Resistance and New Drugs for *Mycobacterium tuberculosis*

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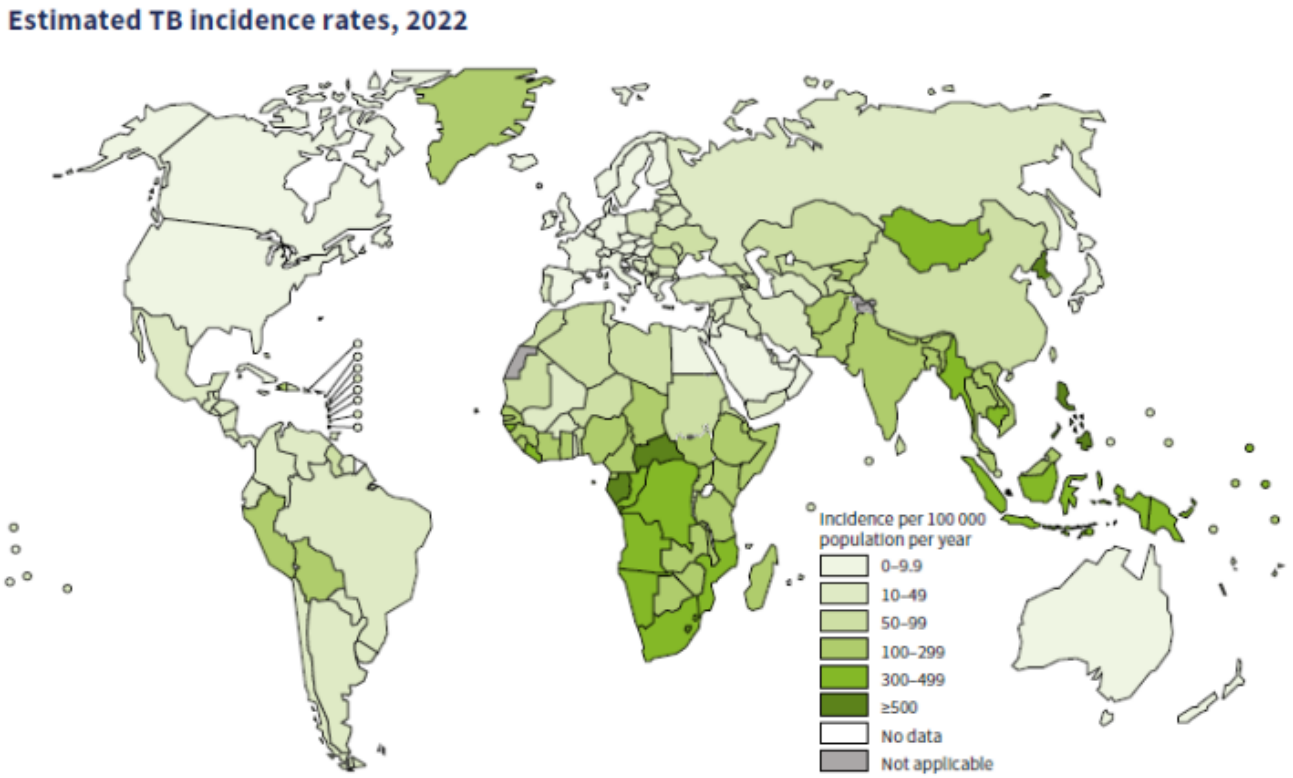
VANDERBILT UNIVERSITY
MEDICAL CENTER


TB ANYWHERE IS EVERYWHERE
The image
The dandelion is a plant which propagates itself by airborne means. In the same way, social action can spread and take root, carried on the winds of our efforts and the global determination to overcome this disease.
ge also represents the vulnerability of
here the disease, located anywhere,
d everywhere.
reventable and curable.
BAL PLAN TO STOP TB.
WORLD TB DAY
REUTERS

A. Problem statement

State-of-the-state: Global burden of TB disease



In 2014, TB surpassed HIV as the **#1 infectious disease killer worldwide** (now it is #2)

In 2022, 10.6M cases
A top 15 global cause of death

In 2021 & 2022, for the first time in a decade, TB mortality increased

WHO Global Tuberculosis Report 2023
Pai, Kasaeva, & Swaminathan, NEJM (2022) PMID 34986295

But TB is easy to treat, right?

The Role of Individual Drugs in "Short Course" Therapy

INH (H): Early **bactericidal** activity, rapid reduction in organism burden

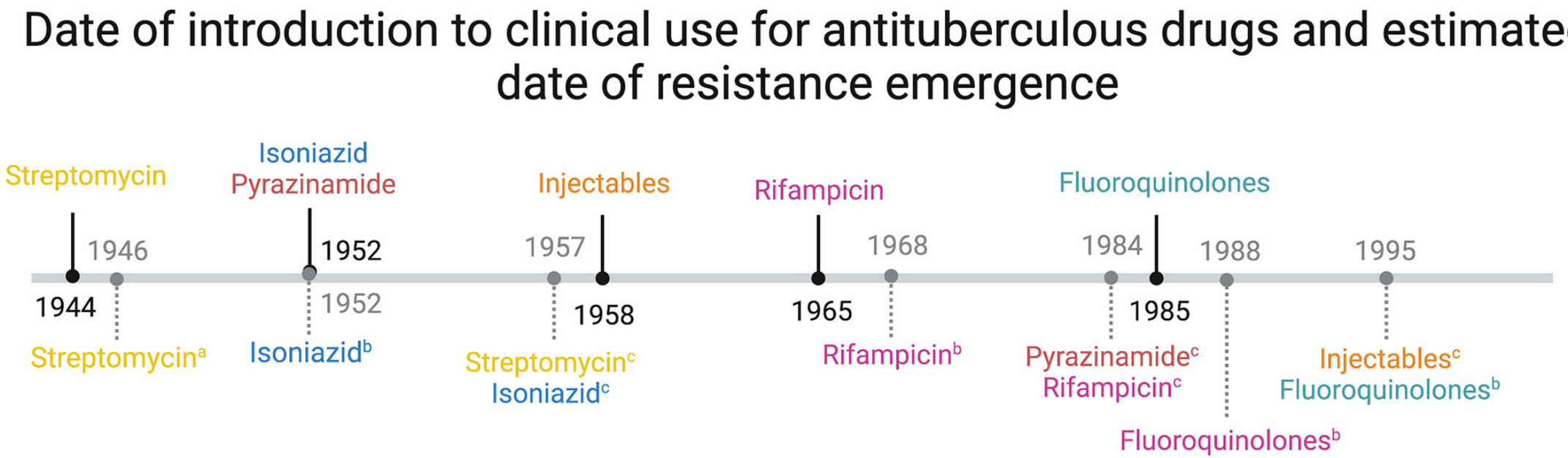
Rifampin (R): **Unique sterilizing** activity against "persisters", key contributor to cure without relapse

Pyrazinamide (Z): Sterilizing activity in **acidic environments** over the first 2 months, allowing for shortening of treatment

Ethambutol (E): **Prevents resistance** to other antibiotics

Each drug has a role. Together, they comprise an effective regimen

Emergence of resistance for anti-TB drugs: Rapid, predictable

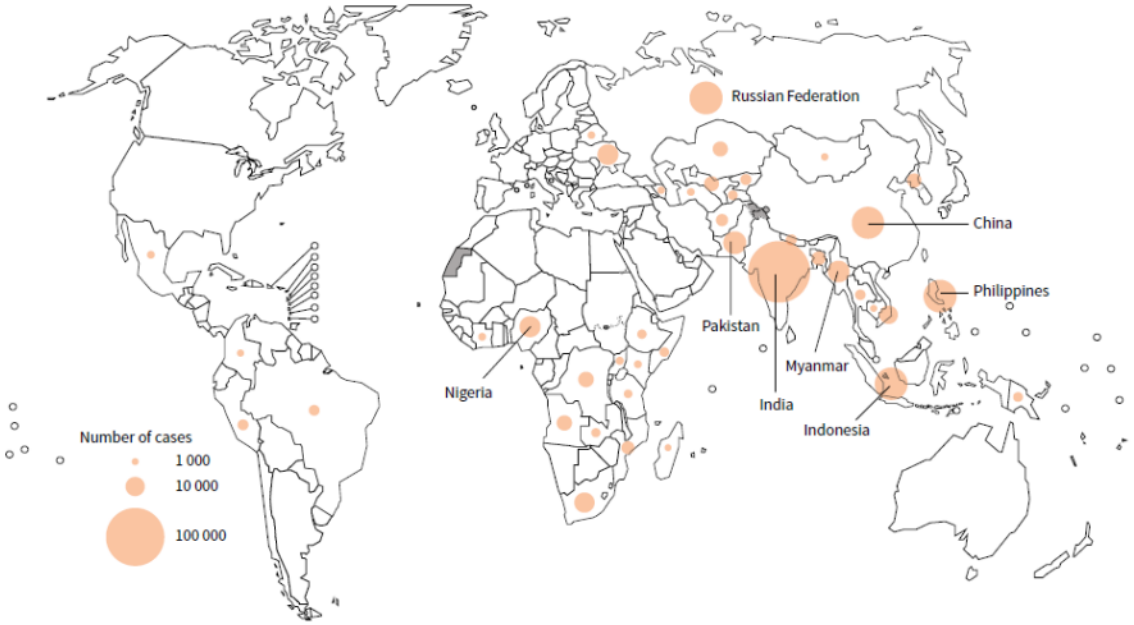


a Clinical case series report (Youmans et al. 1946)
b Global lineage 4 (Brynildsrud et al. 2018)
c Tugela Ferry XDR (Cohen et al. 2015)

MDR- and Totally Drug Resistant-TB: Global Health Emergencies

FIG. 17

Estimated number of people who developed MDR/RR-TB (incident cases) in 2022, for countries with at least 1000 incident cases[a]



[a] The eight countries ranked in descending order of the total number of RR-TB incident cases in 2022 are India, the Philippines, the Russian Federation, Indonesia, China, Pakistan, Myanmar and Nigeria.

Multidrug-resistant TB:
Mycobacterium tuberculosis **resistant to isoniazid and rifampin**: ~410,000 incident cases in 2022

https://www.youtube.com/watch?v=ziB_OwLda-g
India's Ticking Time Bomb! | Dr. Zarir Udwadia | TED

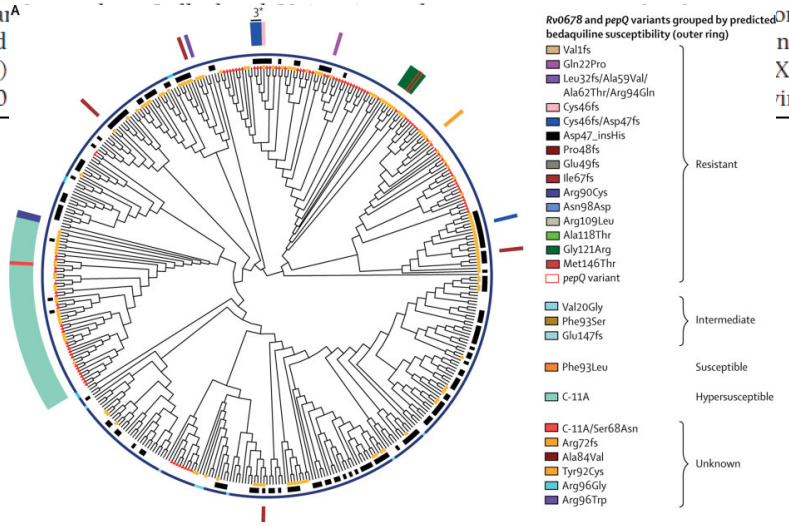
South Africa Warns of Emergence of "Totally" Drug-Resistant Tuberculosis

Anita Slomski

AFTER SPENDING 5 MONTHS VOLunteering at a small hospital in South Africa in 2007, physical therapist Natalie Skipper returned to her hometown of Paris, Tenn—a[A] a diagnosis of extensively d resistant tuberculosis (XDR-TB) took 2 years to treat, including 90

And experts warn it's just a matter of time before the TDR-TB spreads around the world. "Any place there is currently MDR or XDR, there will be TDR," warned Paul van Helden, PhD, professor of molecular and cellular bi-

XDR-TB has been identified in 84 countries. In the United States, MDR-TB accounted for 1.3% of the 10 528 cases of TB in 2011—a slight increase from previous years—and there were 6 cases of XDR-TB, according to the US Centers for on (CDC). nt success XDR, with ring.



Population-level emergence of bedaquiline and clofazimine resistance-associated variants among patients with drug-resistant tuberculosis in southern Africa
Nimmo Lancet Microbe 2020

Slomski JAMA 2013; Udwadia Respirology 2012; Veziris ERJ 2017

Drug-Resistant TB: Why Should We Care?

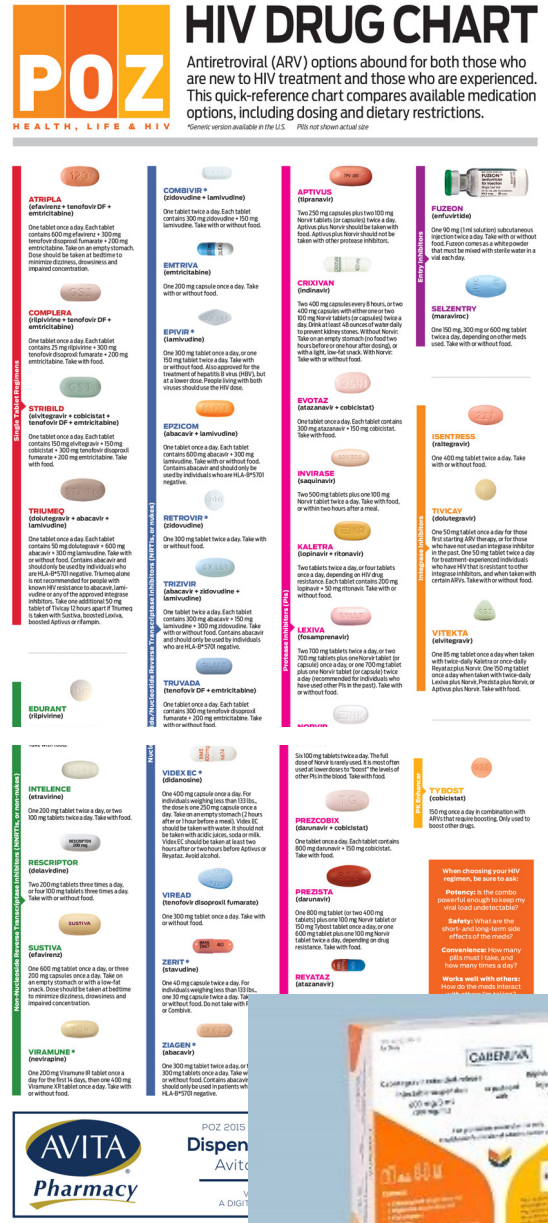
Antimicrobial resistance always happens:

"The emergence of antibacterial resistance is a normal evolutionary process for bacteria…"

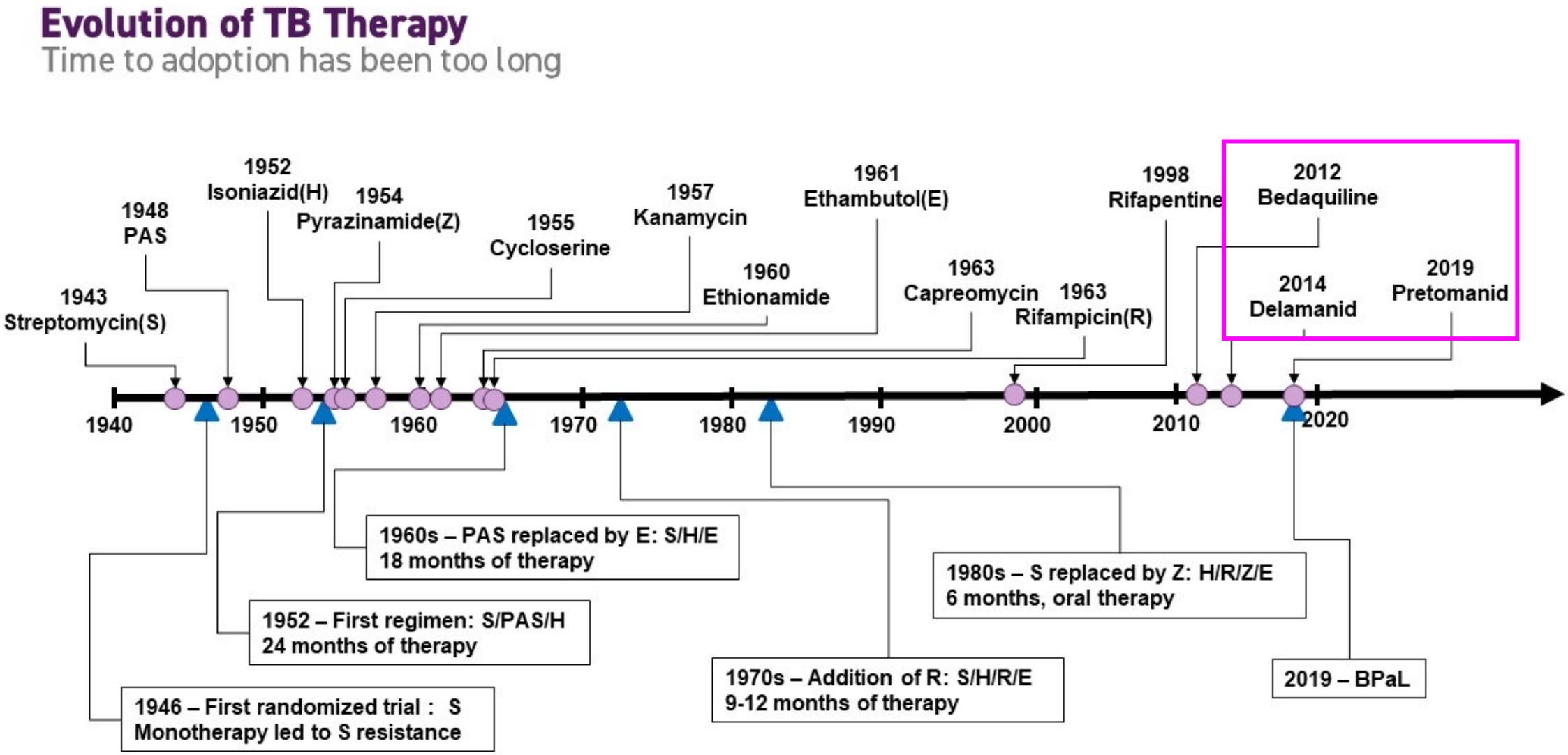
2020 Antibacterial Agents in Clinical and Preclinical Development, WHO 2021, https://www.who.int/publications/i/item/9789240021303

Why we need options

- **Choice**
- **Resistance**
- Forgiveness
- Tolerability
- Efficacy
- Drug interactions
- Duration/burden
- Completion
- Support adherence/reduce stigma



Licensing drugs for MDR-TB-- three new drugs this century



https://www.tballiance.org/sites/default/files/assets/TB-Alliance_TB-Therapy-Evolution_Graphic.jpg

‘Second Wave’ Drugs

	Bedaquiline**	Delamanid	Pretomanid
Class	**Diarylquinoline**	**Nitroimidazole**	**Nitroimidazole**
MOA	ATP synthase inhibitor	Ketomycolate synthesis inhibitor	Cell wall synthesis inhibitor; toxic reactive nitrogen species
Indication/ regulatory	FDA 2012, EMA 2013 MDR-TB; 24 weeks	EMA 2014 MDR-TB, 24 weeks	FDA 2019, EMA 2020 XDR TB with LZD+BDQ
Pediatrics	WHO , all ages	WHO, all ages	IMPAACT 2034, first-in-pediatrics, starting soon
PK quirks	CYP3A substrate Long terminal half-life	Metabolized by albumin Low bioavailability	CYP3A minor pathway
Safety	Moderate QT effects Requires ECG monitoring	Modest QT effects Occasional CNS side fx	Liver toxicity with PZA
HIV Co-Rx	Avoid EFV; caution with PI (CYP3A substrate)	--	Avoid EFV
Current trial landscape	Short-course MDR 4-month drug-sensitive	MDR prophylaxis Short-course DS & MDR	Short-course MDR 3-4 month drug-sensitive

** Similar ‘sterilizing’ activity to rifampicin- unique among new drugs/ drug classes

(Until recently)
Treatment of MDR-TB (*standard-duration* Rx: 12-24 months)

Group	Medicine	
A	Levofloxacin or moxifloxacin*	Generally well-tolerated
	Bedaquiline*	QT prolongation
	Linezolid*	Bone marrow suppression, peripheral neuropathy
B	Clofazimine§	Skin discoloration, ichthyosis
	Cycloserine or terizidone§	(Common) CNS toxicity
C‡	Ethambutol	(generally not active due to resistance)
	Delamanid	(Rare) CNS side effects
	Pyrazinamide	(generally not active due to resistance)
	Imipenem-cilastin or meropenem (+ clavulanic acid)	IV formulation
	Amikacin	Deafness, vestibular dysfunction, kidney toxicity
	Ethionamide or prothionamide	Nausea and vomiting
	p-aminosalicylic acid	GI toxicity, hypersensitivity, drug-induced lupus

*Use all 3; §Add both; ‡Add these, as needed

Lancet (2018) Menzies group; WHO Guidelines 2019

MDR/XDR-TB: A 6-month regimen!
Bedaquiline, Pretomanid, Linezolid (BPaL), the NixTB trial

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 5, 2020 VOL. 382 NO. 10

Treatment of Highly Drug-Resistant Pulmonary Tuberculosis

Francesca Conradie, M.B., B.Ch., Andreas H. Diacon, M.D., Nosipho Ngubane, M.B., B.Ch., Pauline Howell, M.B., B.Ch., Daniel Everitt, M.D., Angela M. Crook, Ph.D., Carl M. Mendel, M.D., Erica Egizi, M.P.H., Joanna Moreira, B.Sc., Juliano Timm, Ph.D., Timothy D. McHugh, Ph.D., Genevieve H. Wills, M.Sc., Anna Bateson, Ph.D., Robert Hunt, B.Sc., Christo Van Niekerk, M.D., Mengchun Li, M.D., Morounfolu Olugbosi, M.D., and Melvin Spigelman, M.D., for the Nix-TB Trial Team*

Summary points:

- Single-arm study of 109 patients in South Africa with XDR-TB or treatment-intolerant MDR-TB
- 6-month regimen of **bedaquiline, pretomanid, linezolid** (BPaL) with 90% treatment success
- Peripheral neuropathy in 81%, myelosuppression in 48%, mostly manageable and reversible

→ Registration of pretomanid, as BPaL

Bedaquiline, pretomanid, linezolid (at lower dose), moxifloxacin (BPaLM) for MDR-TB (an even better 6-month treatment regimen for MDR-TB)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A 24-Week, All-Oral Regimen for Rifampin-Resistant Tuberculosis

Bern-Thomas Nyang'wa, M.B., B.S., Catherine Berry, B.Med., Emil Kazounis, M.Med.Sci., Ilaria Motta, Ph.D., Nargiza Parpieva, Sc.D., Zinaida Tigay, M.D., Varvara Solodovnikova, M.D., Irina Liverko, Sc.D., Ronelle Moodliar, M.B., B.S., Matthew Dodd, M.Sc., Nosipho Ngubane, M.B., B.Ch., Mohammed Rassool, M.B., B.Ch., Timothy D. McHugh, Ph.D., Melvin Spigelman, M.D., David A.J. Moore, M.D., Koert Ritmeijer, Ph.D., Philipp du Cros, M.B., B.S., and Katherine Fielding, Ph.D., for the TB-PRACTECAL Study Collaborators*

Table 2. Primary Efficacy Analysis at 72 Weeks.

Variable	Intention-to-Treat Population		Modified Intention-to-Treat Population	
	Standard-Care Group (N=73)	BPaLM Group (N=72)	Standard-Care Group (N=66)	BPaLM Group (N=62)
Favorable outcome — no. (%)	34 (47)	55 (76)	34 (52)	55 (89)
Primary outcome: unfavorable status — no. (%)	39 (53)	17 (24)	32 (48)	7 (11)
Death — no. (%)	2 (3)	0	2 (3)	0
Early discontinuation — no. (%)	35 (48)	15 (21)	28 (42)	5 (8)
Adherence issues — no./total no. (%)	3/35 (9)	0	3/28 (11)	0
Adverse event — no./total no. (%)	17/35 (49)	5/15 (33)	17/28 (61)	5/5 (100)
Did not meet inclusion or exclusion criteria, detected after first dose — no./total no. (%)	7/35 (20)	10/15 (67)	0	0
Withdrew consent while still receiving treatment — no./total no. (%)	6/35 (17)	0	6/28 (21)	0
Other reason — no./total no. (%)†	2/35 (6)	0	2/28 (7)	0
Treatment failure — no.	0	0	0	0
Lost to follow-up at 72 wk — no. (%)	2 (3)	2 (3)	2 (3)	2 (3)
Recurrence — no.	0	0	0	0
Risk difference for the primary outcome — percentage points (96.6% CI)‡	—	−30 (−46 to −14)	—	−37 (−53 to −22)

World Health Organization

Rapid communication: Key changes to the treatment of drug-resistant tuberculosis

Bedaquiline resistance- the time to worry is now

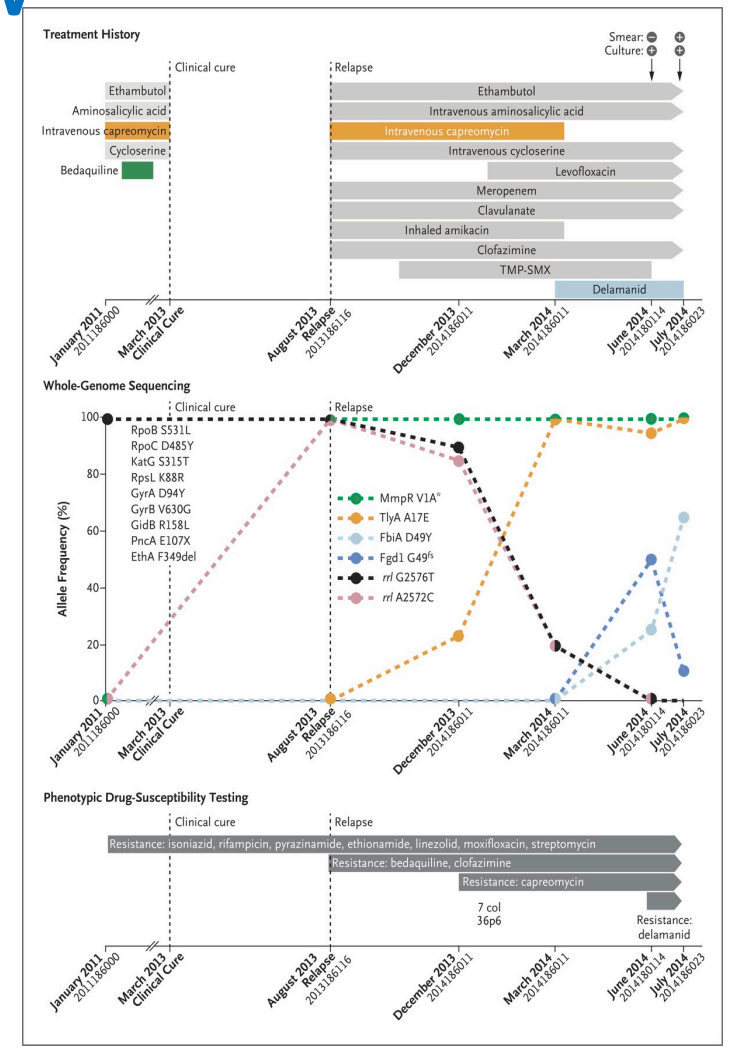


Fig 1. Clinical Features, Treatment History, Amplification of Drug Resistance, and Phenotypic Drug-Susceptibility Testing in the Patient. Bloemberg et al NEJM 2015 373: 1986.

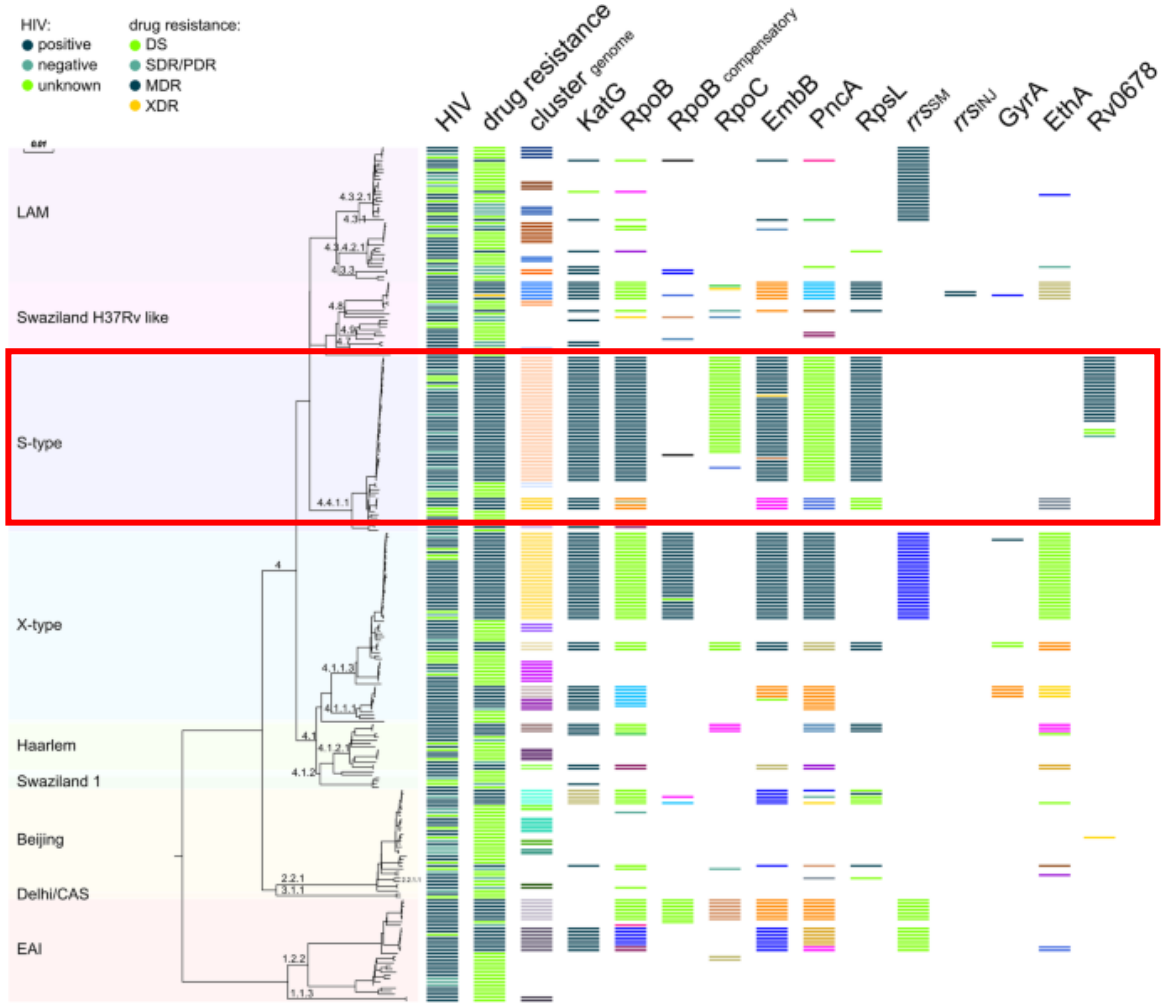
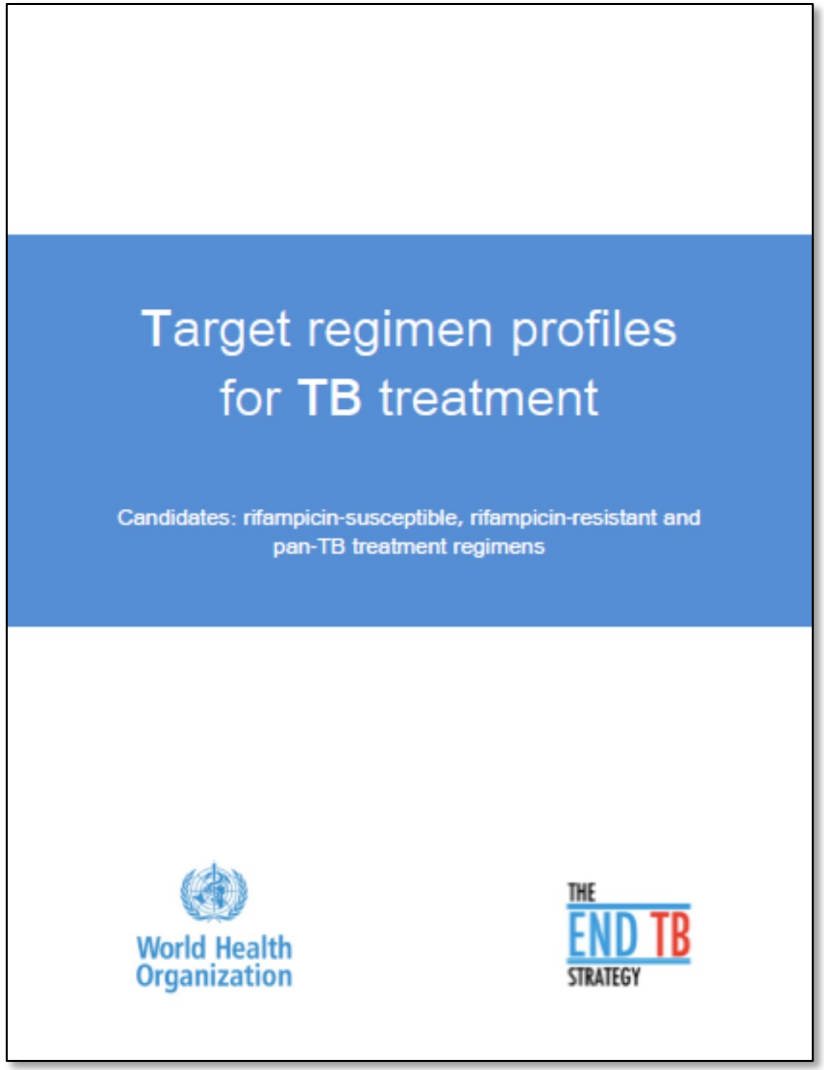


Fig 1. MDR *M. tuberculosis* outbreak strain in Eswatini missed by Xpert has elevated bedaquiline resistance dated to the pre-treatment era. Beckert et al Genome Medicine 2020

B. New Drugs

Target Regimen Profiles (TRP): What are we aiming for?

- TRPs prioritize regimen characteristics
- TRP takes into account the needs of patients, care providers and policy-makers
- Target audience includes pharmaceutical industry, research institutions, PDPs, donors, NGOs & civil society organizations
- TRPs for
  - Rif susceptible TB regimens
  - Rif Resistant TB regimens
  - “Pan TB” regimens*



*Drug-resistant organisms may behave differently from drug-sensitive organisms, aside from response to drug X or Y

2023 Global New TB Drug Pipeline[1] Updated 11/1/2023

Discovery | Preclinical Development | Clinical Development

Lead Optimization

Indazole sulfonamides

Diarylthiazoles

DprE1 Inhibitors

Direct InhA Inhibitors

Mtb energy metabolism

Gyrase Inhibitors

Arylsulfonamides

Inhibitors of MmpL3, Translocase-1, ClpC1, ClpP1P2, PKS13, F-ATP synthase, RNAP

Oxazolidinones

DnaE1 / Nargenicin analogs

Early Stage Development

FIM-253

TBD10 (MK-3854)

CLB-073*

SPR720*

MPL-447*

JSF-3285*

CPZEN-45*

NTB-3119*

MBX-4888A (1810)*

FNDR-20364*

GMP / GLP Tox.

GSK-839*

OTB-658

Phase 1

TBD09 (MK-7762)

GSK-286*

TBAJ-587

TBI-223

Macozinone* (PBTZ-169)

Phase 2

Telacebec* (Q203)

Alpibectir (BVL-GSK098)*

TBAJ-876

Sanfetrinem

Delpazolid, Sutezolid, Tedizolid

BTZ-043*

TBA-7371*

Quabodepistat (OPC-167832*)

Ganfeborole (GSK-656*/070)

Pyrifazimine (TBI-166)

SQ-109*

Phase 3

Sudapyridine (WX-081)

Regulatory Market Approvals

Bedaquiline*

Delamanid*

Pretomanid*

*New chemical class. Known chemical classes for any indication are color coded: rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide, beta-lactam.

[1] New Molecular Entities not yet approved, being developed for TB or only conditionally approved for TB. Showing most advanced stage reported for each. Details for projects listed can be found at http://www.newtbdrugs.org/pipeline/clinical

Ongoing projects without a lead compound identified: http://www.newtbdrugs.org/pipeline/discovery

Underline = updates since November 2022

WORKING GROUP ON NEW TB DRUGS

www.newtbdrugs.org

Updated: November 2023

TB Drug Pipeline- drugs in clinical testing

***Drugs in red will bypass dedicated EBA studies**
****Drugs in similarly-shaded boxes are from same drug class**

Phase 1	Phase 2	Owner	Data
GSK-286*	Telacebec (Q203)	TB Alliance	EBA completed
TBAJ-876 →	Alpibectir (BVL-GSK098)/Eth	BioVersys/GSK	EBA completed
TBAJ-587	Sanfetrinem	GSK	EBA underway
TBI-223 →	Delpazolid	LegoChem Biosciences	Ph2 4BDM+Dpz completed
MK-7762	Sutezolid	TB Alliance	Ph2 4BDM+Stz resulted
	BTZ-043	LMU	EBA completed
	TBA-7371	TB Alliance	EBA completed
	Quabodepistat (OPC-167832)	Otsuka	+ EBA; DBO completed
	Ganfeborole (GSK-656)	GSK	EBA completed
	Sudapyridine (WX-181)	Shanghai Jiatan Pharmatech	EBA completed

Oxazolidinones (like linezolid) Diarylquinolines (like bedaquiline) DprE1 inhibitors

- **Some drugs from completely novel classes**
- **Others from familiar classes, but potential for better therapeutic window**

Current Antimicrobial Therapy Trials Landscape: Drug-Sensitive TB

1. HIGH-DOSE RIFAMYCINS

RIFASHORT
2 $HR_{1200}ZE$/2 HR_{1200}
2 $HR_{1800}ZE$/2 HR_{1800}

TBTC S31/ ACTG A5349
2 HPZE/2 HP
2 HPZM/2 HPM

ACTG Clo-Fast
4 HPZEClofaz

ACTG A5414
HPZM, stratified, duration-randomized

2. REPURPOSING OLD DRUGS
(CLOFAZIMINE, LINEZOLID, FLUOROQUINOLONES)

BMRC TRUNCATE-TB
2 HR_{35}ZELinezolid (up to 3 mos for persistent + sx/smear)
2 HR_{35}ZEClofaz
2 HP_{1200}ZLinezolidLevoflox
2 HBZELevoflox

PANACEA SUDOCU
Hd* R +/- Hd PZA
Bedaquiline/ Delamanid/ Moxifloxacin + Sutezolid (S)

DECODE
BDM+ delpazolid

*Hd= High Dose

TBA SimpliciTB
4 BPaMZ

TBTC S38/ CRUSH-TB
•2 BMZRb/2 BMRb
•2 BMZD/2 BMD

3. EXPLORING NEW & NEWER DRUGS
(E.G. BEDAQUILINE, PRETOMANID, NEW CHEMICAL ENTITIES (NCE))

UNITE4TB
Control arms: HRZE/HR, BDM/HR
GSK656 Arms: BD**G** + M, L, or Z
BTZ043 Arms: BDT + M, L, or Z
BDM, BDGT

ACTG RAD-TB
1: BPaL vs. BPa(TBI223) vs. BPaS vs. HRZE

Otsuka
DBQ (with Q 10, 30, 90)

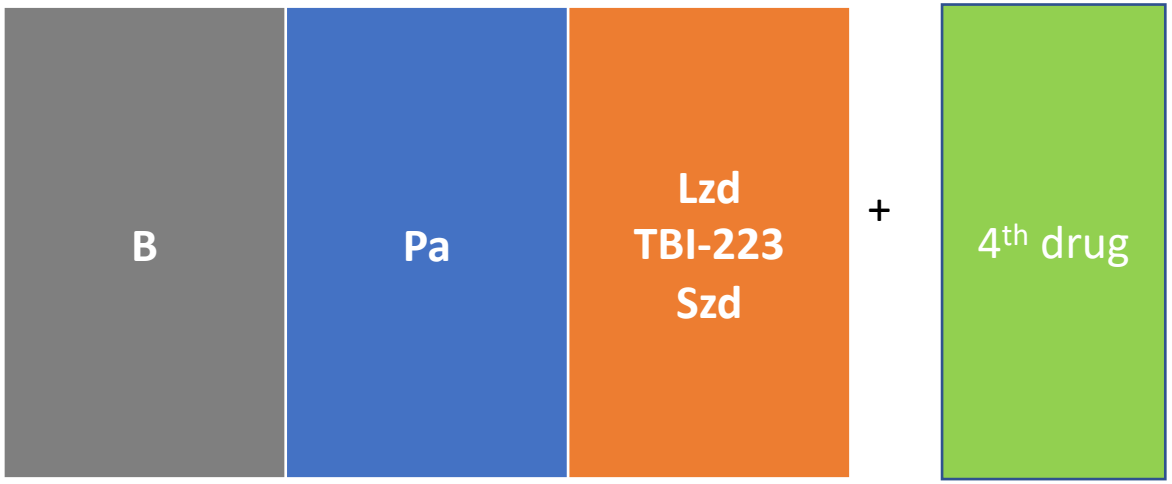
Gates MRI PAN-TB
DBQS
PBQS

Otsuka/GSK
GSK656+B or D or BD

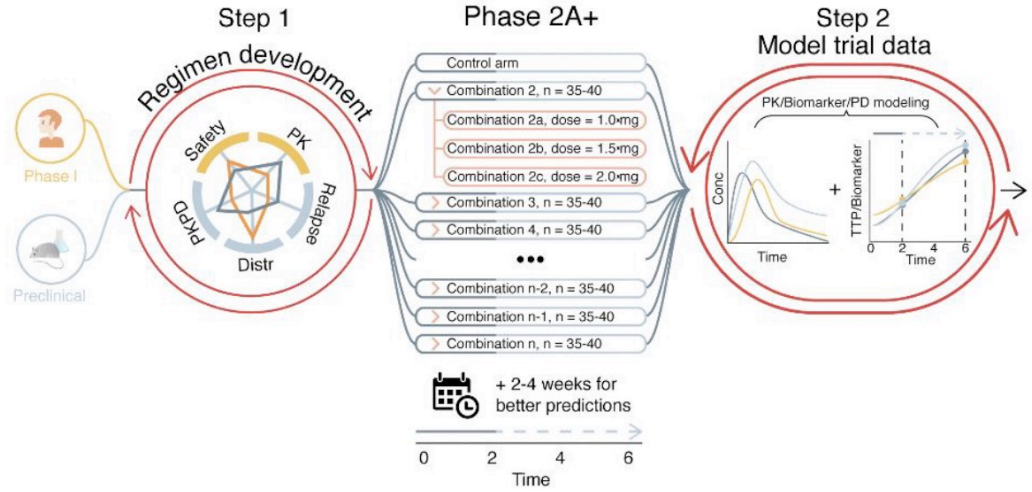
TB Alliance
BPaL vs. (TBAJ876)PaL (dose ranging) vs. vs. HRZE

ACTG A5409: A Phase 2A+ Randomized, Adaptive, Dose-Ranging, Open-Label 6-Week Trial of Novel TB Treatment Regimens

Part 1: Oxazolidinone



Part 2: Optimal 4th drug



Part 3: Diarylquinoline

Optimize DARQ

TBAJ-587
TBAJ-876

Part 1: Oxazolidinone (OXA) selection and dose selection

- **LZD:** 600 mg daily
- **TBI-223 & STZ:** dose ranging

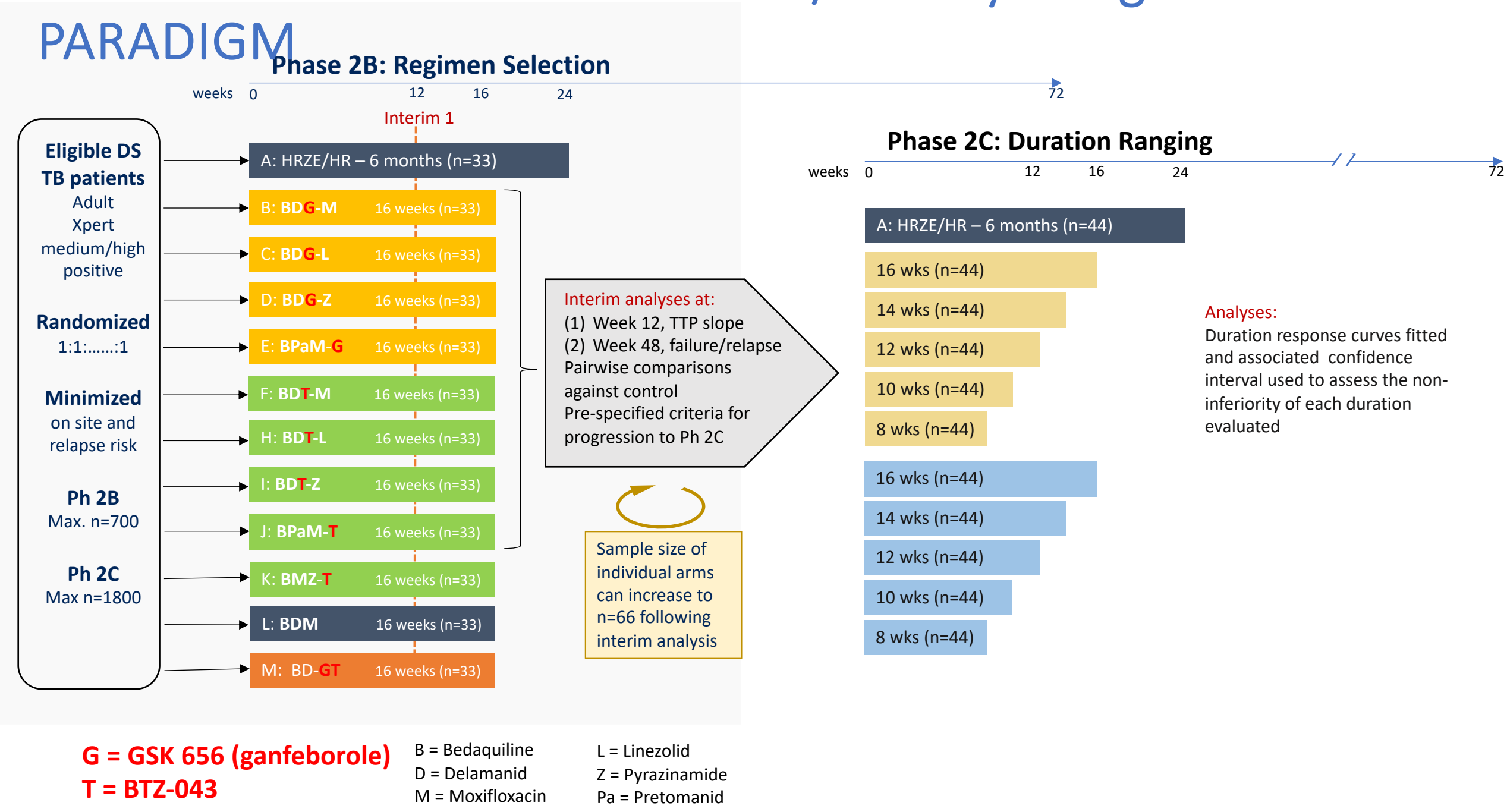
Part 2: Addition of an optimal 4th drug

Part 3: Diarylquinoline (DARQ) selection and dose selection

Tools to rank regimens

- Empirical
- Mechanistic
- Lesion penetration

UNITE4TB-01 seamless Phase 2B/C study design: PARADIGM

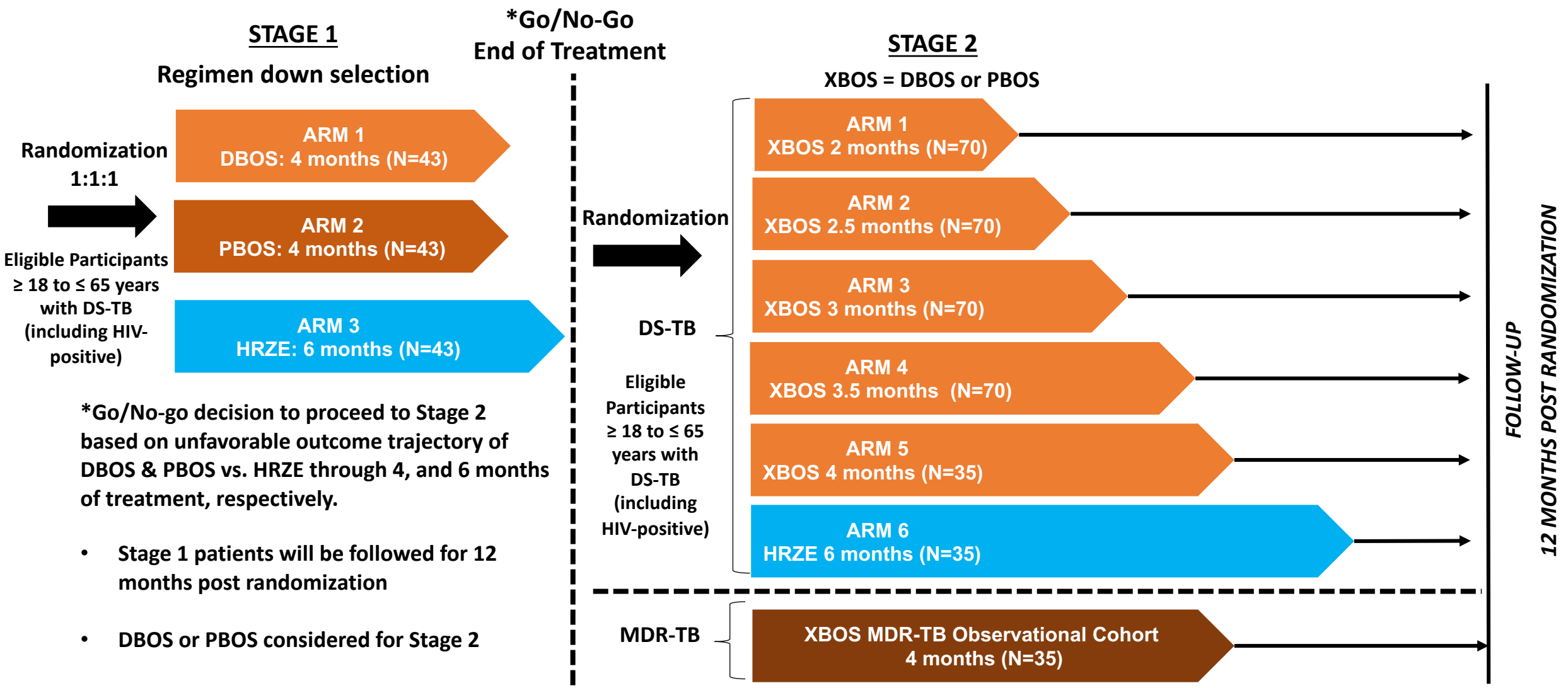


G = GSK 656 (ganfeborole)
T = BTZ-043

B = Bedaquiline
D = Delamanid
M = Moxifloxacin

L = Linezolid
Z = Pyrazinamide
Pa = Pretomanid

Planned PAN-TB Ph2b/2c 2-Stage, De-risking Design



*Go/No-go decision to proceed to Stage 2 based on unfavorable outcome trajectory of DBOS & PBOS vs. HRZE through 4, and 6 months of treatment, respectively.

- Stage 1 patients will be followed for 12 months post randomization
- DBOS or PBOS considered for Stage 2

D – delamanid, P – pretomanid, B – bedaquiline, **O – OPC-167832, S – sutezolid**

C. New Tools/Strategies

Lessons learned

Long Timelines

- Innovation in trial designs
  - MAD/EBA, skip EBA, Ph2C, adaptive design
- Pharmacology-guided drug development

Inclusion/ Generalizability

- Include PWHIV in Ph2
- Adolescents, where possible
- Pediatric studies/formulations
- Community engagement

Resistance

- Development of testing alongside trials
- Surveillance

Safety

- May vary by context (e.g. companion drugs)
- Top of mind: monitoring, clinical importance

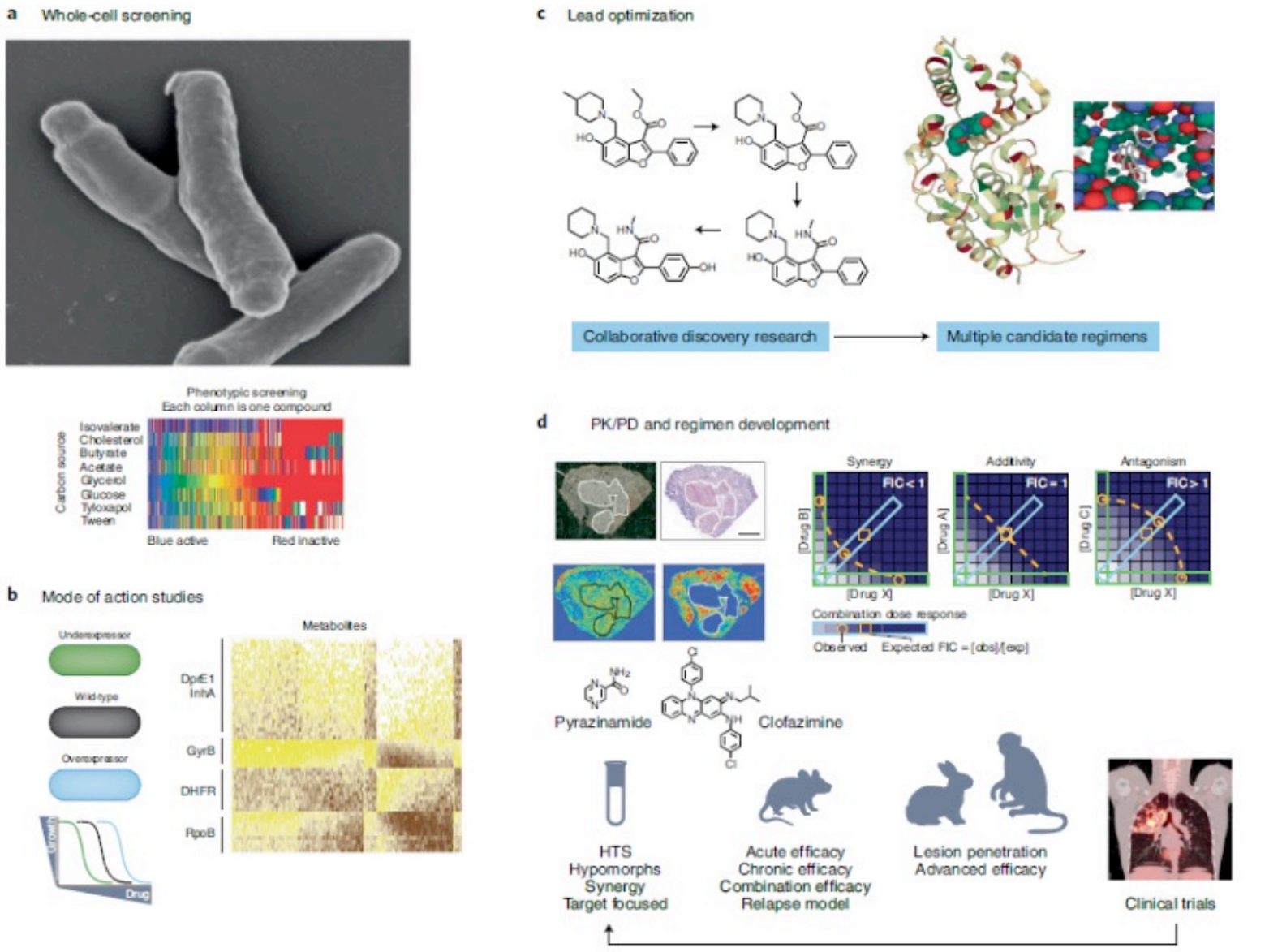
Preclinical-clinical translation

- Grown in sophistication
- Lesion penetration critical
- Patient phenotyping (high vs. low risk for relapse)

Data integration/ sharing/tool devt

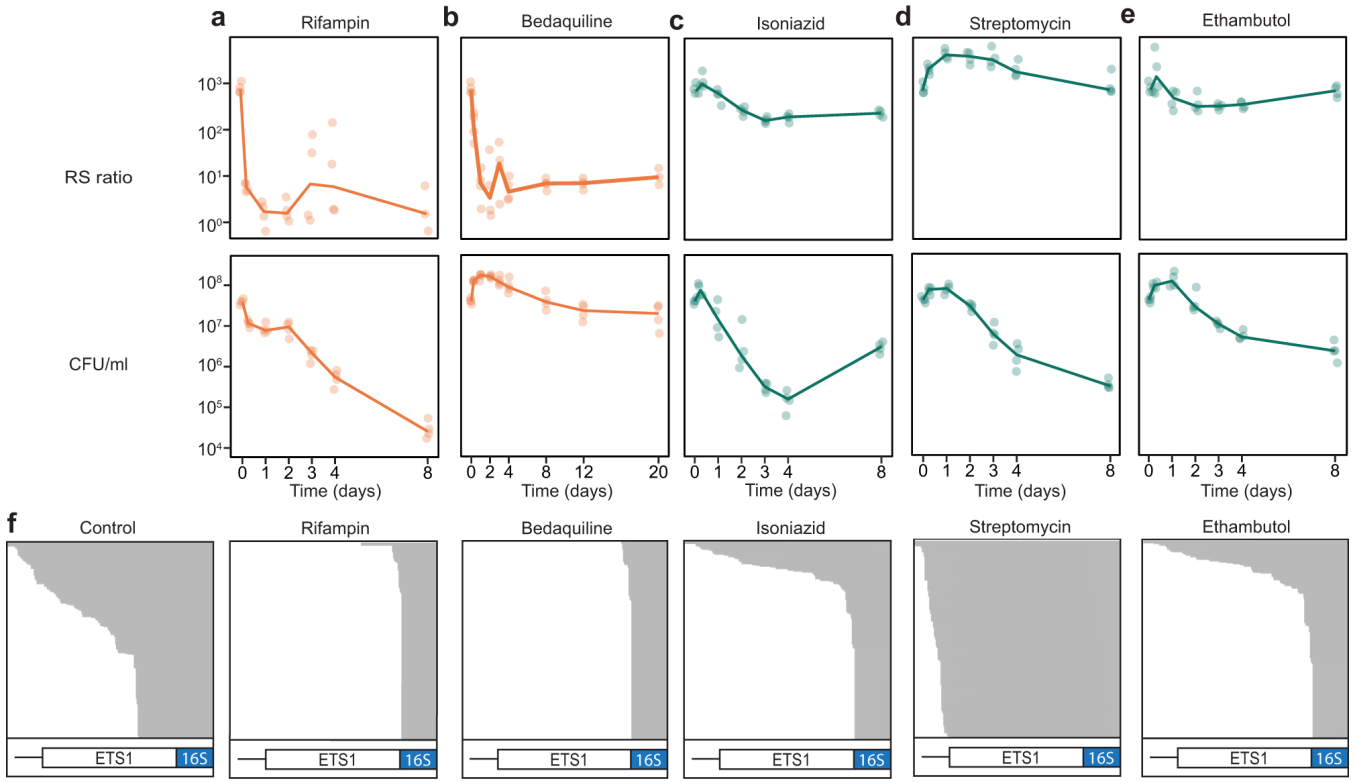
- To streamline drug development
- De-risking, accurate selection of winning regimens

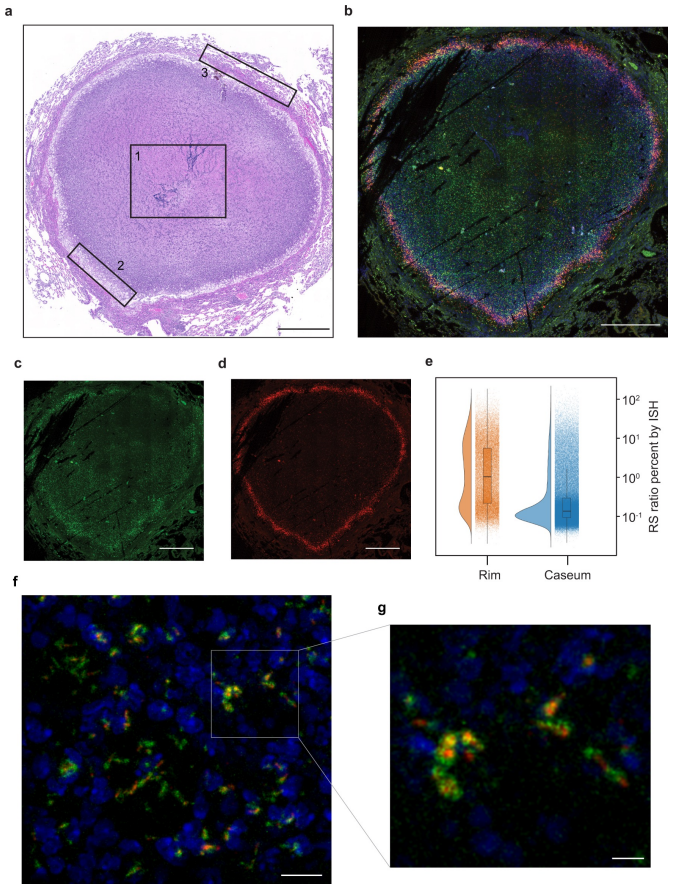
Public-Private Partnerships: Example of TB Drug Accelerator



Aldridge et al , Nature Medicine, 2021

Biomarkers for activity against ‘persisters’: RS Ratio





RS ratio (precursor rRNA vs. mature rRNA) as a marker of *M.tb. r*eplication

Physiologic marker correlating with growth

Predictor of treatment response *independent of & complementary to* culture

“While 23S rRNA signals were similar in the rim and caseum ($P = 0.62$), the pre-rRNA mean fluorescent intensity (MFI) was significantly lower in the caseum ($P < 0.0001$), indicating a **quiescent caseum *Mtb* population** with decreased rRNA synthesis.”

Walter et al Nature Comm 2021 12: 2899. See also AAC 2023 PMID 37565762

Trial design innovations

Preclinical-translational modeling

First-in-Human (individual drug X), Phase I

Single dose, Multiple dose
Safety and PK studies
Healthy volunteers without TB

Early Bactericidal Activity (EBA) trial (Phase 2A)
Individual drug X
Or Drug X in combination
Dose-Ranging
7-14 days
15-20 patients/arm
Outcome: Sputum colony forming units over time with treatment
Deliverable: Evidence of single drug microbiologic effect; Dose to take forward

Multidrug treatment trial Phase 2B
Combination therapy
Limited number of doses
8 weeks
50-75 patients/arm
Outcome: Sputum culture conversion to negative at 8 weeks
Deliverable: Safety, comparative early microbiologic activity, go/no-go for Phase 3

Confirmatory trial Phase 3
Combination therapy
Single dose of X
Full course of treatment
500-1000 patients/arm
Outcome: Failure/relapse
Deliverable: Noninferiority compared to standard treatment

Post-marketing studies
Pediatric studies
HIV, drug interactions
Novel combinations
Regroup following Ph3 failures

Preclinical-translational modeling

Preclinical/translational

Phase I/Phase IIA Combined
(MAD in PWTB)

Ph2 Duration Randomization
Early data on optimal treatment duration

Phase 2A+
Dose-finding in combination
Intra-class comparisons
Longitudinal time-to-positivity data

Phase 2C
Intended-duration studies with f/u for clinical (not just microbiologic) outcomes

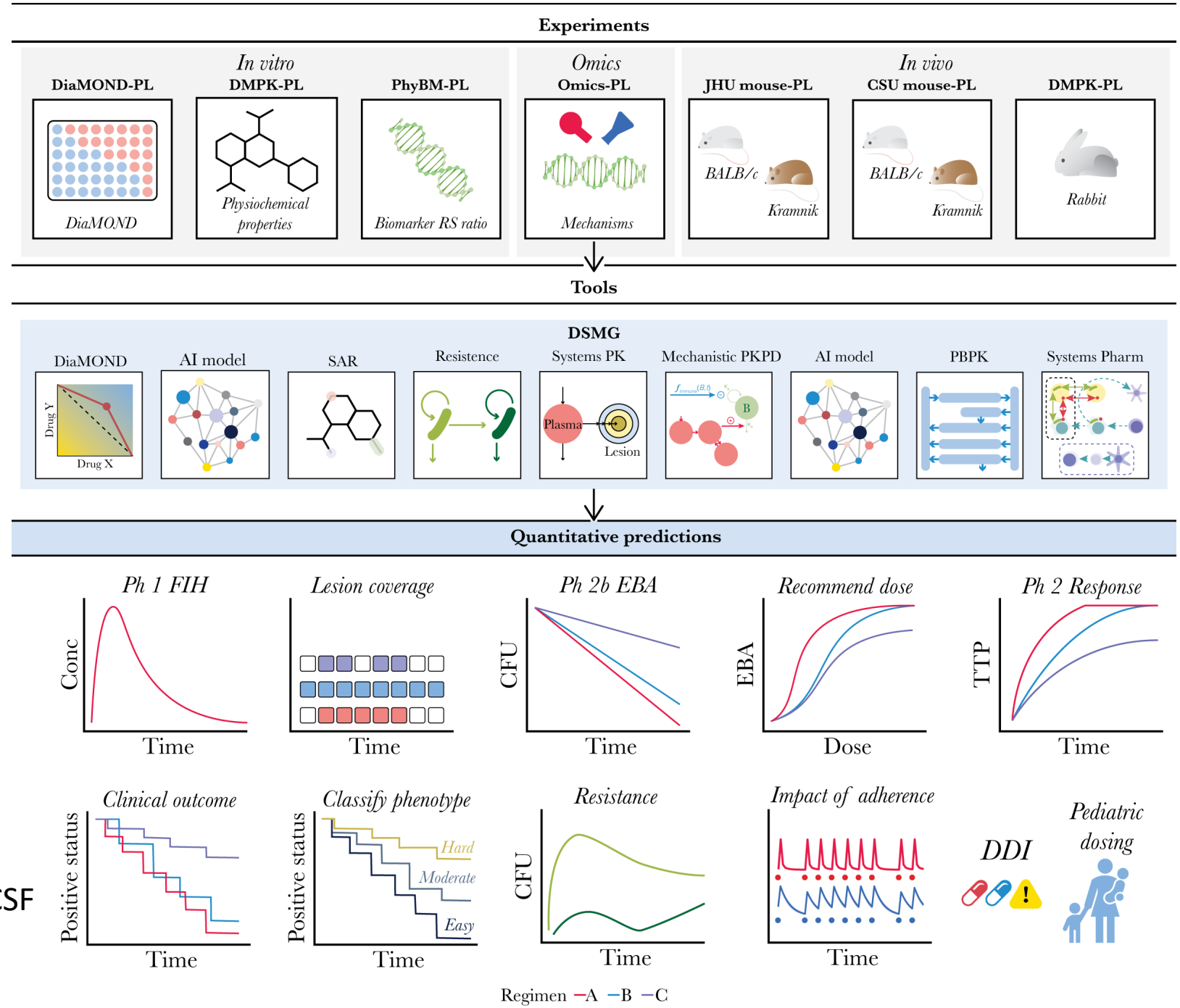
Skip Ph2A/EBA
Use pre-clinical results and PhI to predict Phase 2B/C doses/regimens

Earlier inclusion
Children
PWHIV
Pregnant persons

Knowledge Integration

Building/Validating Tools

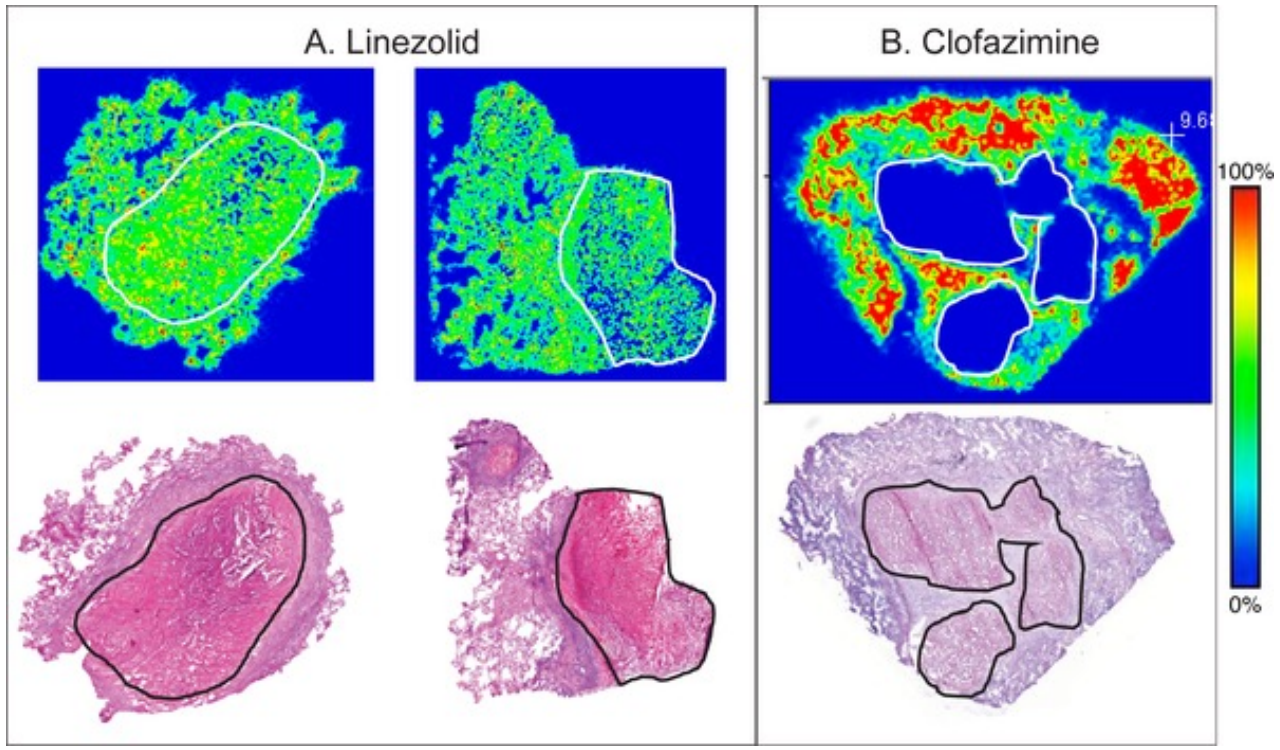
Synthesis of Data/Platforms



Slide courtesy of Rada Savic, UCSF

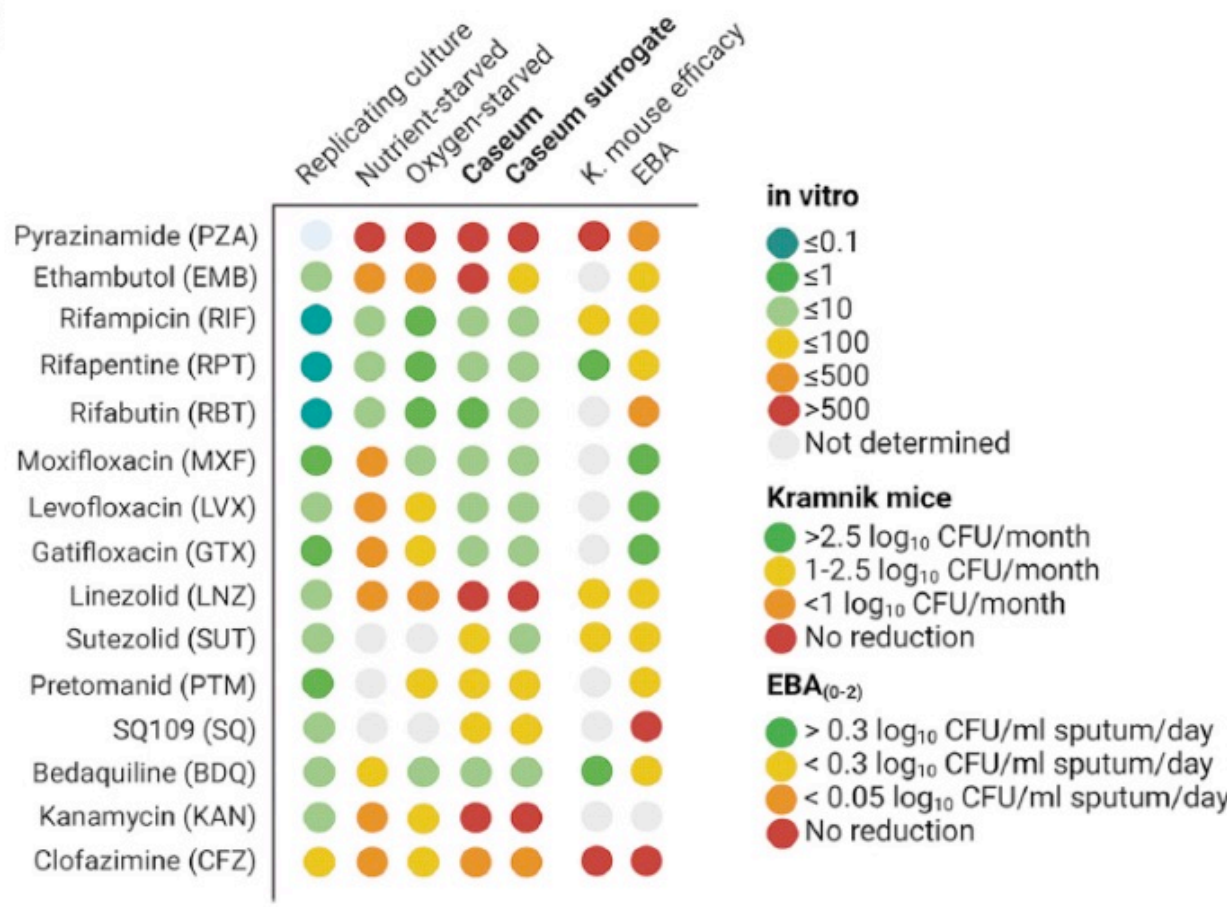
PK & Activity in Caseum (e.g. site-of-disease)

Drug penetration into lesions



Strydom N, Gupta SV, Fox WS, Via LE, Bang H, et al. (2019) Tuberculosis drugs' distribution and emergence of resistance in patient's lung lesions: A mechanistic model and tool for regimen and dose optimization. PLOS Medicine 16(4): e1002773.

Drug activity in caseum



Sarathy et al, mBio, 2023

Knowledge Integration for Tuberculosis Therapeutics (KITT)

Goal and Objective

The overall goal of KITT is to accelerate TB drug and regimen development through synergizing global efforts and reducing duplication and competition for scarce resources.

KITT aims to create an *inclusive, collaborative platform for relevant consortia and groups involved in TB treatment R&D to share trial plans, designs, information and data to advance research outcomes.*

Expected Outcome

KITT members will establish a *global community of TB drug trialists* to enable sharing of ideas and plans, and build trust for the sharing of potentially sensitive information, as needed.

Through early sharing of knowledge, KITT will stimulate the creation of *model-informed drug development frameworks* for a new generation of *knowledge-based TB regimen development*.

Kick-off meeting
London, September 2023

Slide, adapted, from Christian Lienhardt

Summary

- *Mycobacterium tuberculosis* is a millennia-old, wily pathogen
- As we develop new therapeutics, resistance always emerges
- Solution is to:
  - Maintain a robust pipeline of new chemical entities
  - Continue to develop novel tools aimed at smarter drug & regimen development
  - Integrate & share data
  - Motivate for the need for multiple safe, effective options
  - Continue to attract young, talented people into the field (of AMR, of TB), the most pressing area of unmet medical need

Thank you for the invitation and for your attention!