# Discovering and developing new treatments for tuberculosis

Guest speaker: Nader Fotouhi

Moderator: Lydia Nakiyingi

Host: Astrid Pentz-Murr (GARDP)

**24 March 2021**

GARDP
Global Antibiotic Research & Development Partnership

In collaboration with:

TB Alliance

This webinar was collaboratively organized by GARDP and the TB Alliance

TB Alliance

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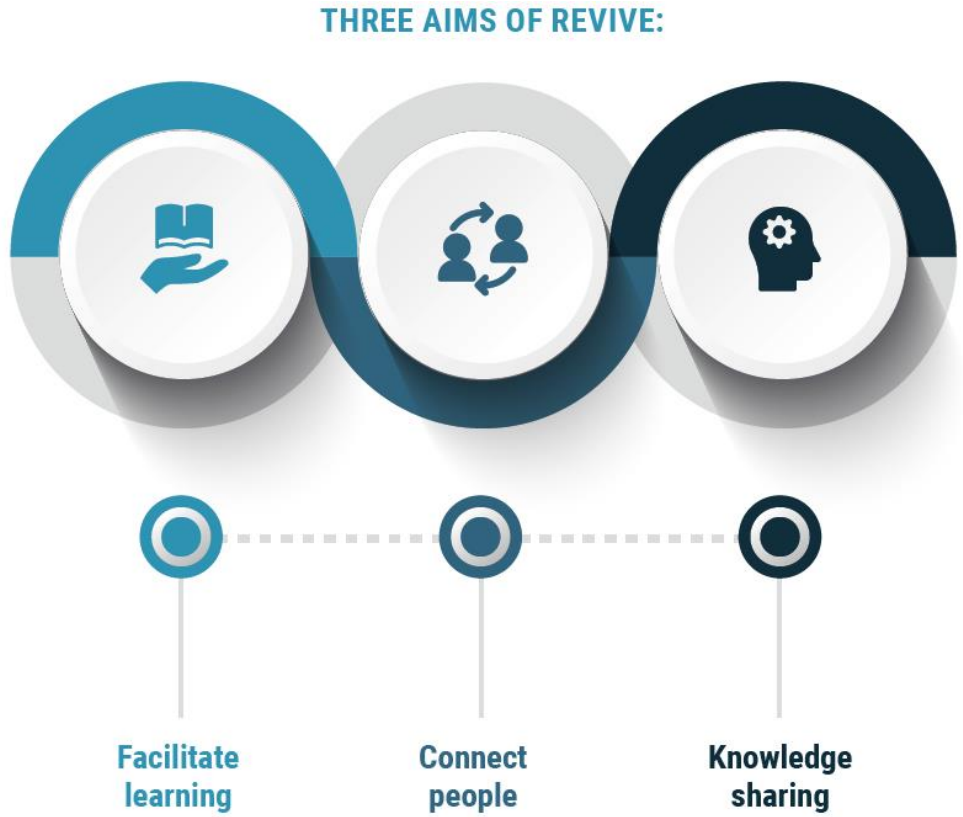
An online space to connect and support the antimicrobial discovery, research, and development community



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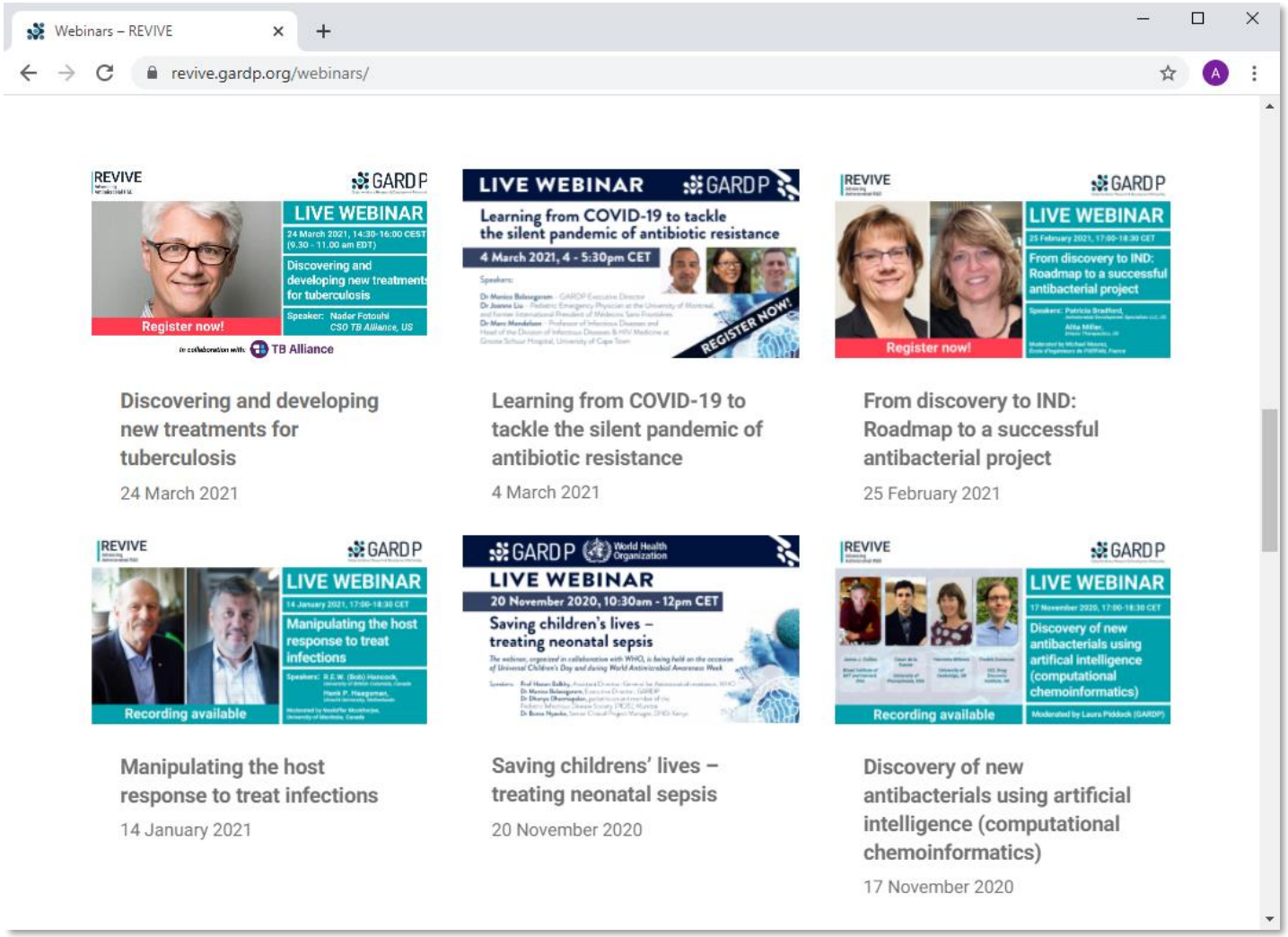


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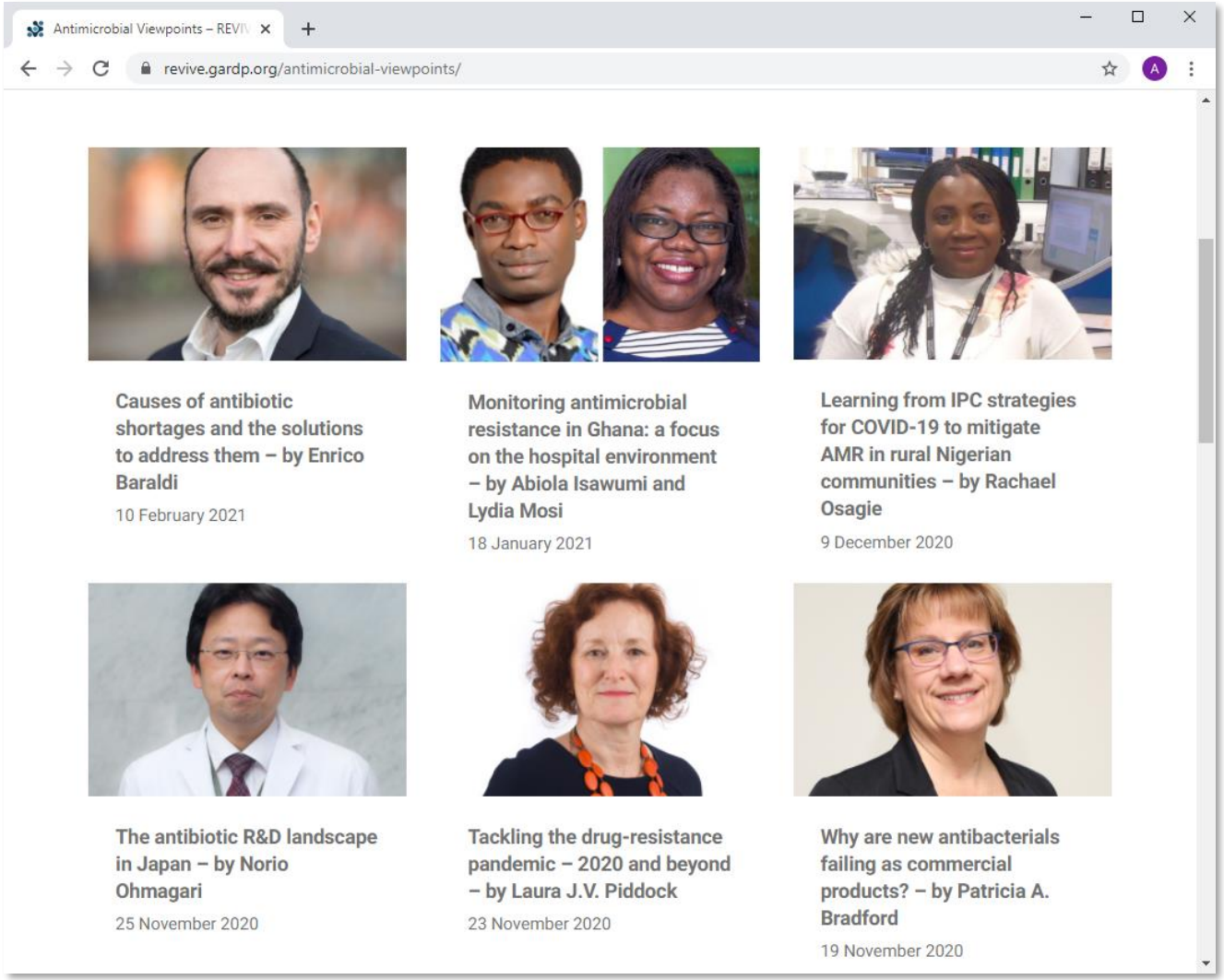
# Antimicrobial Viewpoints

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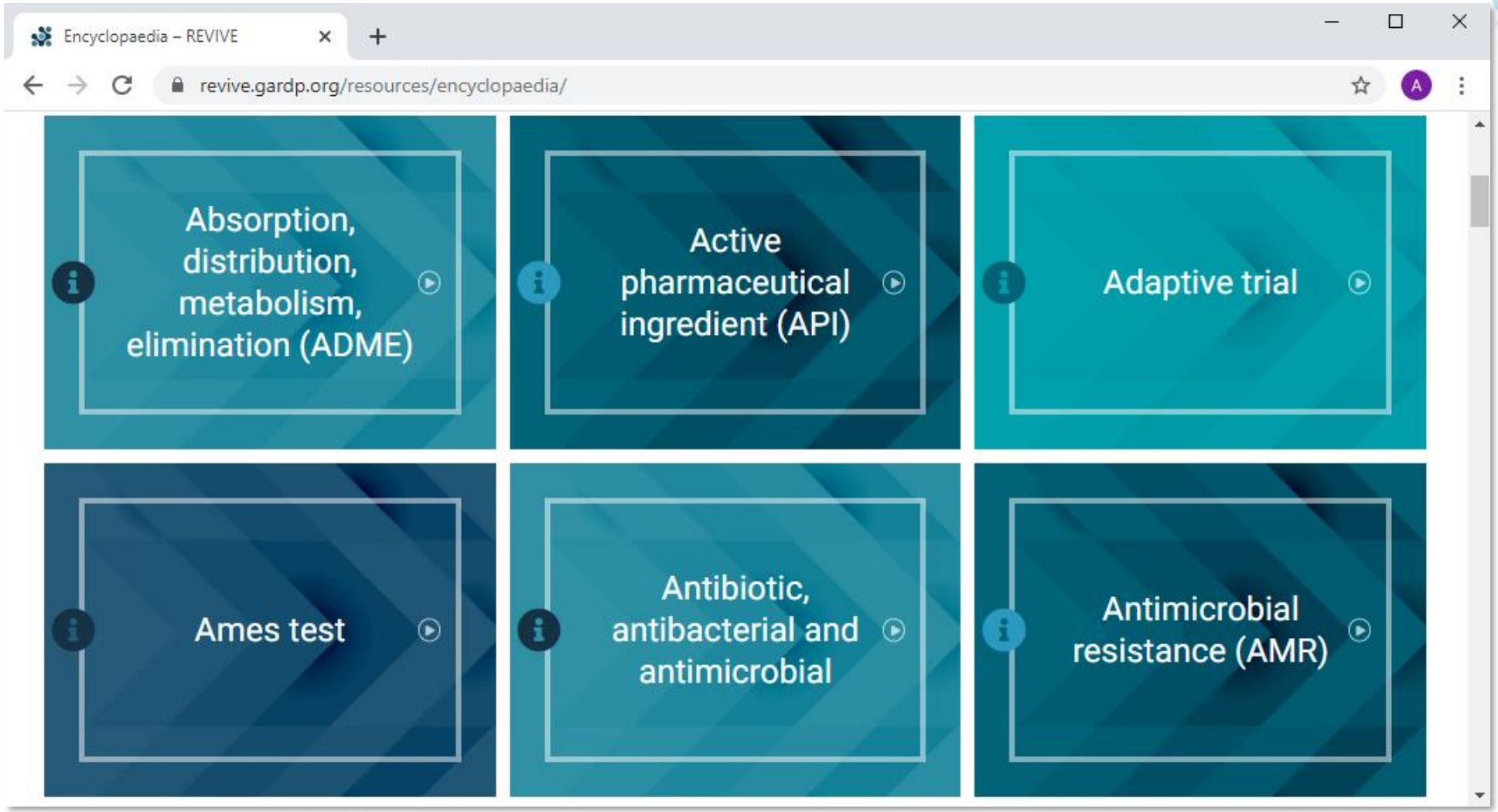
# Antimicrobial Encyclopaedia

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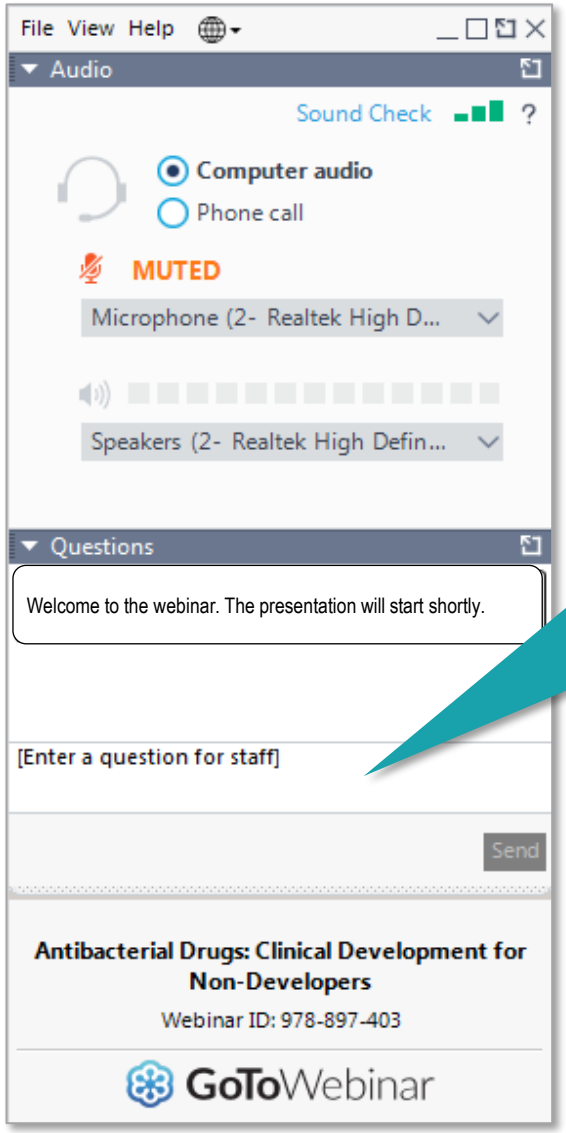
# How to submit your questions




The presentation will be followed by an interactive Q&A session.

Please submit your questions via the ‘questions’ window. We will review all questions and respond to as many as possible after the presentation.

# Today’s speakers

## Discovering and developing new treatments for tuberculosis

**Nader Fotouhi**
*Chief Scientific Officer*
TB Alliance (US)

**Moderator:**
**Lydia Nakiyingi**
*Infectious diseases physician, research scientist and senior lecturer*
Makerere University College of Health Sciences, Kampala (Uganda)

# Nader Fotouhi

As Chief Scientific Officer for the TB Alliance, Dr. Nader Fotouhi guides and oversees the organization’s research and preclinical development activities.

Nader has 24 years of experience in the pharmaceutical industry, with significant research and early development expertise in a variety of therapeutic areas. Prior to joining the TB Alliance, Nader held various leadership positions at Hoffmann-La Roche, including the head of the Discovery Chemistry group at the Nutley New Jersey site, the global head of Discovery Technologies, and served as the Nutley New Jersey Pharma Research and Early Development Site Leader.

Nader holds a Ph.D. and post-doctoral fellowship in Organic Chemistry from the Massachusetts Institute of Technology. Nader has authored or co-authored more than 50 articles and presentations and holds 20 patents.

TB Alliance | 20 YEARS OF IMPACT

# Discovering and developing new treatments for tuberculosis

Nader Fotouhi, SVP, Chief Scientific Officer, TB Alliance

**March 24, 2021**

TB Alliance is a not-for-profit organization dedicated to the discovery, development and delivery of better, faster-acting and affordable tuberculosis drugs that are available to those in need.

TB Alliance

# 20 Years of Impact

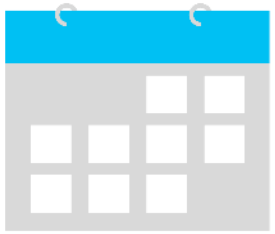
# TB is a Pandemic

TB is the **LEADING** infectious disease killer

and a **TOP 10** killer worldwide

killing one person every **22 SECONDS**

every year

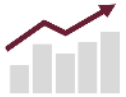


**1 MILLION** children become ill with TB

**1.4 MILLION** people die from TB

**10 MILLION** new TB cases develop

Leading killer of people with HIV/AIDS



Drug-resistance is on the rise with about half a million cases annually

# TB Therapy

Obsolete
Arsenal of drugs developed mostly in 1960s

Long
TB treatment today takes 6-18+ months

Complicated
Can exceed 14,000 pills for drug-resistant TB

Expensive
Drug-resistant TB medication can cost more than $10,000 per treatment

Inadequate
Can lead to resistance; can be incompatible with some HIV treatments; unacceptably high failure rate for DR-TB

*Patient with drug-resistant TB in the Philippines*

TB Alliance | 20 YEARS OF IMPACT

*Putting science to work for better, faster TB cures*

As an NIH-assigned Center of Excellence, we are a nonprofit R&D organization that has:

- Developed a **new treatment** for highly drug-resistant TB
- Launched **improved treatments** for children with TB
- **Transformed** how TB treatments are developed
- **Revived** the pipeline for new TB drugs
- **Mobilized** a global network of partners


***AAA Mandate**: Ensuring TB Alliance products are accessible to every person who needs them*

# Our Vision: Better TB Medicines for All

## Discover, develop and deliver better and faster TB regimens

Achieving maximum impact will require:

- A sustainable pipeline of novel drugs to form the basis for universal regimens effective in all people with active TB
- An ultra-short and effective therapy for latent infection
- All TB treatments appropriately formulated for children

**Simple**
All-oral, highly effective regimens

**Short**
Two to four months of treatment

**Accessible**
Adopted, available and affordable to people with TB

**Millions of lives saved**
Fight the TB epidemic and accelerate eradication

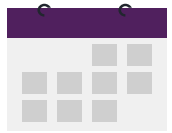
# Challenges of Treating Drug-Resistant TB

If treatment isn't strictly adhered to, it can lead to drug resistance.

About **500,000** new cases of DR-TB each year

More than **50%** of DR-TB cases are caused by direct transmission

Only **43%** historical XDR-TB treatment success rate



DR-TB treatment typically takes 9 months to **2 years** or longer

It can take **14,000+** pills to cure a single case of DR-TB

Estimated **75M** people will die from DR-TB by 2050 without new cures

About **1 in 3** deaths from antimicrobial resistance are due to DR-TB

Estimated **$16.7 T** financial toll of DR-TB by 2050 without new cures

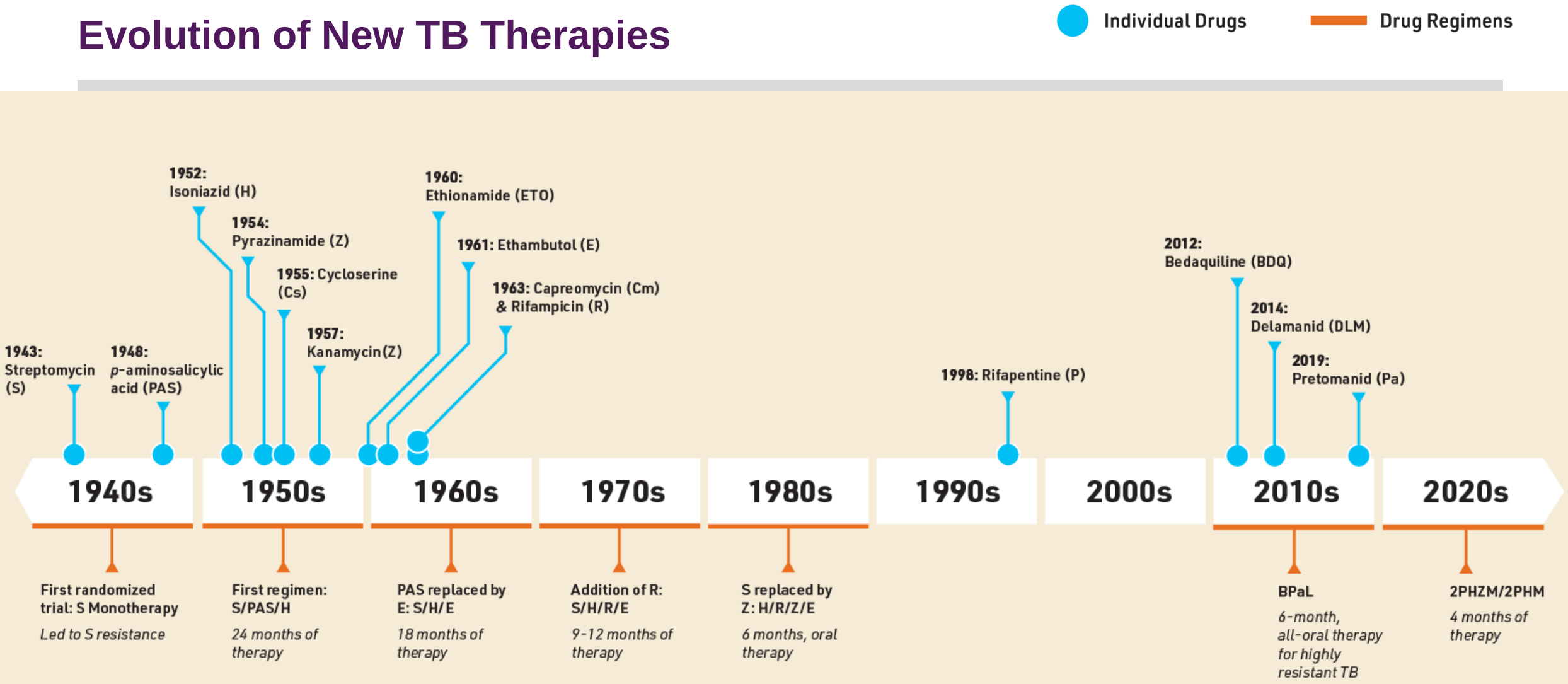
# Benefits of New Regimens

Potential positive impacts of new treatments are wide-reaching and multi-faceted

| | | | |
|---|---|---|---|
| Lower cost | More lives saved | Better outcomes | Reduced health system burden |
| Fewer side effects | More patient satisfaction | Simple supply management | Reduced transmission |

**Novel regimens can simplify TB treatment, facilitate its scale-up and reduce its burden on health systems.**

# Evolution of New TB Therapies



# TB Drug Development Pipeline As of March 2021*

TB Alliance 20 YEARS OF IMPACT

## Discovery

### Lead Identification

**Clp Lead ID Programs**
- Harvard University
- UIC
- CETR

**GHIT Hit ID Programs**
- Daiichi Sankyo RD Novare

**GHIT Hit-to-Lead Programs**
- Astellas
- Chugai
- Daiichi Sankyo RD Novare
- Takeda

**Malate Synthetase Inhibitors**
Texas A&M

**Pantothenamide**
- TropIQ
- WCM

**PknB**
UoA/Schrödinger

**RNA Polymerase Inhibitors**
CETR

**Whole Cell Hit-to-Lead Program**
GSK

### Lead Optimization

**Anti-TB Natural Products**
Evotec

**ClpC1**
- Harvard University
- UIC
- CETR

**InhA Inhibitors**
GHDDI

**Intracellular Active Series**
GSK

**KasA**
GSK

**MmpL3 Inhibitors**
AbbVie
ERA4TB

### Preclinical Development

**Preclinical TB Regimen Development**
JHU

## Early Development

### Phase 1

**TBAJ-876 / Diarylquinoline**

**TBAJ-587 / Diarylquinoline**
ERA4TB

**TBI-223 / Oxazolidinone**
IMM

### Phase 2A/2B

**Sutezolid / Oxazolidinone**
Gates MRI

**TBA-7371 / DprE1 Inhibitor**
FNDR
Gates MRI

## Late Development

### Phase 3

NixTB

**Bedaquiline / Pretomanid / Linezolid**
(BPaL)
Mylan

ZeNix

**Bedaquiline / Pretomanid / Linezolid**
(BPaL)
Mylan

SIMPLICITB

**Bedaquiline / Pretomanid / Moxifloxacin / Pyrazinamide**
(BPaMZ)
PanACEA
Mylan
Radboud

### Marketed Products

**Optimized Pediatric Formulations**

**Ethambutol**
Macleods

**Isoniazid**
Macleods

**Pyrazinamide**
Macleods

**Rifampicin/Isoniazid**
Macleods

**Rifampicin/ Isoniazid / Pyrazinamide**
Macleods

**Pediatric Formulation Development**

**Pretomanid**
Mylan

**Pretomanid for use in BPaL**

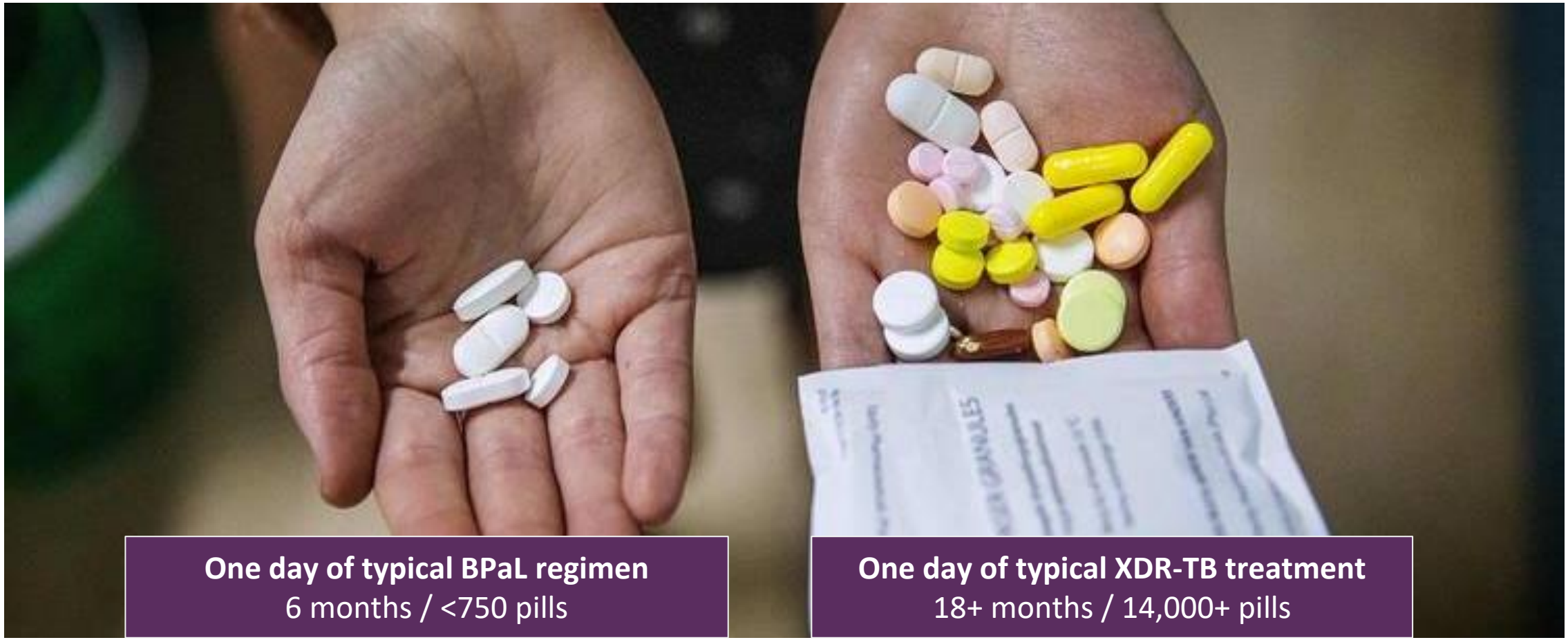
**Pretomanid for use in BPaL Regimen**
Mylan
Macleods
Hongqi
KNCV
ITRC

## TB Alliance Portfolio Partners

AbbVie
Astellas
Bill & Melinda Gates Medical Research Institute (Gates MRI)
Center for Excellence in Translational Research (CETR)
Chugai
Daiichi Sankyo RD Novare
ERA4TB Consortium
Erasmus University Rotterdam
Evotec
Foundation for Neglected Disease Research (FNDR)
GlaxoSmithKline (GSK)
Global Health Drug Discovery Institute (GHDDI)
Harvard University
Hongqi Pharmaceutical
Institute of Materia Medica (IMM)
IMPAACT
International Tuberculosis Research Center (ITRC)
Johns Hopkins University (JHU)
KNCV Tuberculosefonds
Macleods Pharmaceuticals
Medical Research Council (MRC) at UCL
Médecins Sans Frontières (MSF)
Mylan
US National Institutes of Health (NIH)
PanACEA
Radboud University Nijmegen
Schrödinger
Stellenbosch University
Takeda Pharmaceuticals
TB Drug Accelerator (TBDA)
Texas A&M University
TropIQ
University College London (UCL)
University of Auckland (UoA)
University of Illinois at Chicago (UIC)
Weill Cornell Medical (WCM)
Yonsei University

* Phase 3 clinical trials are added to the pipeline after enrollment of the first patient and are removed after completion of the Clinical Study Report. This document is updated on a quarterly basis.

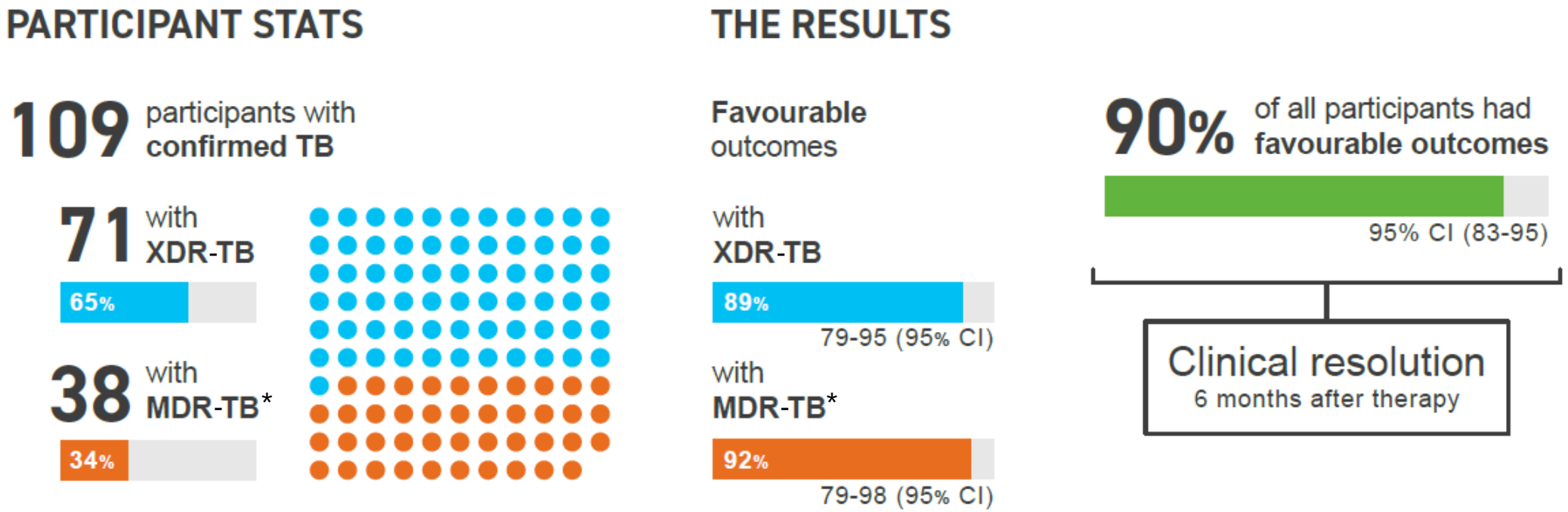
# Shorter, Simpler Treatment for Highly Drug-Resistant Forms of TB




Please see Full Prescribing Information at: www.accessdata.fda.gov

# Nix-TB Results

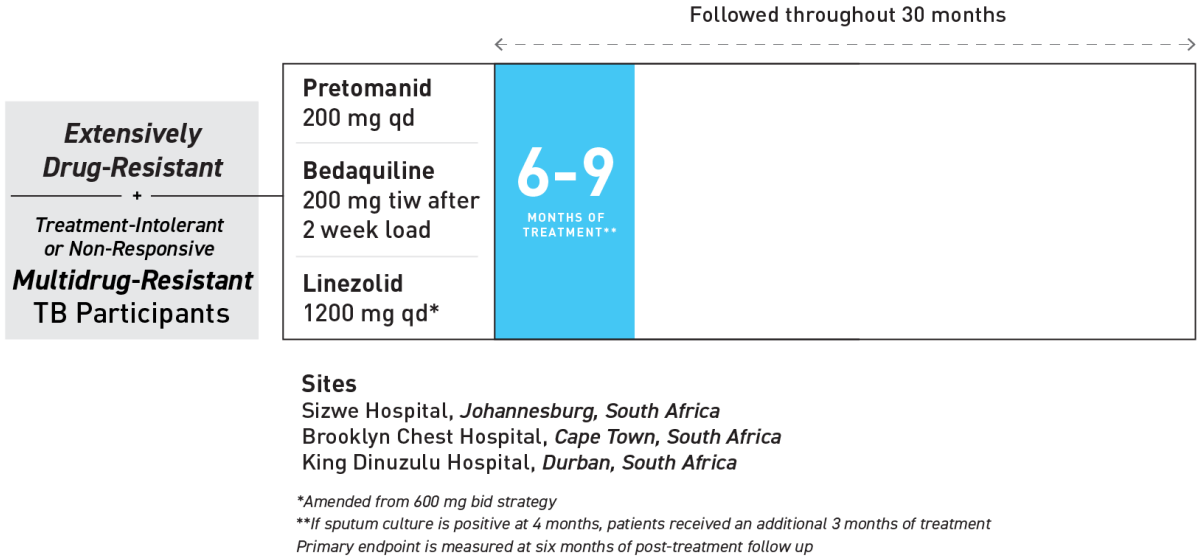
*New England Journal of Medicine*, March 2020




*Treatment intolerant or non-responsive MDR-TB

# Methods

## NixTB Phase 3 Trial in XDR-TB



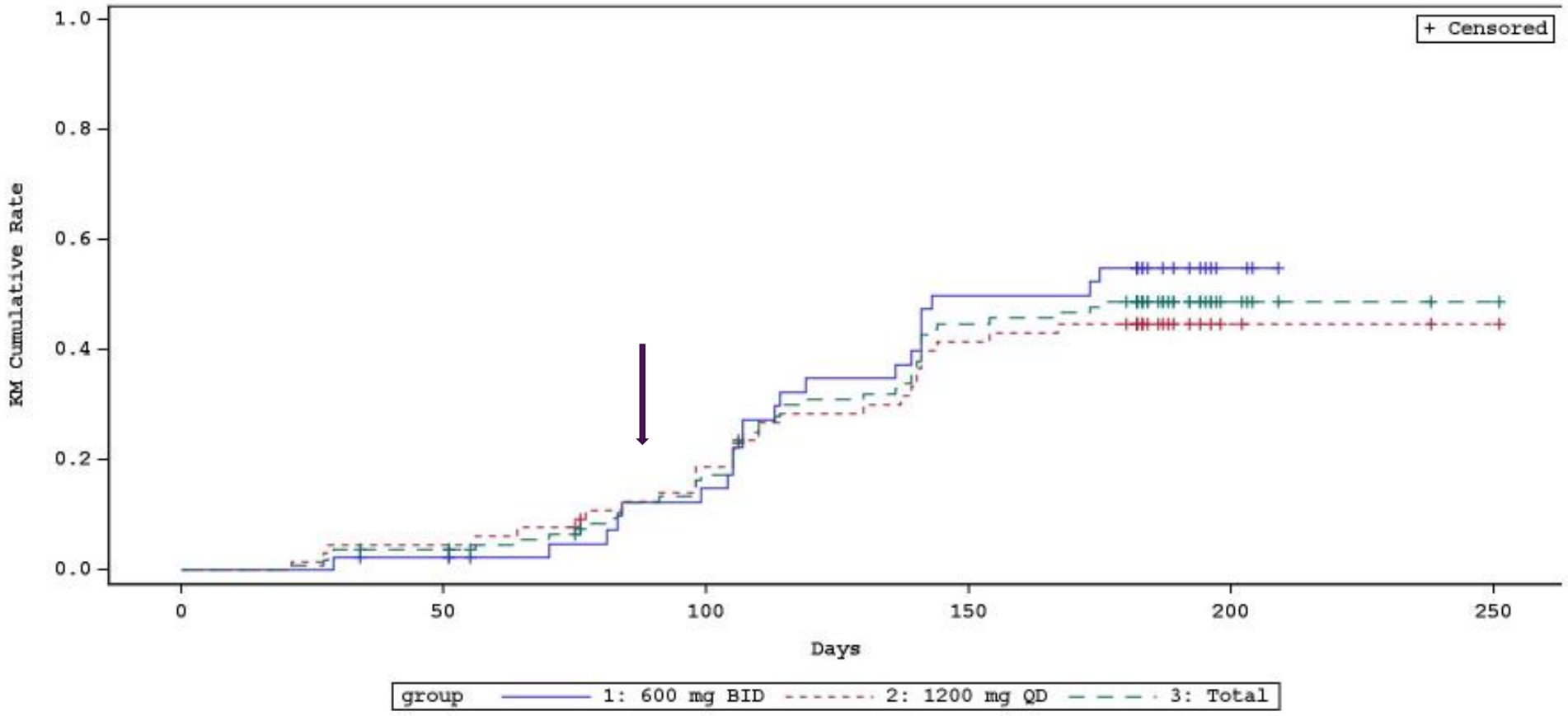

- Primary and secondary endpoint = bacteriologic or clinical failure or relapse at 6- and 24-months post-treatment respectively
- Success of trial - lower bound of 95% CI > 50% favorable rate
- Peripheral neuropathy associated with linezolid was assessed serially with standard symptoms rated from none (0) to worst (10) using the Brief Peripheral Neuropathy Symptom questionnaire (BPNS)
- Explore the fate of those participants with no neuropathy symptoms at baseline who completed treatment i.e.
  - Maximum score post baseline
  - Score at end of the study (24 months)

# Results - Efficacy

- 109 participants (65% XDR-TB, 35% MDR-TB; 51% HIV+) were enrolled and comprised the ITT* population (MITT* population = 107)
- All surviving participants, except 1 withdrawal, completed the full course of therapy
- At the primary endpoint six months after treatment, as previously reported, there were 98 with favorable outcomes (90% ITT, 92% mITT)
- After the primary endpoint one participant relapsed 15 months after treatment and one was lost to follow up
- Favorable outcomes 24 months post completion of treatment were sustained (88% ITT, 91% mITT) independent of sex or HIV status.

* ITT – Intention to treat, mITT – modified intention to treat

# Kaplan Meier curve of time (days) to 1st Linezolid dose interruption and/or reduction due to Peripheral Neuropathy (Safety Analysis Population)




NIX-TB. CSR. Jan 2021

# Peripheral Neuropathy Score (Pain, aching, burning in feet or legs)

| Linezolid (LZD) | | 600mg BD (n = 44) | 1200mg QD (n = 65) | Total (n = 109) |
|---|---|---|---|---|
| Participants who completed treatment | n | 40 | 63 | 103 |
| Participants received full uninterrupted 26 weeks of LZD at any dose | n | 10 | 27 | 37 |
| Participants received full uninterrupted 26 weeks of LZD at 1200mg daily | n | 4 | 12 | 16 |
| LZD duration in treatment completers | Mean (weeks) | | | 23,3 |

| Baseline | Max. After Baseline | Month 24 After End-of-Treatment | | | |
|---|---|---|---|---|---|
| | | None | Mild/Mod | Severe | N/A |
| None: 84 | Always None: 27 | 27 | 0 | 0 | 0 |
| (Mild/Mod: 15) | Max. Mild/Mod: 34 | 29 | 3 | 0 | 2 |
| (Severe: 1) | Max. Severe: 23 | 13 | 7 | 1 | 2 |
| | 84 | 69 | 10 | 1 | 4 |
| | | 82% | 12% | 1% | 5% |

*0 = None*

*1-7 = Minimal/moderate*

*8-10 = Severe*

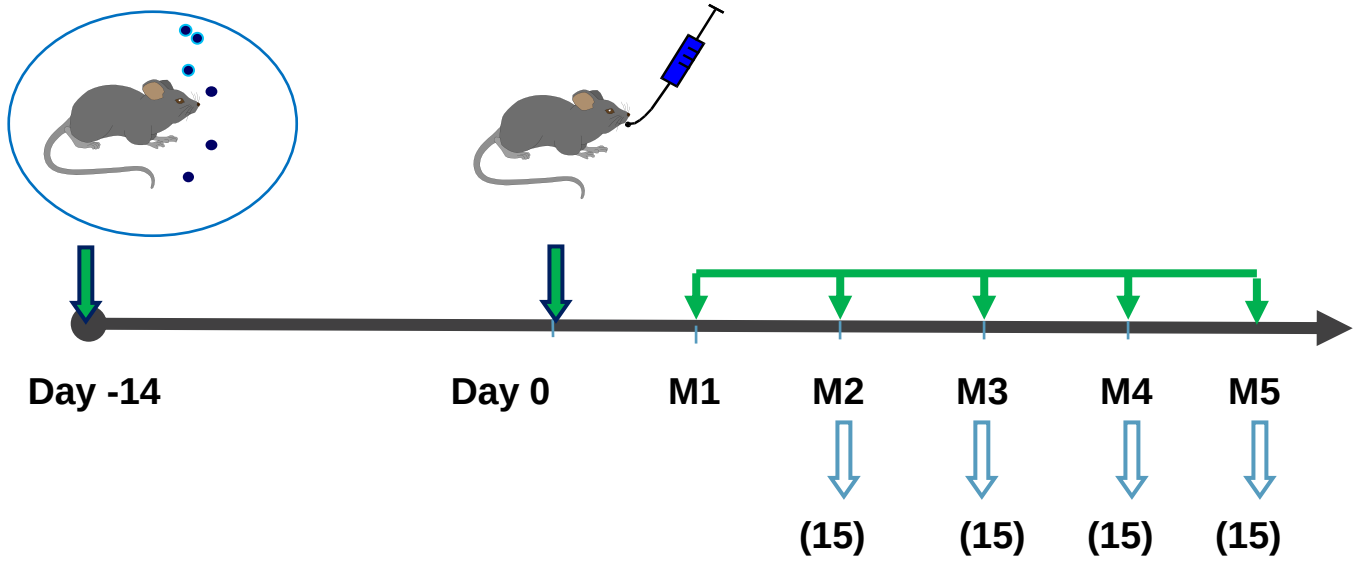
# Conclusion

- Results of this simplified, shortened all oral regimen for highly drug resistant TB show sustained high efficacy through 2-year follow-up from end of treatment

- Peripheral neuropathy from linezolid was common, but manageable, and symptoms improved over 24 months of follow-up

- Can we manage the peripheral neuropathy through an optimal dosing and scheduling of linezolid?

# Scheme for Murine Relapse Experiments to Evaluate New Regimens




**(15) mice held for (3) months without treatment and then sacrificed to determine permanent cure without relapse**

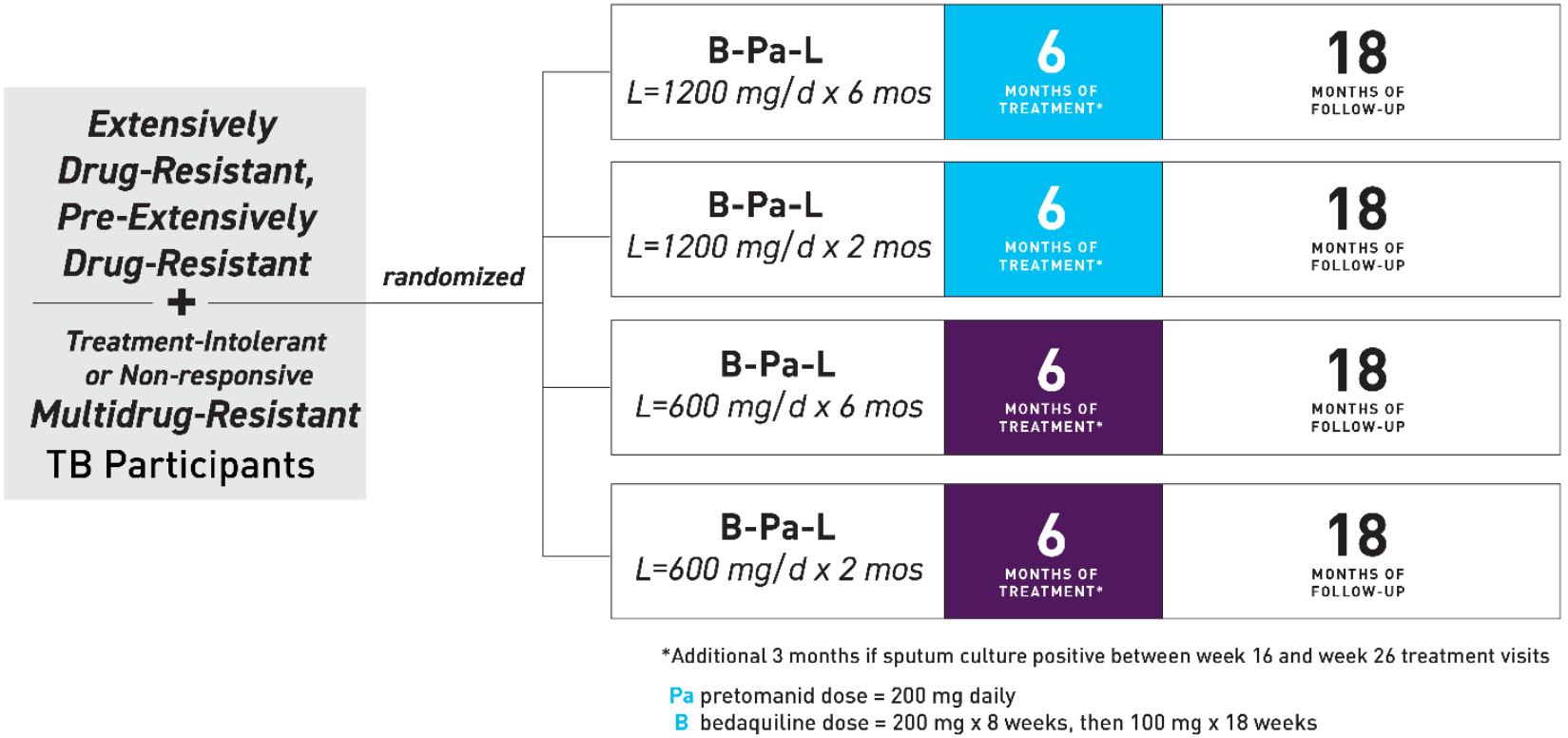
# The duration of Linezolid (L) treatment does not affect the Sterilizing Activity on Background of Bedaquiline Plus Pretomanid (BPa) in BALB/c Mice

| | Proportion relapsing after treatment for: | |
|---|---|---|
| **Regimen** | 2 months | 3 months |
| **2RHZ/RH** | | 8/14 (57%) |
| **BPa** | | 3/14 (21%) |
| **3BPaL** | 6/15 (40%) | 0/15*† (0%) |
| **2BPaL/1BPa** | | 0/15*† (0%) |
| **1BPaL/2BPa** | 9/15 (60%) | 0/15*† (0%) |

*p = 0.11 vs. BPa; †p≤ 0.001 vs. RHZ

# ZeNix: Linezolid Optimization Trial

Patients with XDR-TB, Pre-XDR-TB or who have failed or are intolerant to MDR-TB treatment




Enrollment completed Dec 2019. 181 patients enrolled from Georgia, South Africa, Russia and Moldova

# Strategic Overview

## A new standard of TB drug development

- Nix-TB has provided proof of principle that the most resistant forms of TB can be treated in the same timeframe and with as few drugs as is used for drug-sensitive TB - and with comparable results
- Next challenge is one regimen for all patients with active TB (Universal Regimen)
- Initial goal is to shorten timeframe of treatment to 2-3 months
- Long term objective is a universal regimen that cures in days to weeks
- Needs of the market dictate our R&D agenda – requires a constant feedback loop

# Early-Stage Research: Filling the Pipeline

## A three-pronged approach

TB Alliance leverages industry and other partners to support the continued growth of the global TB drug pipeline.

### Optimize known compound classes

Fully capitalize on the success of compounds already in development or approved

### Develop novel classes based on known targets

Leverage validated drug targets, discover novel classes to address resistance

### Develop novel classes based on novel targets

Discover new drug classes with novel modes of action

# What's Next: Finding the Next Regimen

## Substituting linezolid with a safer oxazolidinone

*O = TBI-223

| | Mean lung CFU (log10) | | | Proportion of mice relapsing after treatment ending at: | | |
|---|---|---|---|---|---|---|
| **Regimen** | **D-15** | **D0** | **M1** | **M1.5 (+3)** | **M2 (+3)** | **M3 (+3)** |
| **Untreated** | 4.7 | 8.9 | | | | |
| **$B_{25}Pa_{100}$** | | | 5.9 | | | **14/15** |
| **$B_{25}Pa_{100}L_{100}$** | | | 4.5 | | **14/15** | **7/15** |
| **$B_{25}Pa_{100}O_{100}$** | | | 4.9 | | **15/15** | **2/15** |

**B, Bedaquiline; Pa, Pretomanid; L, Linezolid, O, TBI-223. Subscripted figures are daily doses of drugs in mg/kg**

- TBI-223 is a novel oxazolidinone with efficacy similar to linezolid and significantly reduced inhibition of mammalian protein synthesis
- No bone marrow toxicity observed in preclinical safety studies up to 3 months
- Single ascending dose (SAD) in healthy human volunteers completed up to 3000 mg dose
- Well tolerated

JOHNS HOPKINS MEDICINE

# A more potent diarylquinoline and a safer oxazolidinone is significantly more effective than the Nix regimen

Substituting bedaquiline with a more potent and safer diarylquinoline

*O = TBI-223

| | Lung CFUs | | Proportion of Mice Relapsing After: | | |
|---|---|---|---|---|---|
| **Regimen** | W-2 | D0 | W4 (+12) | W6 (+12) | W8 (+12) |
| **Untreated** | 4.0 | 6.6 | | | |
| **B25 PaO** | | | | 11/15 | 2/14 |
| **$587_{25}$PaO** | | | 7/13 | 3/15 | 0/15 |
| **$587_{50}$PaO** | | | 2/15 | 0/15 | |
| **$876_{6.25}$PaO** | | | | 2/15 | 1/15 |
| **$876_{12.5}$PaO** | | | 3/15 | 0/15 | |

BPaL typically cures all mice in 3-4 months, and would perform similarly to BPaO here

- TBAJ-587 and TBAJ-786 are significantly more potent than bedaquiline in vitro (MIC90 = 0.003 ug/mL) and in vivo with a better safety profile
- TBAJ-876 completed SAD studies and was well tolerated up to 400 mg
- TBAJ-587 initiated Phase 1 SAD studies

# Further advantage of the novel diarylquinolines

- Emerging evidence of BDQ resistance in BDQ-treated and BDQ-naïve TB patients is a concern
- BDQ resistance in *Mtb* isolates is rarely due to mutations in its target, *atpE*, but rather in *Rv0678*, a regulator of the MmpL5/MmpS5 efflux transporter

**MICs against H37Rv and a panel of Rv0678 (165 aa) mutants**

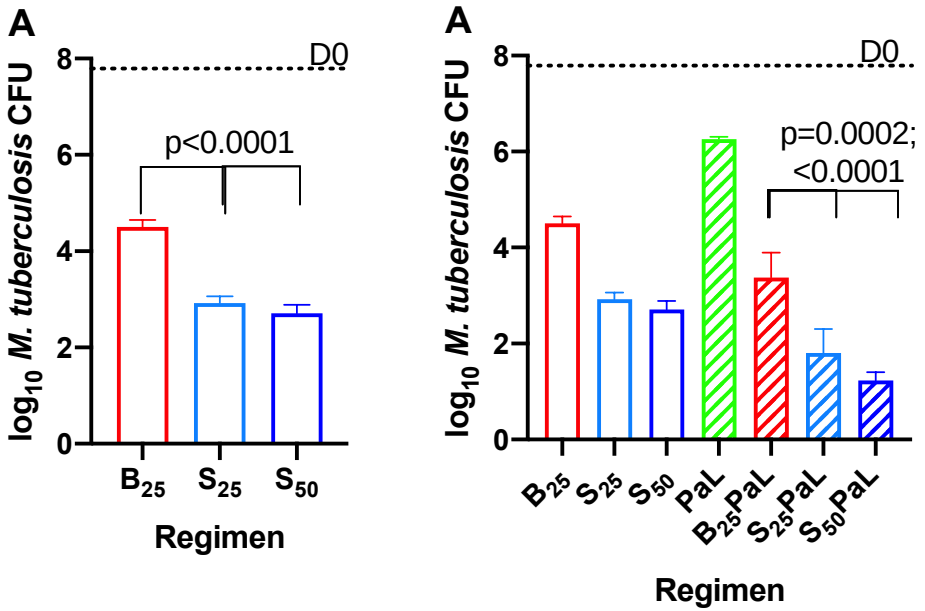
| | MIC (µg/mL) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Compound | H37Rv | Rv0678* **S63R** | ITM-1 **FS** | ITM-2 **Y92X** | ITM-3 **FS** | ITM-4 **R135W** | ITM-5 **S63R** | ITM-6* **FS** | ITM-7 **Y92X** |
| BDQ | 0.03 | 0.3 | 0.9 | 1.0 | 0.9 | 0.7 | 0.5 | 0.5 | 0.6 |
| BDQ-M2 | 0.1 | 0.8 | > 1 | > 1 | > 1 | > 1 | > 1 | > 1 | > 1 |
| TBAJ-587 | < 0.004 | 0.02 | 0.06 | 0.06 | 0.06 | 0.04 | 0.03 | 0.03 | 0.03 |

- Rv0678: provided by Stewart Cole, EPFL, Switzerland (Hartkoorn et al, AAC, 2014)
- ITM 1-7 provided by Leen Rigouts, ITM, Belgium

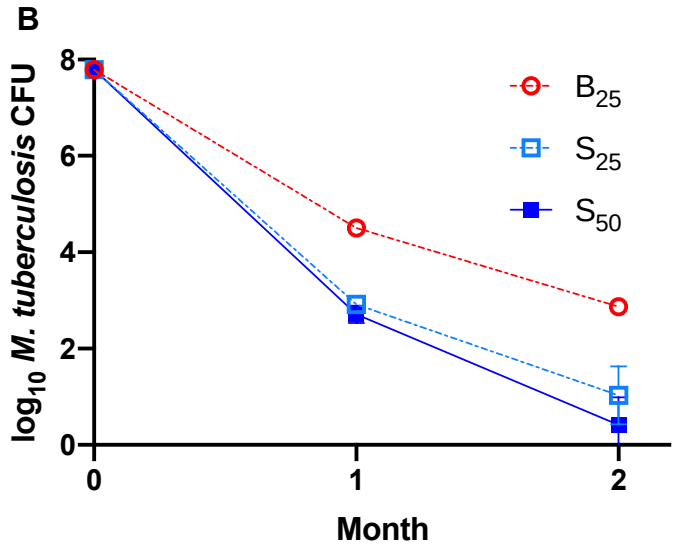
A. Upton et al, ASM Microbe, 2017
S. Franzblau et al, ASM Microbe, 2017

# Efficacy of B- and S-containing regimens against wild-type *M. tuberculosis* H37Rv

One month of treatment



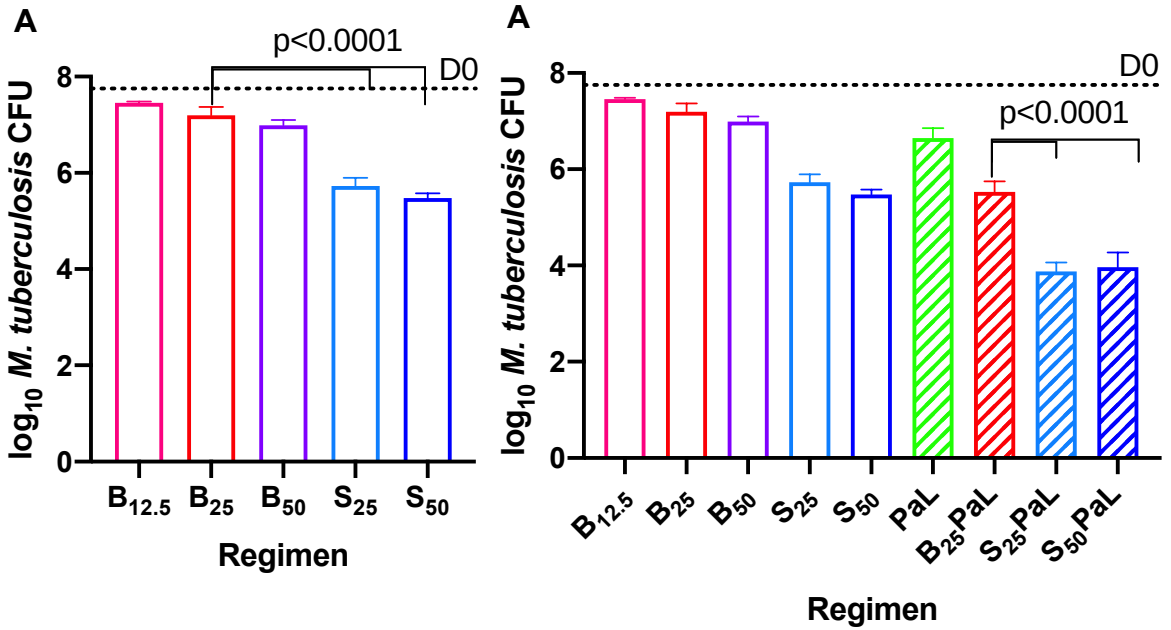

Two months of treatment



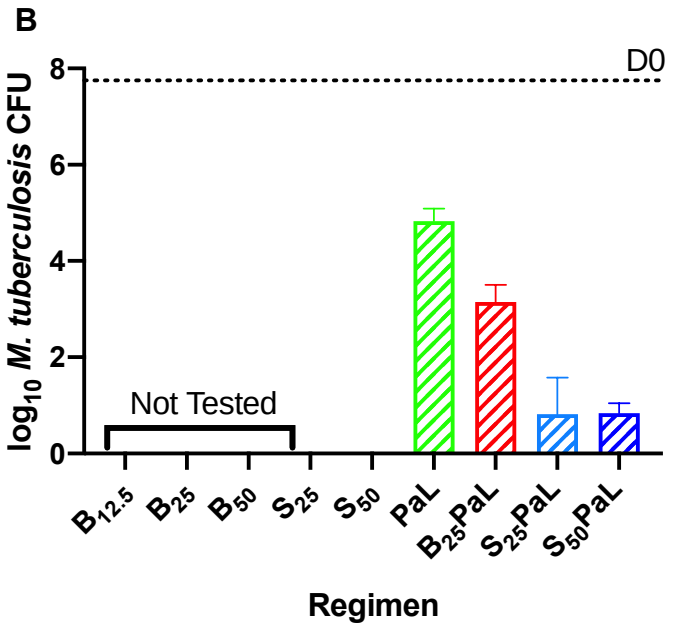

- TBAJ-587, is more active than B, BDQ, as monotherapy, and in combination with either PaL

# Efficacy of B- and S-containing regimens against *M. tuberculosis* with *Rv0678* mutation

One month of treatment

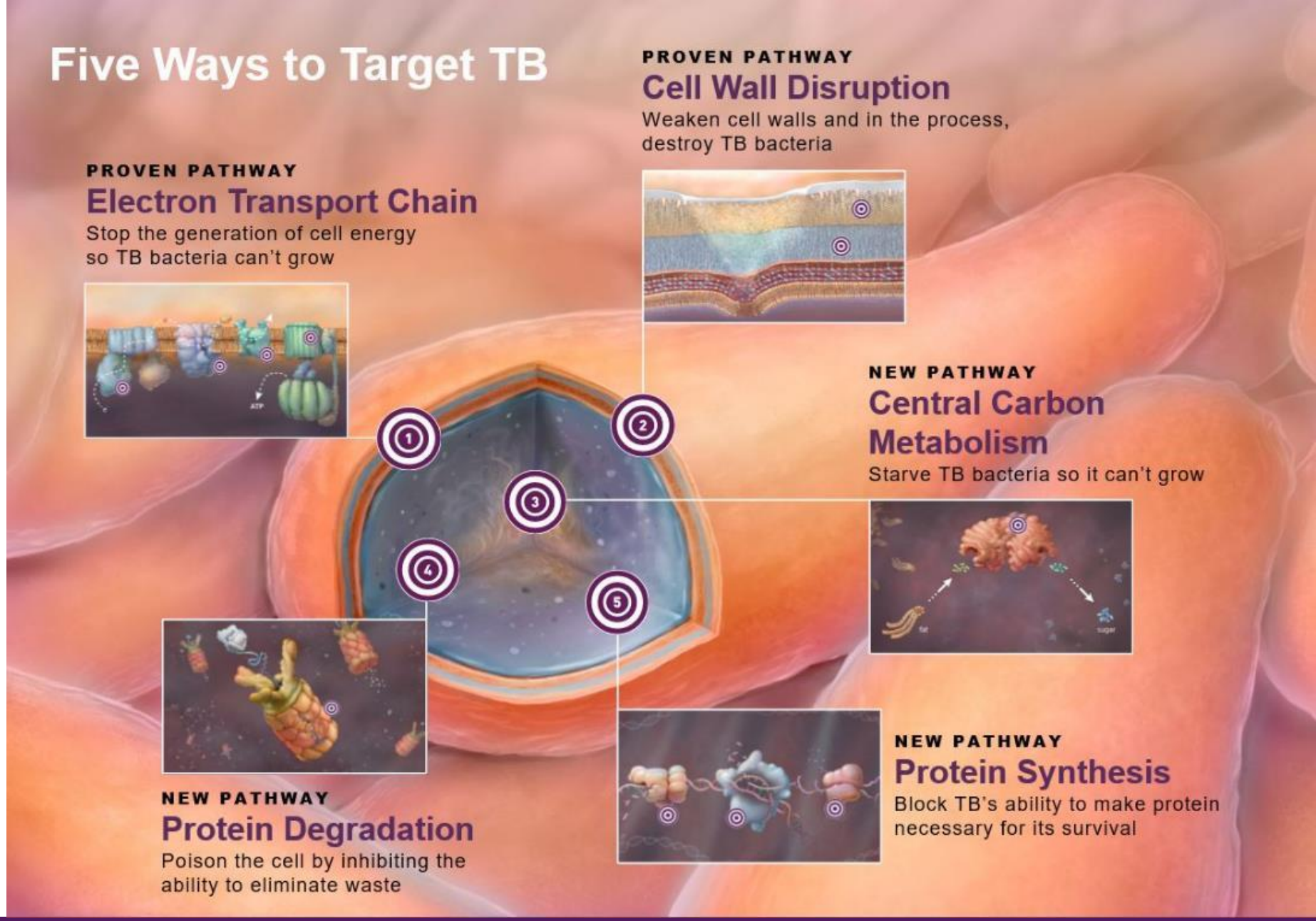



Two months of treatment



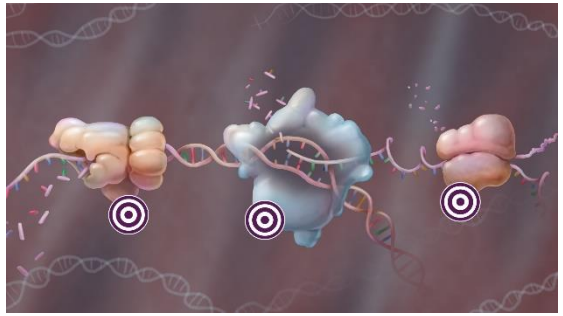

- Against the *Rv0678* mutant (IS*6110* insertion, aa116/nt349): S, TBAJ-587, is more active than B, BDQ, as monotherapy, and in combination with PaL.

**Mid term:**
Targeting Pathways to find alternative short regimens

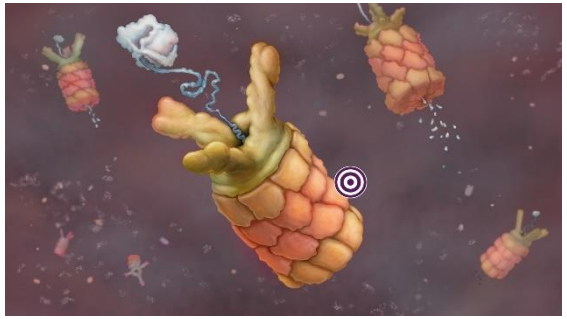


# Modulation of Protein Synthesis and Protein Degradation

Integrated targeting of proteostasis



- **Protein Synthesis**
  - Clinically well validated
  - Inhibition of ribosome
    - Oxazolidinones
  - Inhibition of RNA polymerase
    - Rifamycins



- **Protein Degradation**
  - Demonstrated essentiality of ClpC1 and ClpP1P2 complexes
  - Genetic validation
  - Natural product modulators
    - Rufomycin, Ecumicin, Cyclomarin
  - Peptidic inhibitors

# CETR (Center of Excellence in Translational Research)

National Institute of Allergy and Infectious Diseases (NIAID)


HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

UIC UNIVERSITY OF ILLINOIS AT CHICAGO COLLEGE OF PHARMACY

JOHNS HOPKINS MEDICINE

SCHRÖDINGER

TEXAS A&M UNIVERSITY

# Setting a New Course for TB Drug Development

Exploring Immunotherapy and Leveraging Artificial Intelligence

**2000s**

Establishing the PDP* Paradigm for TB Drugs

**2010s**

Proving the Theory of Regimen Development and Advancing New Drugs

**2020s**

What comes next?

* PDP – Product development partnership

# The Next Innovations in TB Treatments: Artificial Intelligence

## New Partnerships to Identify the Components of Tomorrow's TB Regimens

### AI to Support Immunotherapy

- AI driven analysis of immunomodulatory pathways and targets with greatest impact on bacterial clearance (InveniAI)
- Targets and pathways have either clinical or research compounds available
- With Advisory group select top candidates to evaluate in a relapse mouse model on top of a novel regimen and standard of care (SOC)

InveniAI
Innovate with Intelligence

### AI-Assisted Screening Process

- Combine large scale screening approach such (DNA encoded Library) and AI to select advanced drug like lead (ZebiAI)
- Could significantly reduce the time and cost to discover novel leads against traditional targets as well as potential immunotherapy targets of value

zebi AI

# The Next Innovations in TB Treatments: Immunotherapy

## Harnessing the Immune System to Shorten Treatment Duration

### Available TB Therapies

1st line regimen (HRZE)

BPaL

**6+ months** to cure

### Universal Regimen

All-novel regimen

**<3 months** to cure

### The Next Paradigm

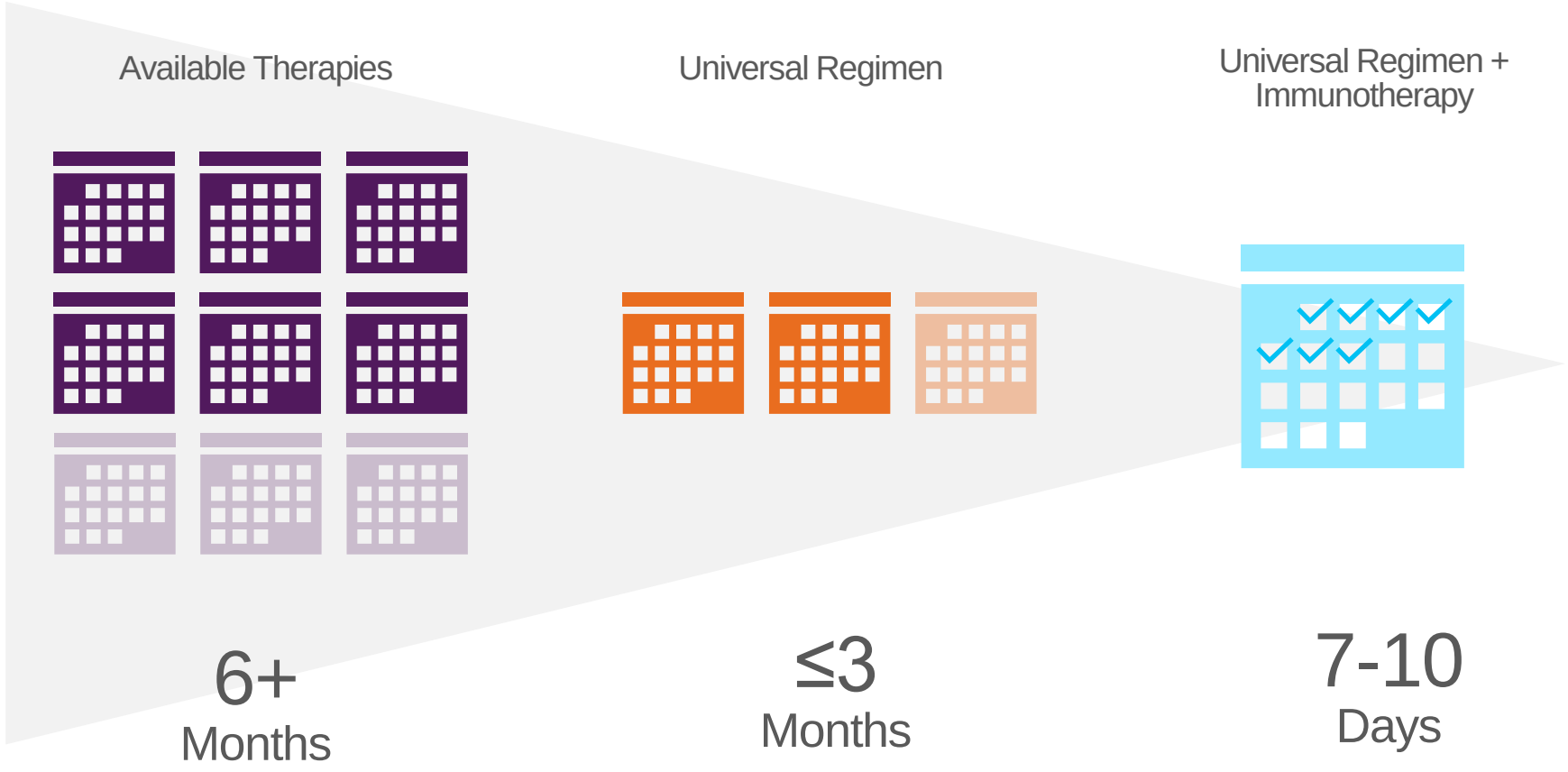
All-novel regimen

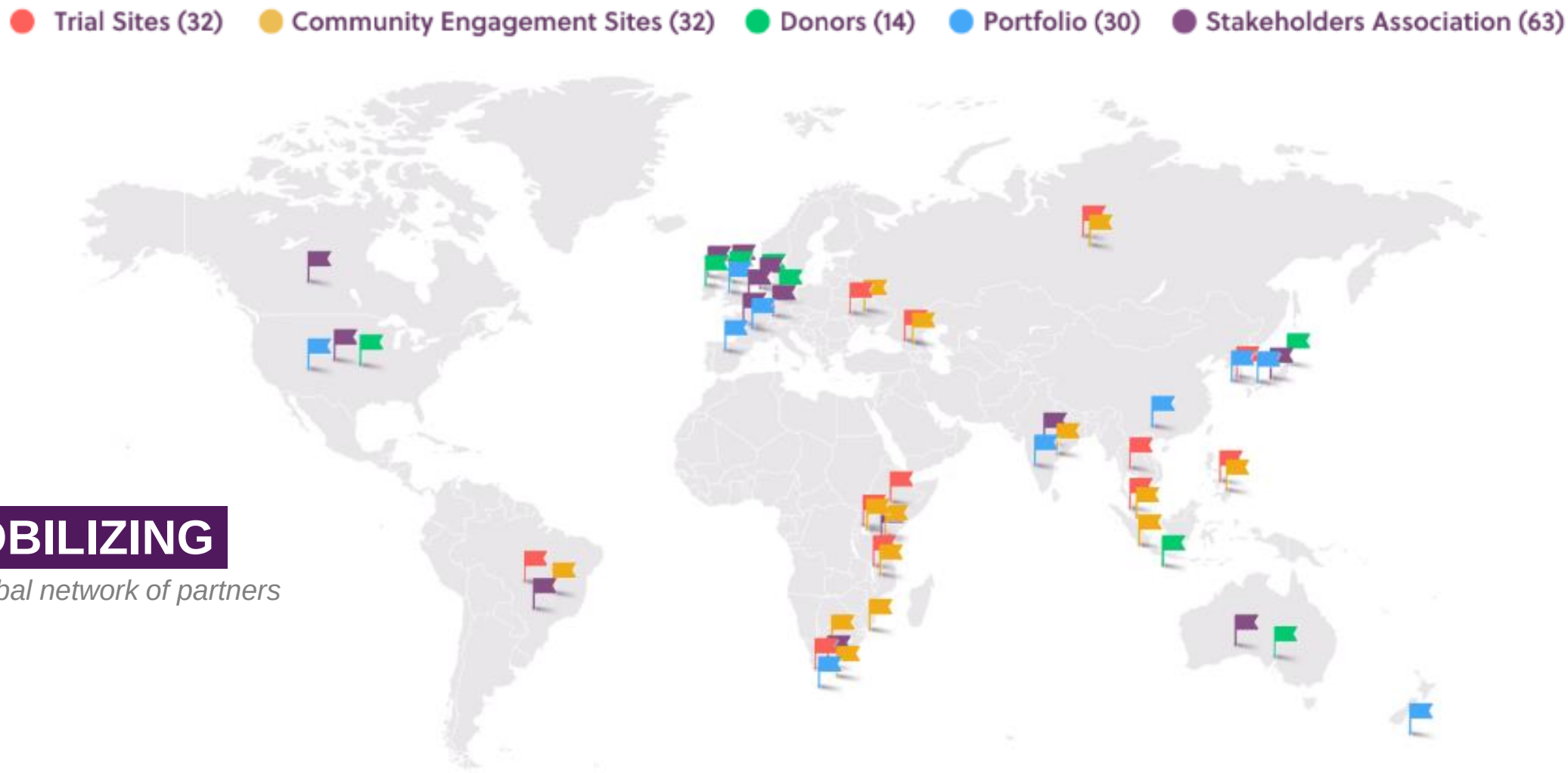
\+

Immunotherapy

**7-10 days** to cure

# What Could the Patient Experience Look Like in the Future?






# MOBILIZING

*a global network of partners*

# TB Alliance Donors

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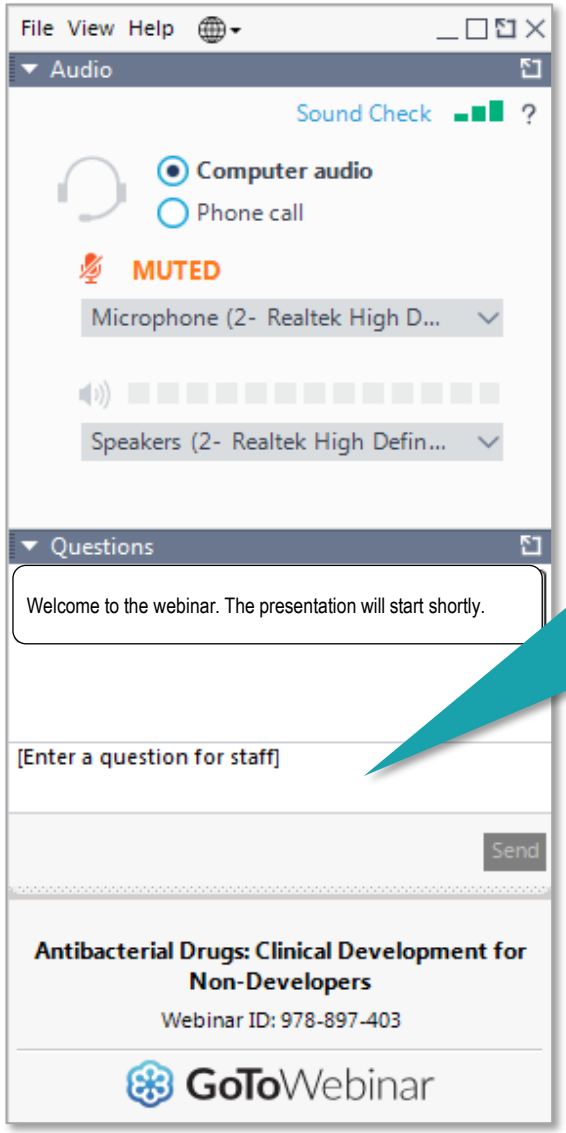
FROM THE AMERICAN PEOPLE

# How to submit your questions




The presentation will be followed by an interactive Q&A session.

Please submit your questions via the ‘questions’ window. We will review all questions and respond to as many as possible after the presentation.

# Today’s speakers

## Discovering and developing new treatments for tuberculosis

**Nader Fotouhi**
*Chief Scientific Officer*
TB Alliance (US)

**Moderator:**
**Lydia Nakiyingi,**
*Infectious diseases physician, research scientist and senior lecturer*
Makerere University College of Health Sciences, Kampala (Uganda)

# Join us for our next webinar

29 April 2021, 17:00-18:30 CEST

**AMR R&D efforts in the CMC and formulation arena: Do it right the first time!**

Speaker:

- Aleksandar Danilovski, Xellia Pharmaceuticals

**Registration link and more information available on:**
revive.gardp.org/webinars

# Thank you for joining us

Visit now revive.gardp.org/webinars to find more webinars about antimicrobial drug R&D