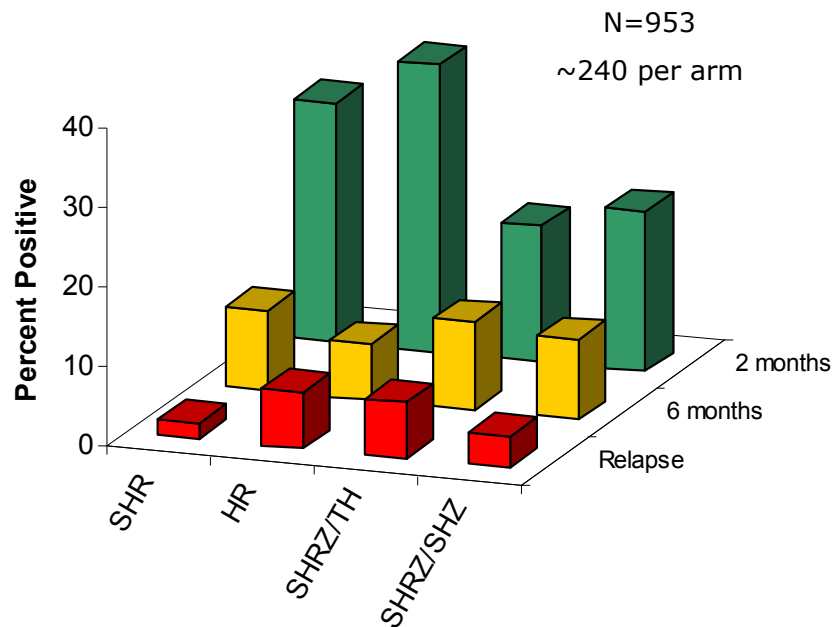


TB Treatment 1978

THE LANCET, NOVEMBER 9, 1974

CONTROLLED CLINICAL TRIAL OF FOUR SHORT-COURSE (6-MONTH) REGIMENS OF CHEMOTHERAPY FOR TREATMENT OF PUMONARY TUBERCULOSIS

SECOND EAST AFRICAN / BRITISH MEDICAL RESEARCH COUNCIL STUDY

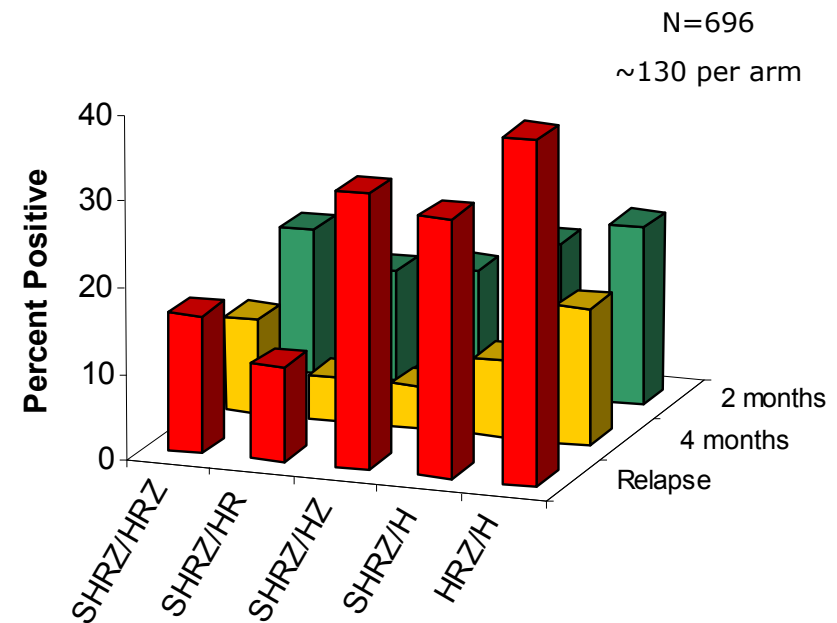


THE LANCET, AUGUST 12, 1978

CONTROLLED CLINICAL TRIAL OF FIVE SHORT-COURSE (4-MONTH) CHEMOTHERAPY REGIMENS IN PULMONARY TUBERCULOSIS

First Report of 4th Study

EAST AFRICAN AND BRITISH MEDICAL RESEARCH COUNCILS



Complexity of TB Treatment

Drug-sensitive TB

Rifampicin



Isoniazid



Pyrazinamide



Ethambutol



6
months

Multidrug-resistant TB

Amikacin



Pyrazinamide



Moxifloxacin



Prothionamide



Cycloserine



Linezolid



24
months

2a

AMAPHILISI ASEBENZA KANJANI ?

YIDLA AMAPHILISI NJENCOBA OTSHELWE UNESI NOMA UDOKOTELA. UMA USUWADLILE AMAPHILISI OKOKUQALKA AWUSEKHO ENGOZINI YOKUSA NALESIFU. AMAPHILISI ASINULACA KANCANE, KANCANE LESIFO NGENKATHI OLULAMA.



2b

KUFANELE UWAQEDE AMAPHILISI

UMA UNGAWAQEDI . . .

LESIFO SOFUBA SIYAVUKA, NGALESIKATHI SIKUKE SESIKAMANDLA BESE SENZA UYIBOSHO EZINKULU. UMA SEKUYEKA KUDIBOKEKA OLUNYE UHLISO LWAMA PHILISI OLUKASEKO LA ANGIASEKHA NOMI ANO EBENZI UNGASE UFE FUTHI.



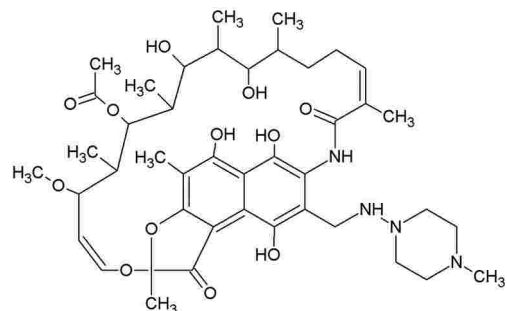
2c

NGINGA YEKA NINI UKUDLA AMAPHILISI?

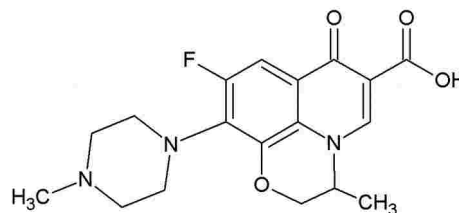
UMA UDOKOTELA NOMA UNESI ESHILO KUPHELA. UZOBE USUYAPHILA FUTHI!



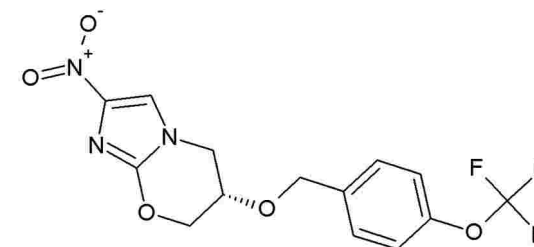
New anti-tuberculosis drugs



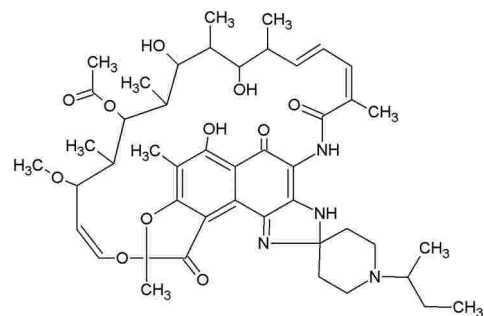
Rifampicin



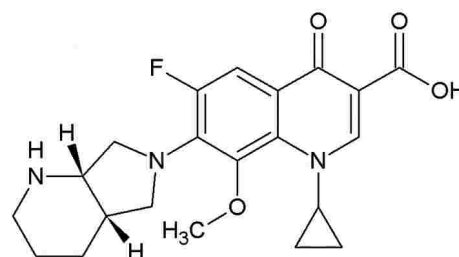
Levo/ofloxacin



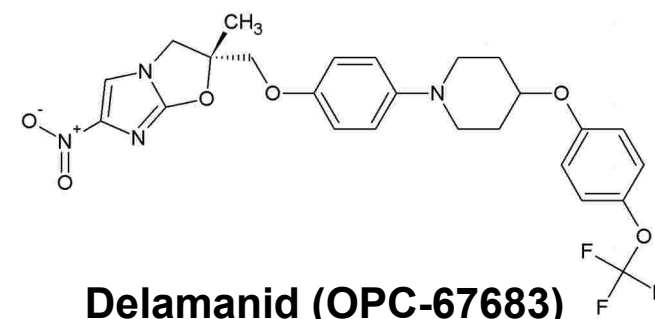
Pretomanid (PA-824)



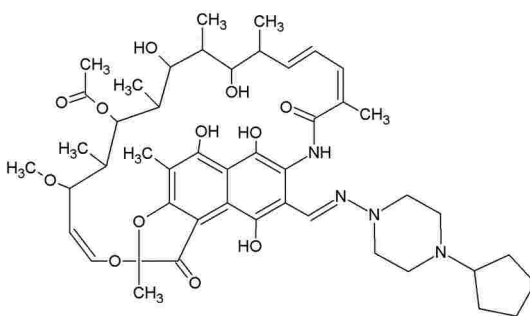
Rifabutin



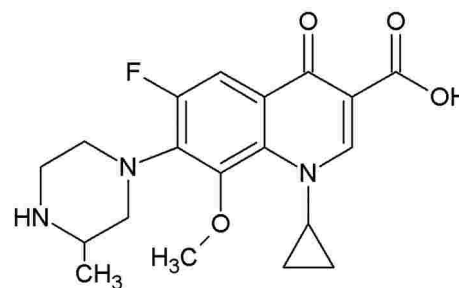
Moxifloxacin



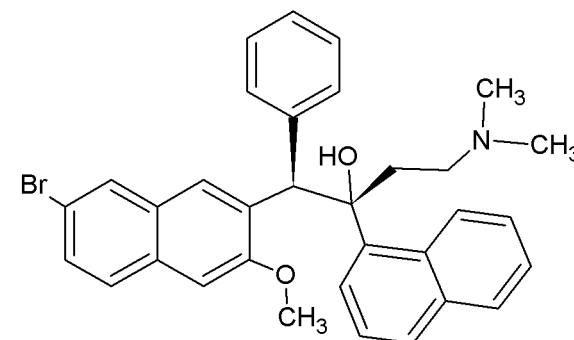
Delamanid (OPC-67683)



Rifapentine

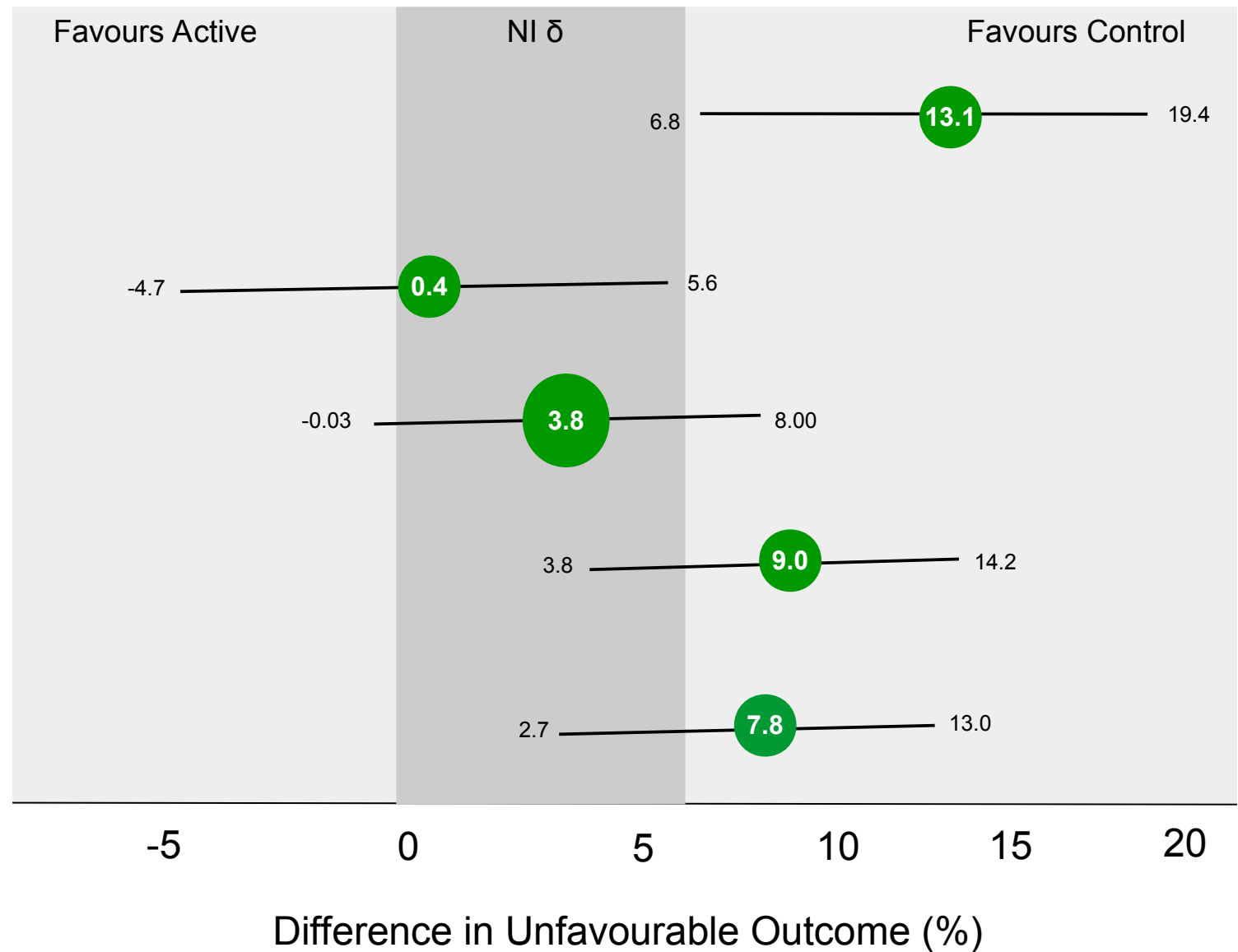


Gatifloxacin

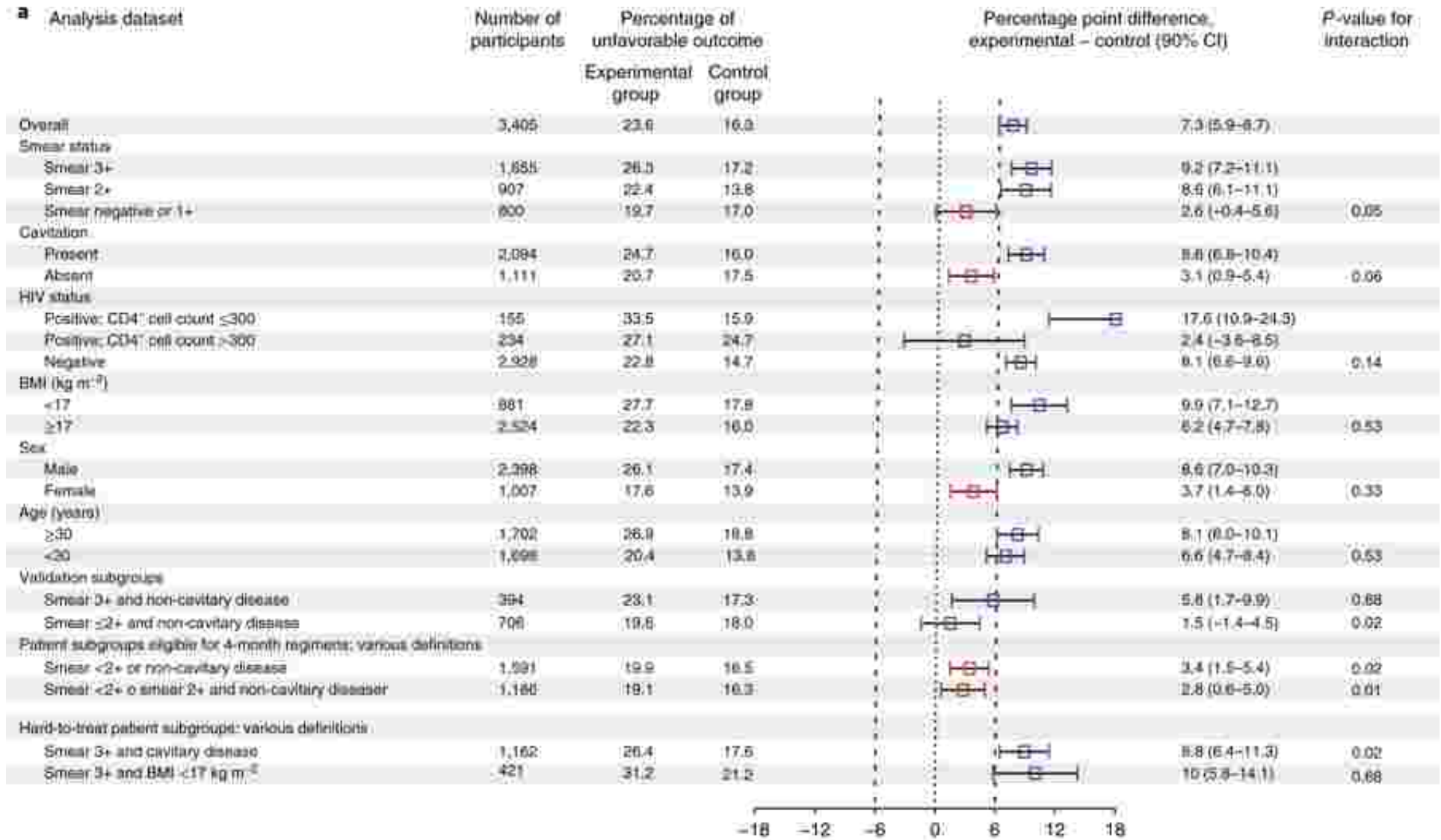


Bedaquiline (TMC-207)

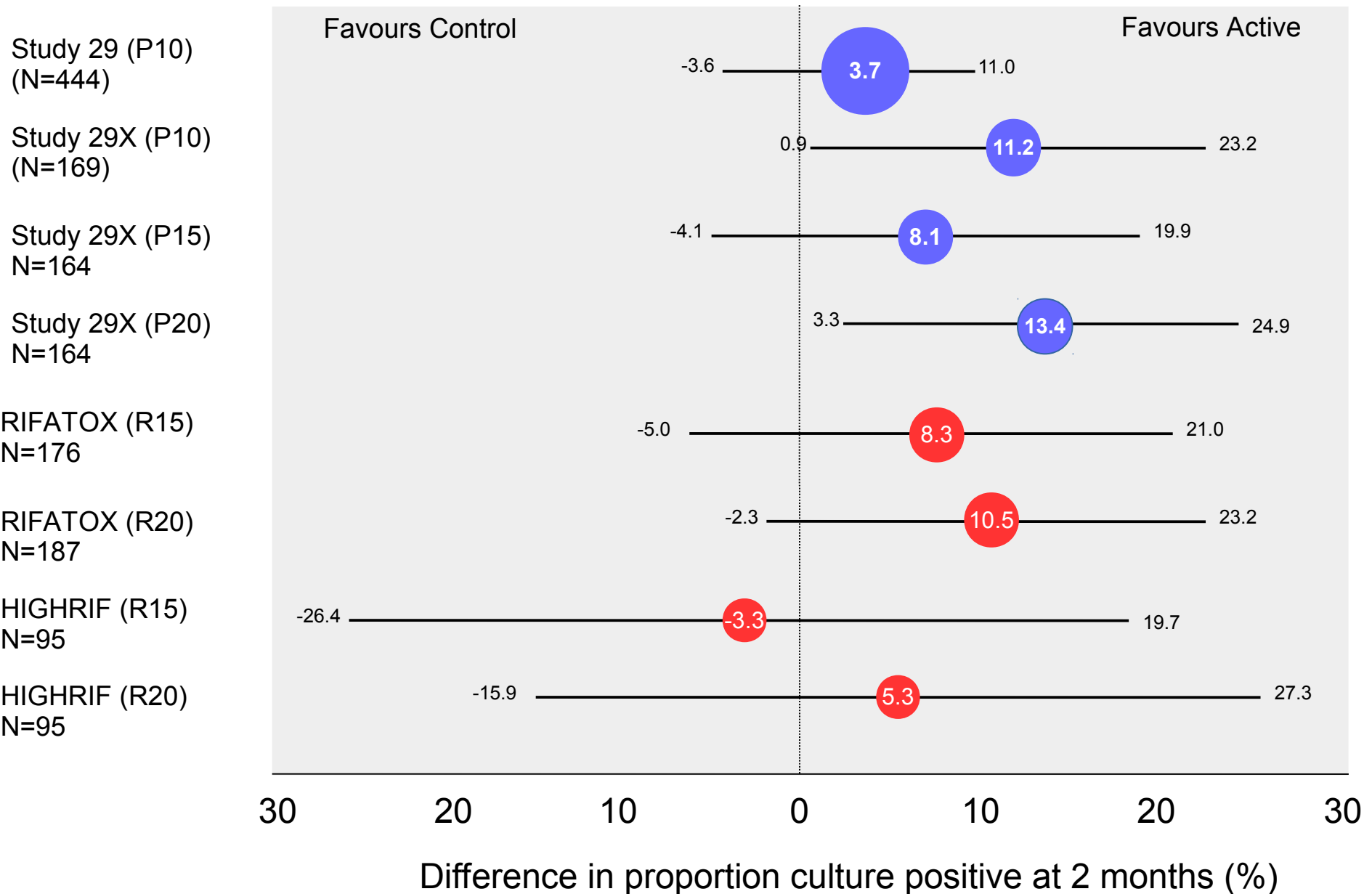
DS-TB : Fluoroquinolones



DS-TB : TB-Reflect

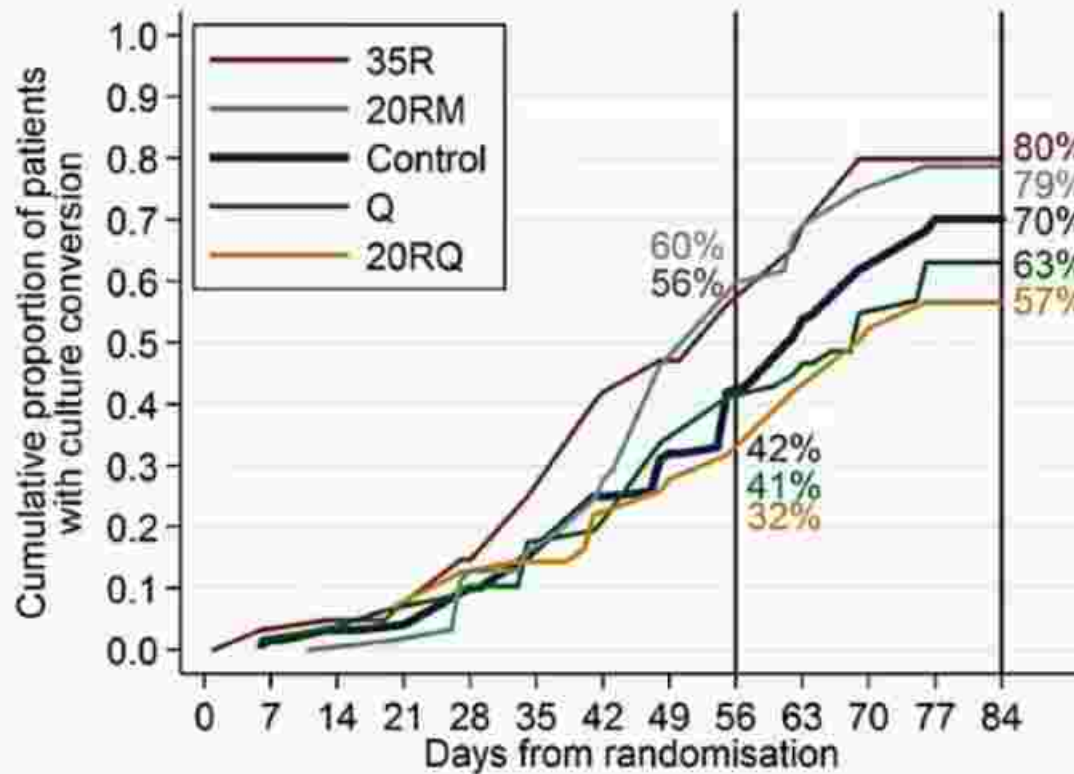


DS-TB : Rifamycins



DS-TB : MAMS TB 01

Time to stable culture conversion on MGIT liquid media



HR

1.75 (1.21-2.55)

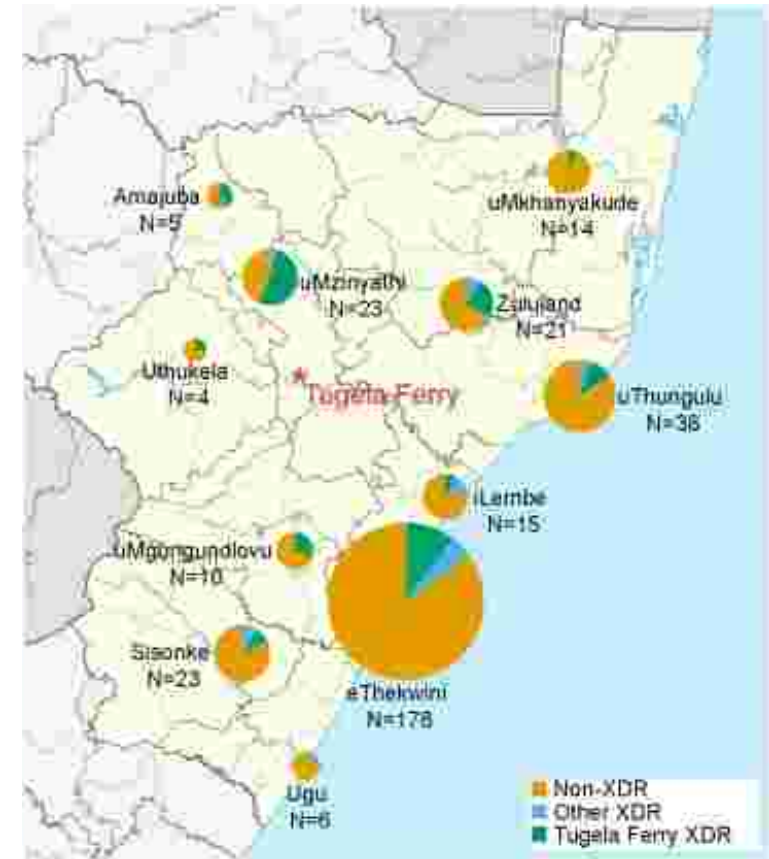
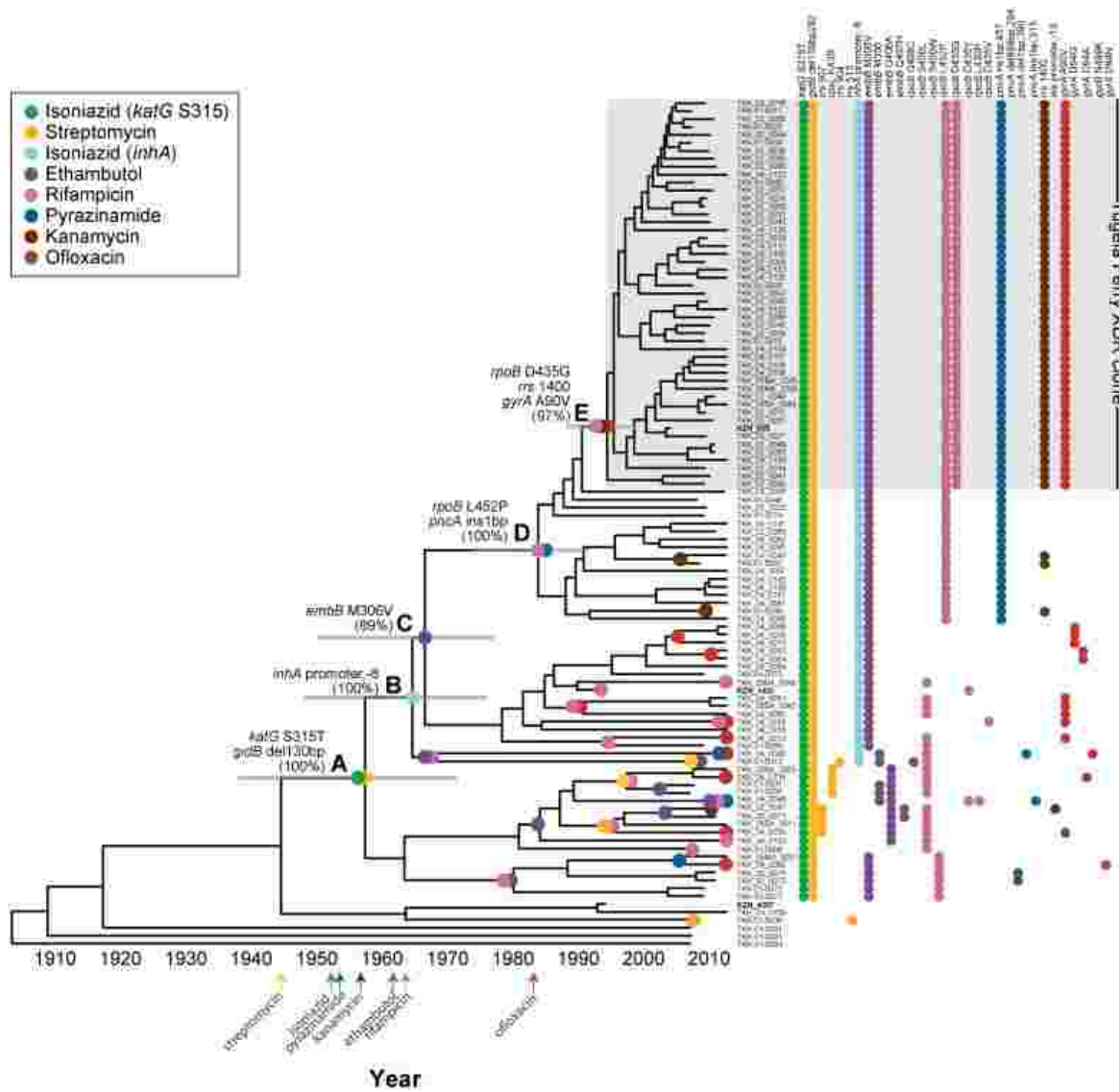
1.42 (0.98-2.05)

0.82 (0.55-1.24)

0.73 (0.48-1.13)

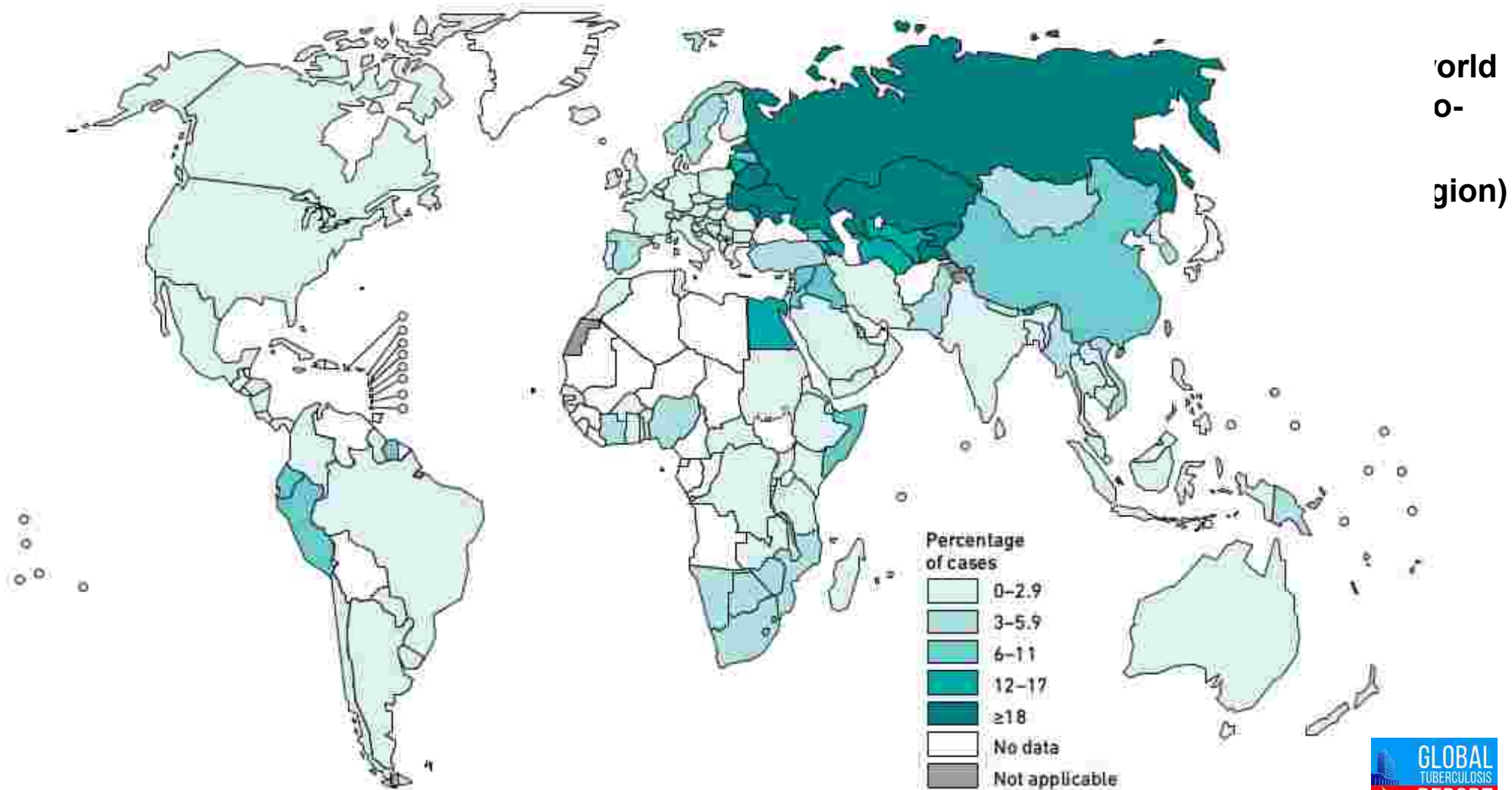
N=365

Rifampicin resistance



Multi-drug resistant TB

Percentage of new TB cases with MDR/RR-TB^a

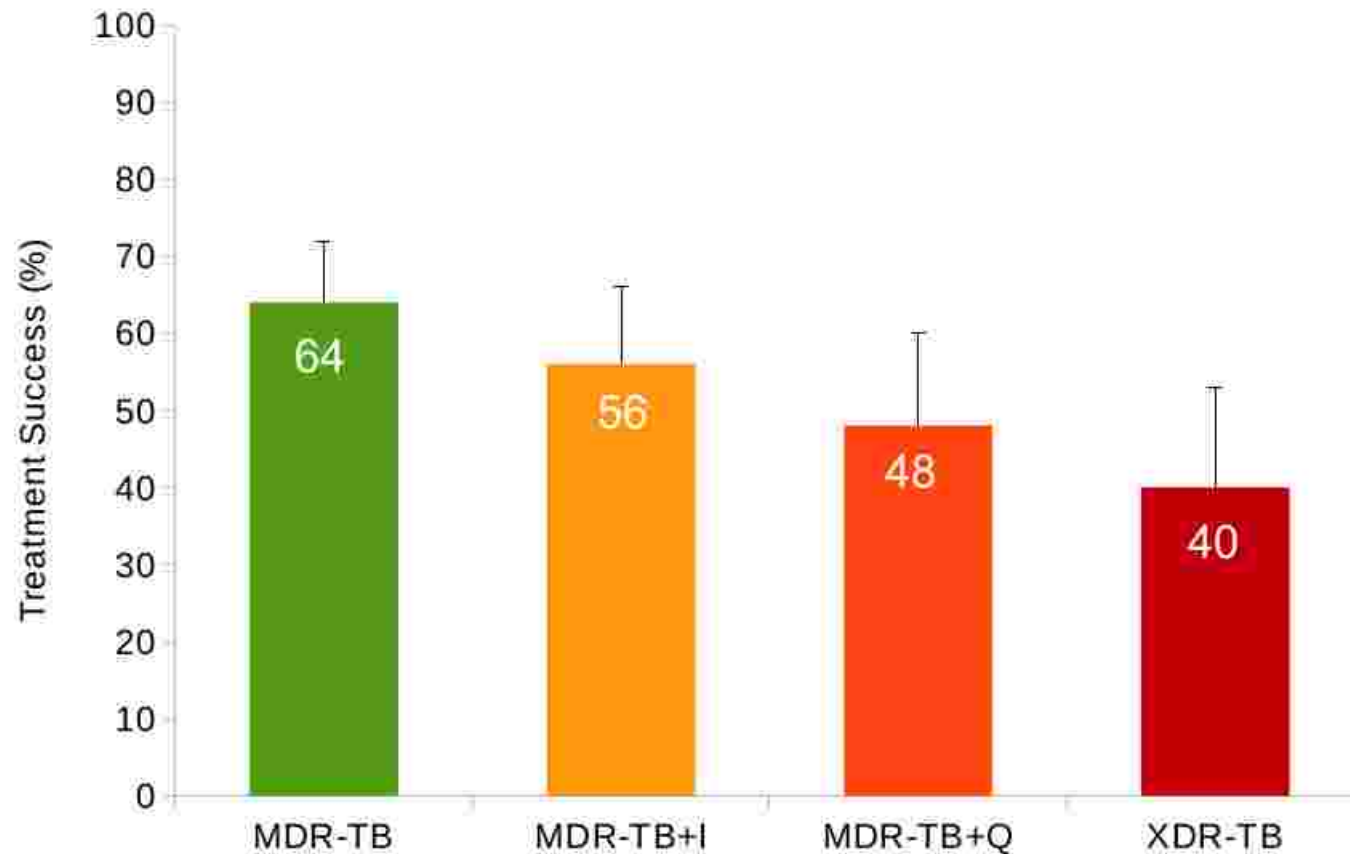


^a Figures are based on the most recent year for which data have been reported, which varies among countries. Data cover the period 2002-2018.



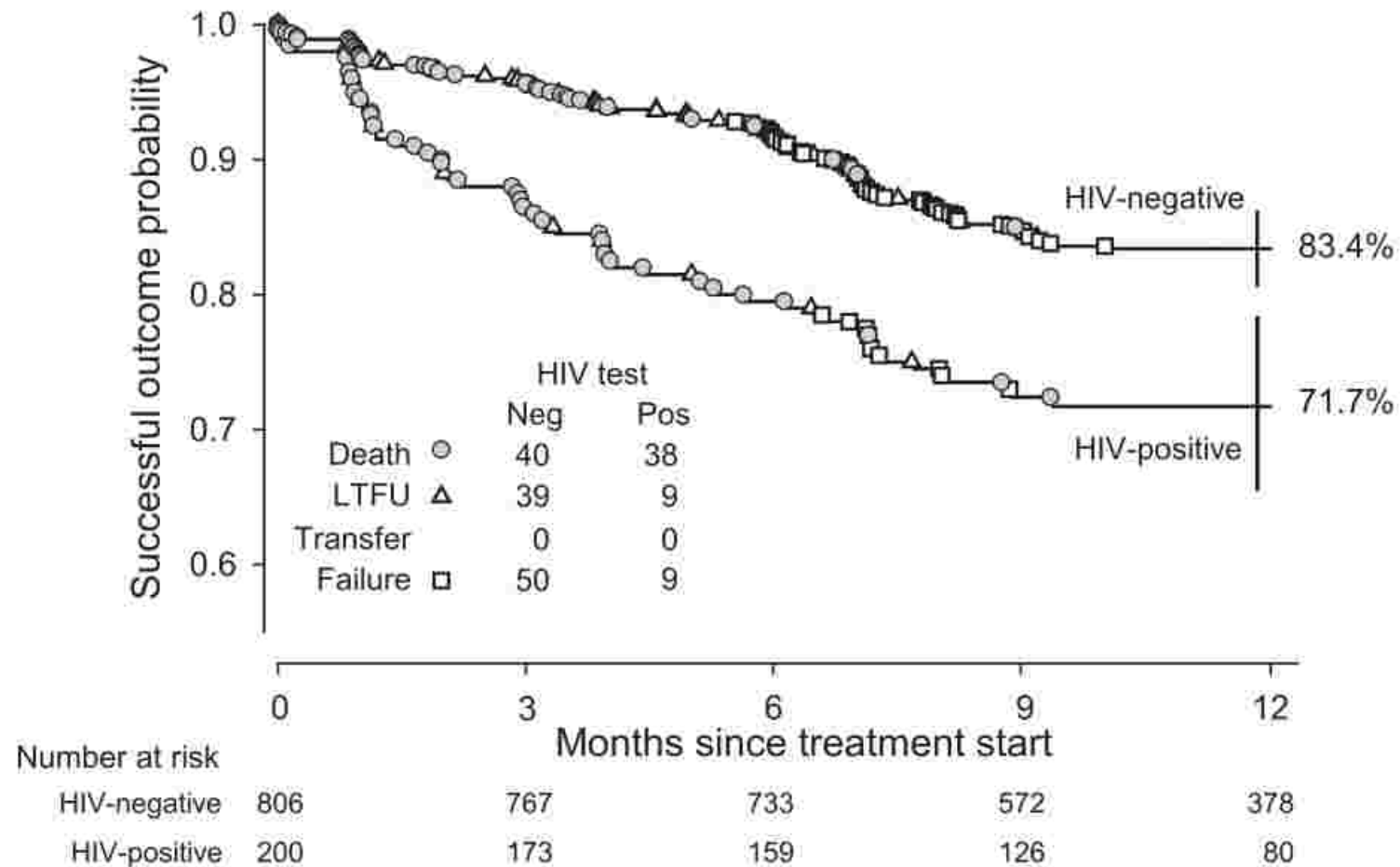
Outcomes of MDR-TB Treatment

Collaborative meta-analysis of 6724 patients on individualised regimens from 26 centres

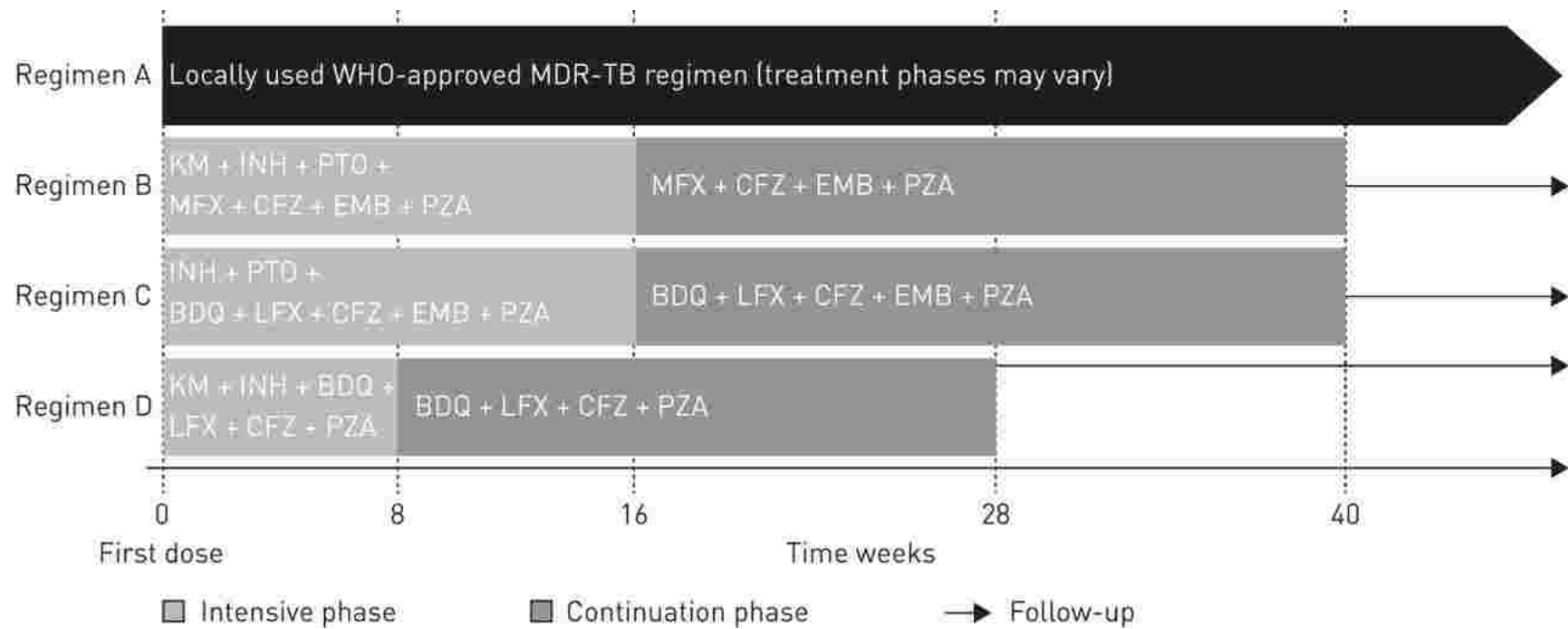


MDR-TB : Bangladesh Regimen

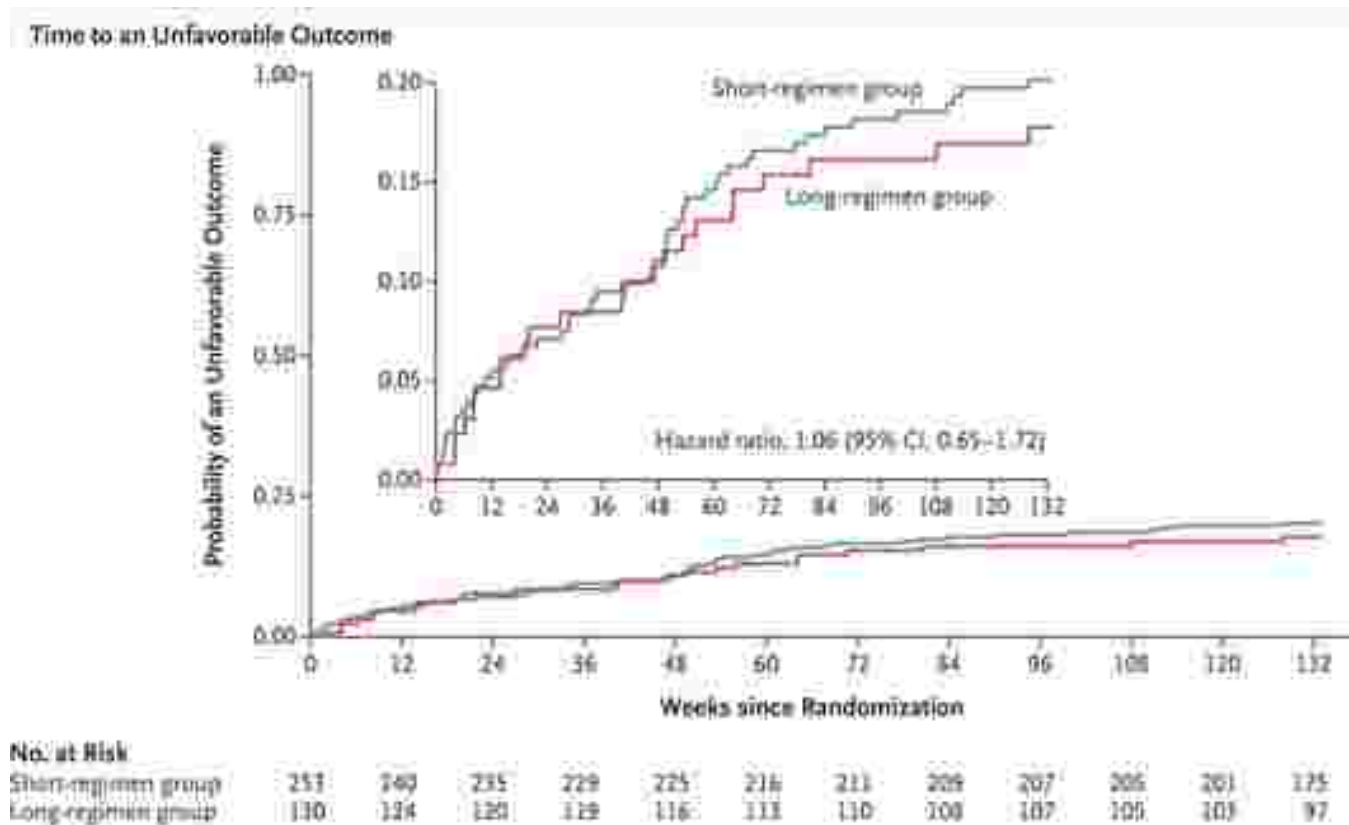
N=1006



MDR-TB : STREAM Trial



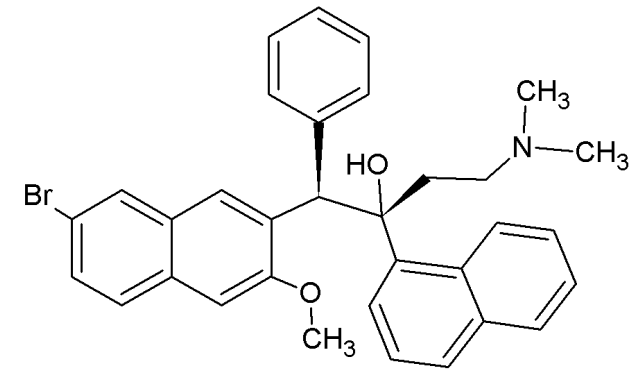
MDR-TB : STREAM Trial



- MITT RD -1% (-7.5 – 9.5%) p=0.02 for non-inferiority
- Bacteriological failure 10.6% versus 5.6%
- LTFU 2.4 versus 0.4%

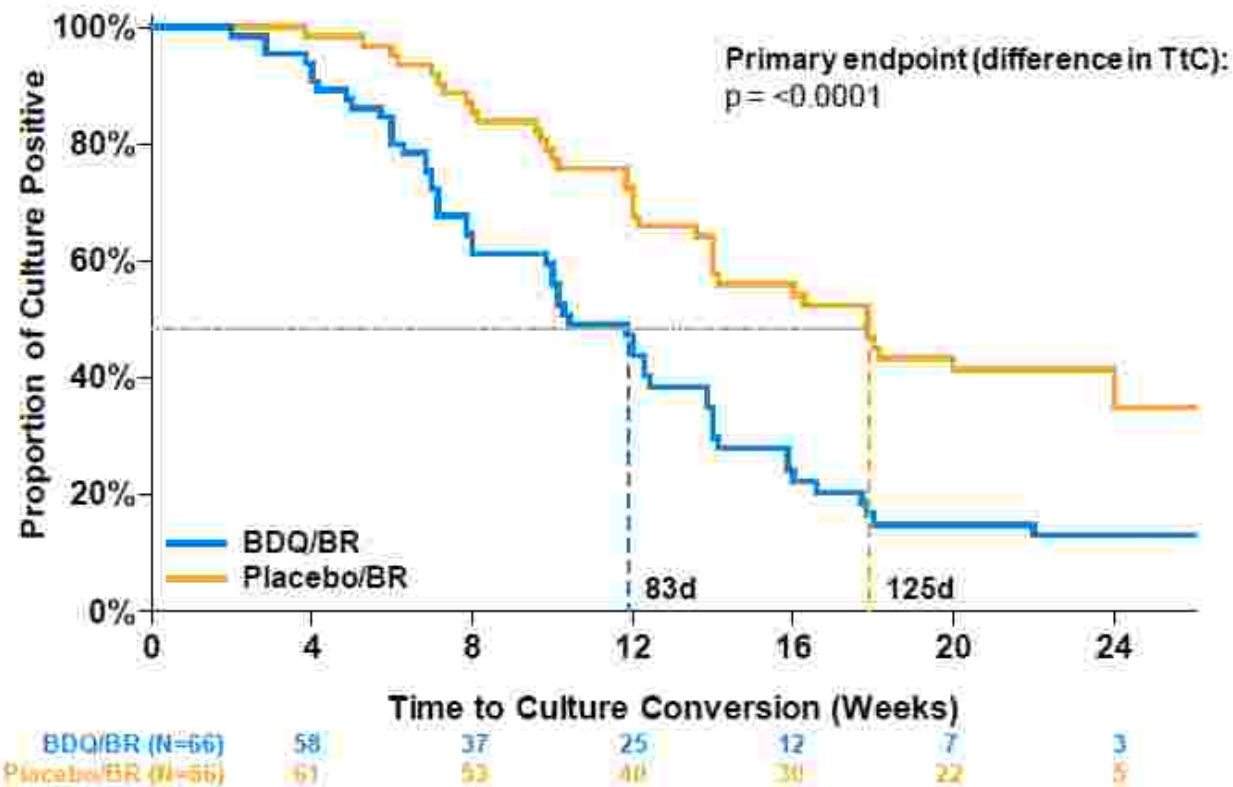
Bedaquiline : pharmacology

- Targets mycobacterial ATP synthase
- Protein-binding >99%
- Metabolised by CYP3A4, exposure reduced 50% with RIF
- Complex PK with $t_{1/2}$ 6 months
- Concerns about QTc prolongation



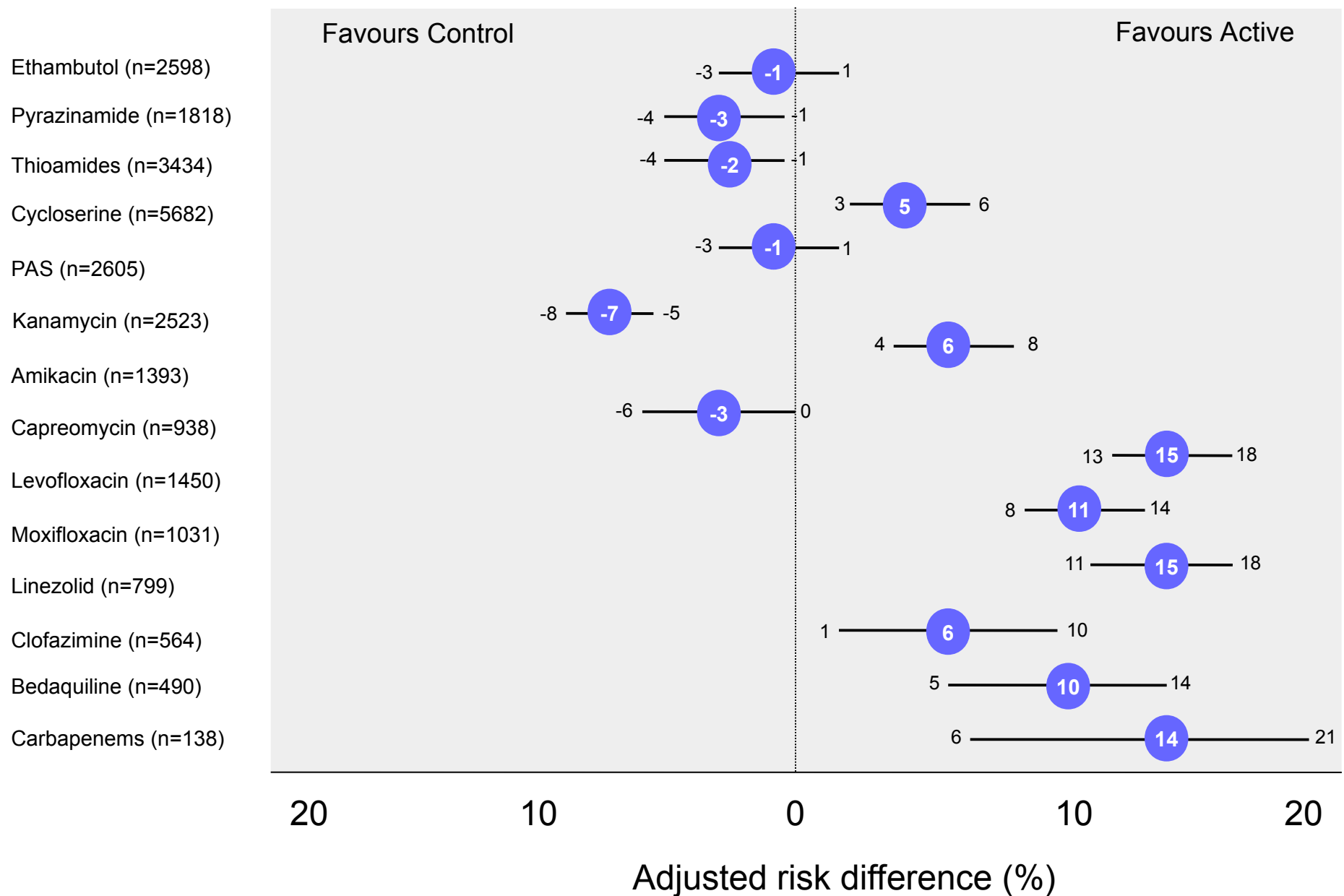
MDR-TB : Bedaquiline

C208 Stage 2: Time to Culture Conversion (Wk 24 – mITT)



Median time to culture conversion was 12 weeks in the BDQ group and 18 weeks in the placebo group
 p -value from Cox proportional model adjusting for strata

MDR-TB : IPD Meta-analysis

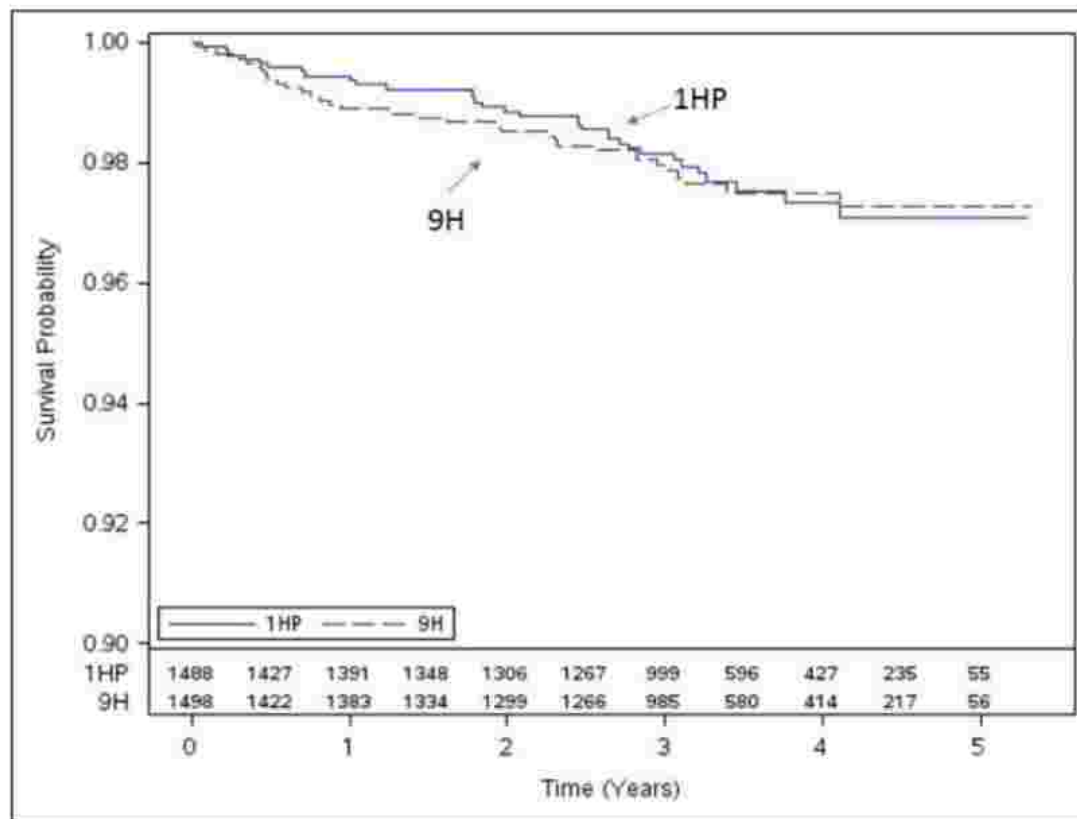


New WHO MDR-TB Guidance

GROUPS & STEPS	MEDICINE	
Group A: Include all three medicines	Levofloxacin <u>OR</u> Moxifloxacin	Lfx Mfx
	Bedaquiline ^{2,3}	Bdq
	Linezolid ⁴	Lzd
	Clofazimine	Cfz
Group B: Add one or both medicines	Cycloserine <u>OR</u> Terizidone	Cs Trd
	Ethambutol	E
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	Delamanid ^{3,5}	Dlm
	Pyrazinamide ⁶	Z
	Imipenem-cilastatin <u>OR</u> Meropenem ⁷	Ipm-Cln Mpm
	Amikacin (<u>OR</u> Streptomycin) ⁸	Am (S)
	Ethionamide <u>OR</u> Prothionamide ⁹	Eto Pto
	<i>p</i> -aminosalicylic acid ⁹	PAS

<https://www.who.int/tb/areas-of-work/drug-resistant-tb/guideline-update2018/en/>

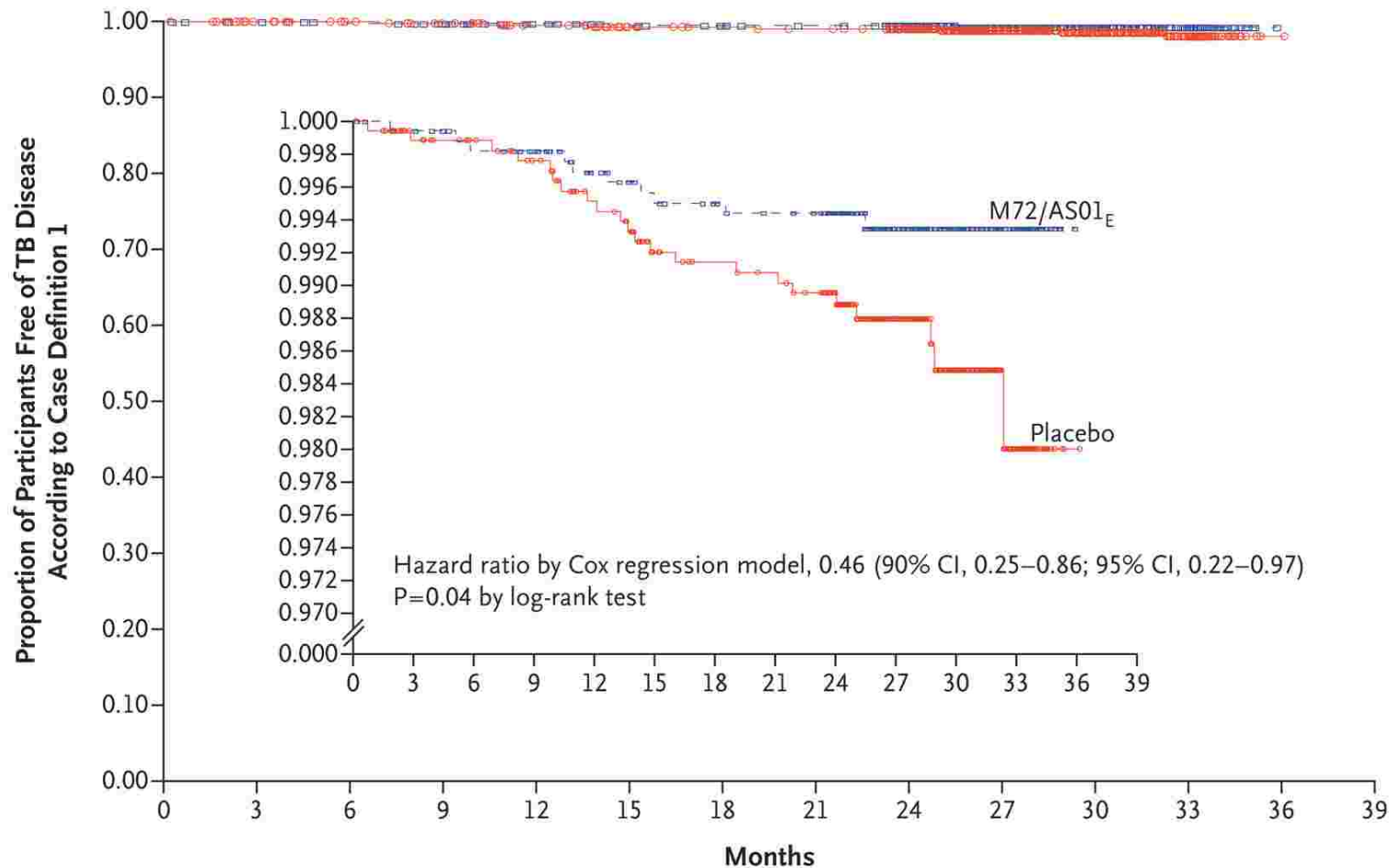
Ultra-short chemoprophylaxis



	9H	1HP	IRR Difference
Events/PY of follow up	33/4896	32/4926	0.023
Incidence per 100 PY	0.67	0.65	(95% CI -0.30-0.35)

Non-Inferiority margin = 1.25 per 100 PY

Therapeutic vaccination



No. at Risk

M72/AS01 _E	1623	1618	1612	1607	1593	1584	1580	1576	1354	847	500	166	0
Placebo	1660	1648	1640	1630	1613	1594	1587	1584	1347	849	509	170	1

TB Treatment 2024

- Four month regimens for DS-TB using high dose rifamycins
- Stratification to even shorter regimens for DS-TB
- Simpler safer nine month regimens for MDR-TB using BDQ
- One month treatment of LTBI using rifapentine
- Therapeutic vaccination for LTBI