Global TB Elimination: Aspiration or Delusion?

December 12, 2024

Pablo Picasso, Don Quixote

Richard E. Chaisson, MD
Center for TB Research and Center for AIDS Research
Johns Hopkins University

A Tale of Two Outbreaks

San Francisco, 1990-1991

- Residential facility for people with HIV/AIDS
- Two residents admitted with TB under treatment in Fall 1990
- Third resident hospitalized and diagnosed with active TB in 12/90
- Four additional residents diagnosed with TB from 1/91 to 3/91
- Outbreak investigation begun in 3/91:
  - Five additional residents found to have active TB
  - 11/13 remaining residents received INH preventive therapy

AN OUTBREAK OF TUBERCULOSIS WITH ACCELERATED PROGRESSION AMONG PERSONS INFECTED WITH THE HUMAN IMMUNODEFICIENCY VIRUS

An Analysis Using Restriction-Fragment–Length Polymorphisms

CHARLES L. DALEY, M.D., PETER M. SMALL, M.D., GISELA F. SCHECTER, M.D., M.P.H., GARY K. SCHOOLNIK, M.D., RUTH A. MCADAM, D.PHIL., WILLIAM R. JACOBS, JR., PH.D., AND PHILIP C. HOPEWELL, M.D.

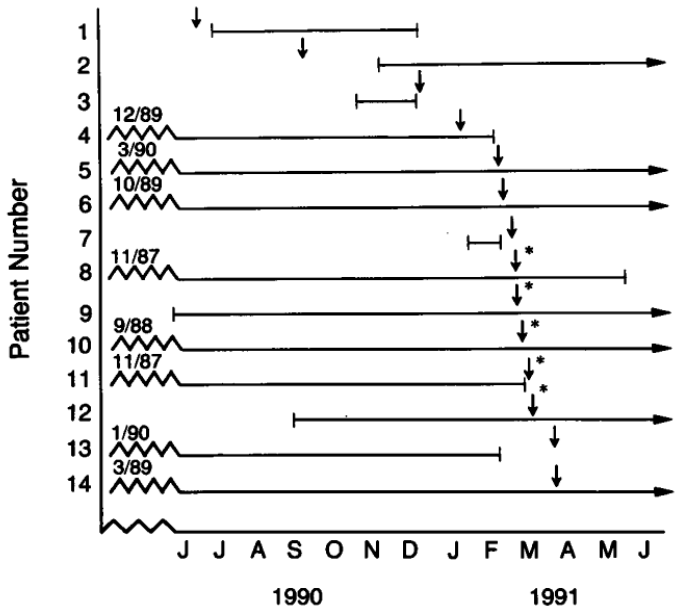

Figure 1. Sequence of the Tuberculosis Outbreak in a Residential Facility for HIV-Infected Patients.

The date of entry into the facility is indicated in the case of long-term residents. Vertical bars indicate the time of entry into or exit from the facility, and arrows the time of diagnosis. Asterisks indicate patients whose tuberculosis was identified when the outbreak was investigated. Brief absences from the facility for hospitalizations are not shown.

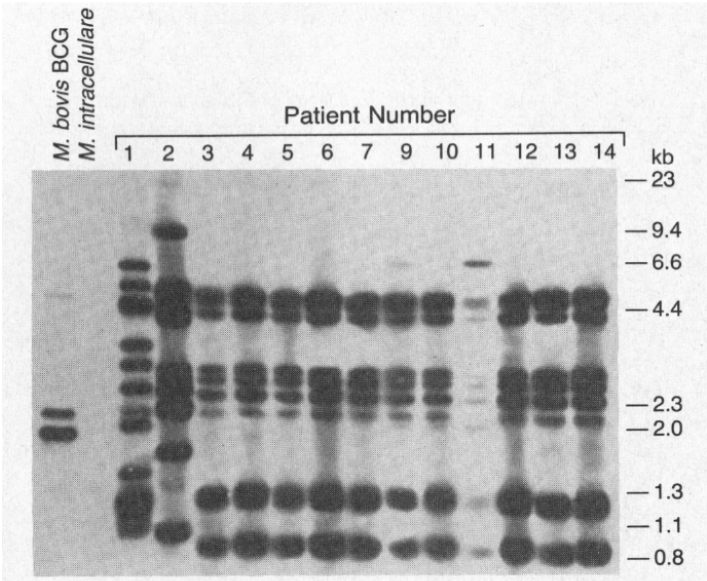

Figure 2. RFLPs of *M. bovis* BCG, *M. intracellulare,* and Clinical Mycobacterial Isolates from Residents of the HIV Congregate-Living Site.

Patients 1 and 2 were receiving antituberculosis therapy when they entered the facility. Tuberculosis developed in the remaining patients while they lived at the facility. Patient 8, who did not have positive cultures, is not shown.

Meanwhile, in Baltimore

Winter 1991

- 22-bed subacute care unit for patients with AIDS
- Patient A admitted after 5-day hospitalization for CAP
- Gregarious and helpful, socialized with all 21 other residents and assisted dietary services with delivering trays
- 18 days after admission, referring hospital called and said TB cultures from CAP admission were positive
- Patient A transferred back to referring hospital (subsequently died of TB)
- All 21 other patients had chest x-ray performed
- Patient B with diffuse infiltrates, hospitalized and diagnosed with active TB
- Patients C-V put on INH preventive therapy
- No additional cases of TB diagnosed

The NEW ENGLAND JOURNAL of MEDICINE

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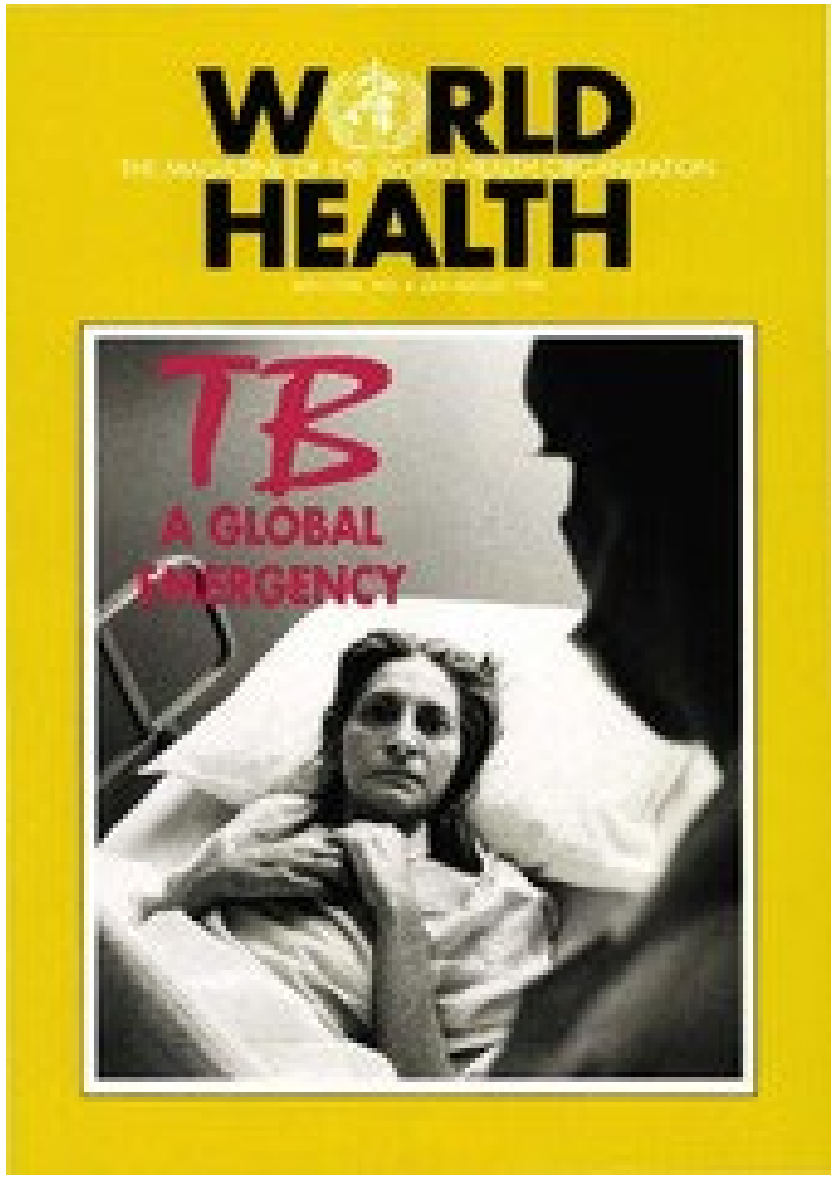
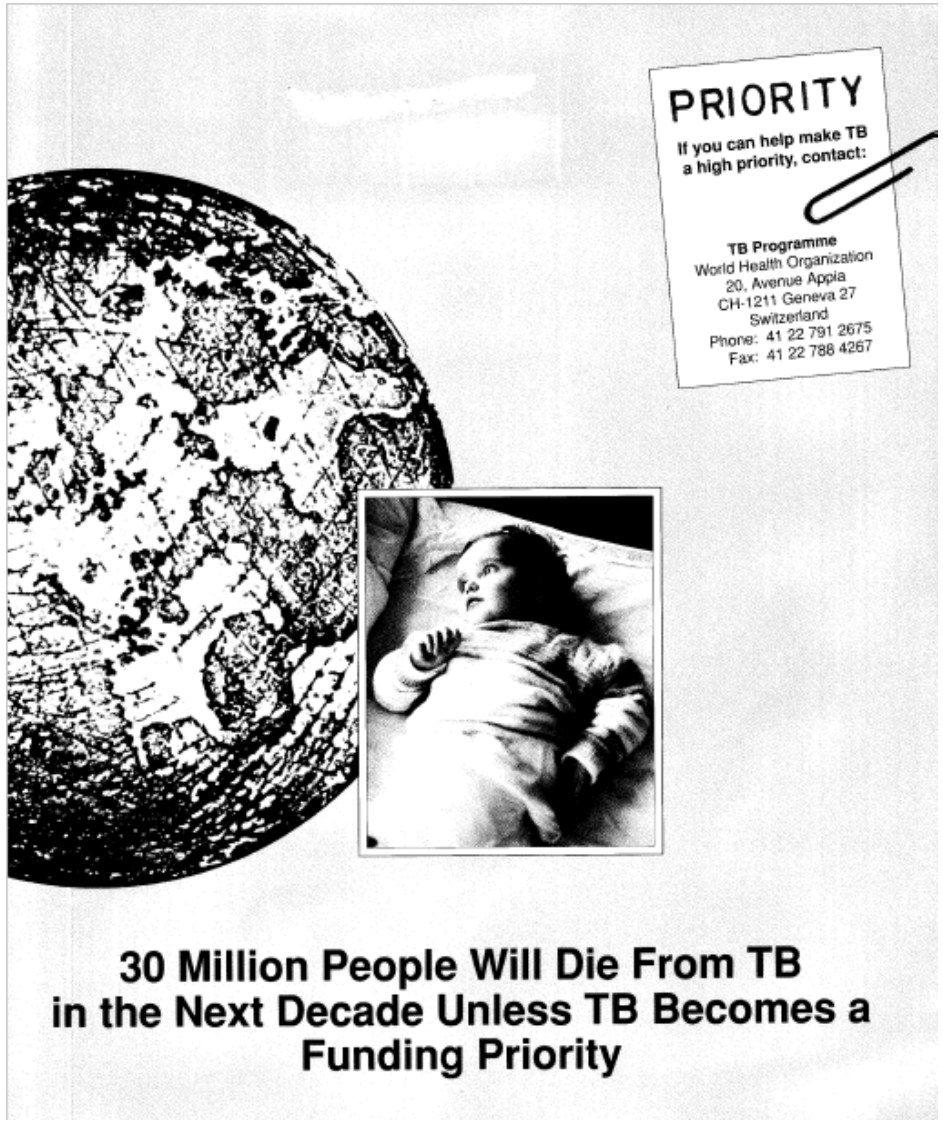
ESTABLISHED IN 1812

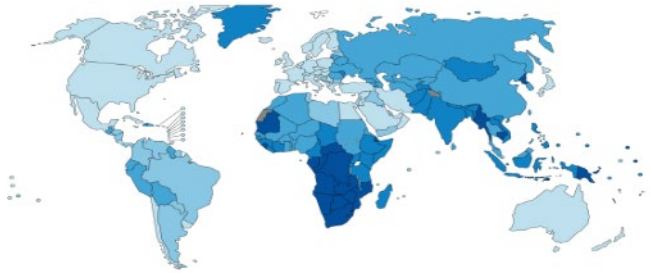
January 02, 1992

TB Declared a Global Health Emergency, April 23, 1993





The Global Burden of TB -2023

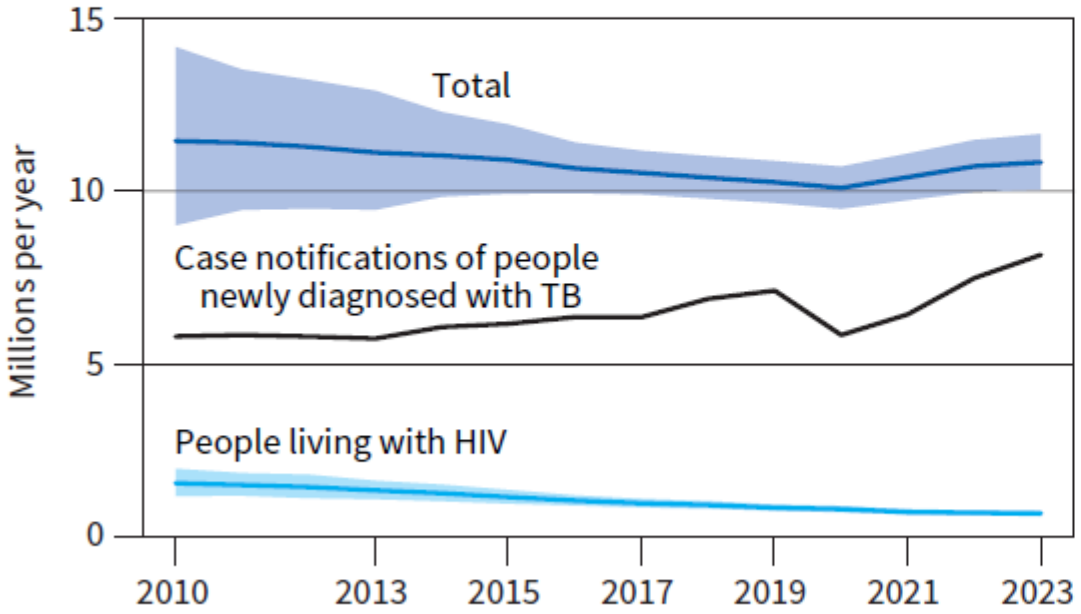


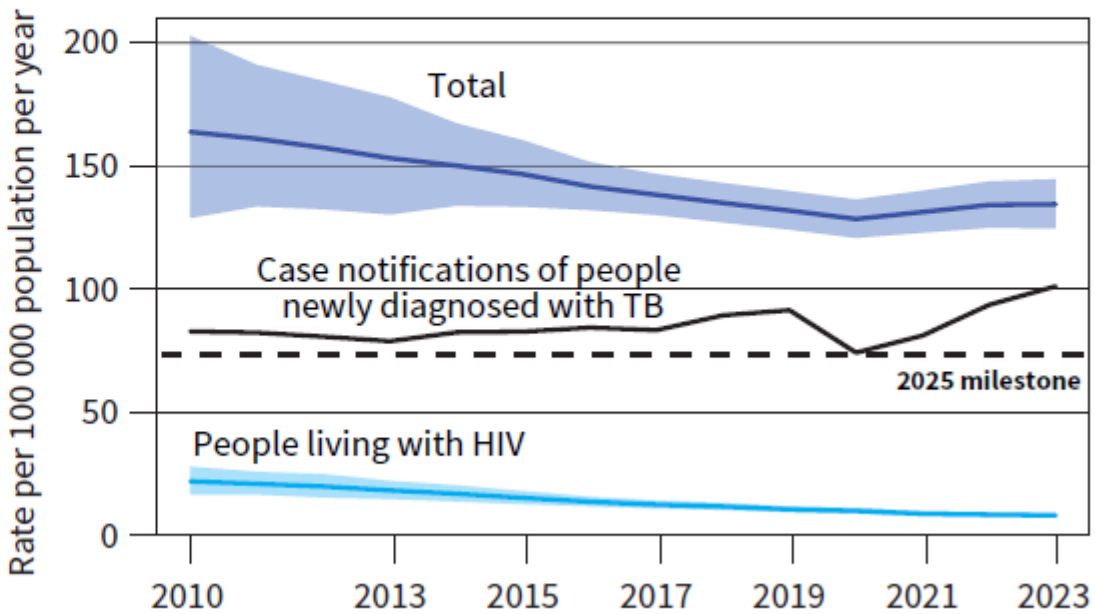
	Estimated number of cases	Estimated number of deaths
All forms of TB	10.8 million (10.1-11.7million)	1.25 million (1.1-1.4 million)
HIV-associated TB	658,800 (6.1%)	161,000 (25% HIV+/13% total)
MDR/RR TB	400,000 (4.2%) (360,000-440,000)	? ~200,000 (only 175,000 treated)

Source: WHO Global Tuberculosis Report 2024

Global trends in the estimated number of incident TB cases (left) and the incidence rate (right), 2010–2023

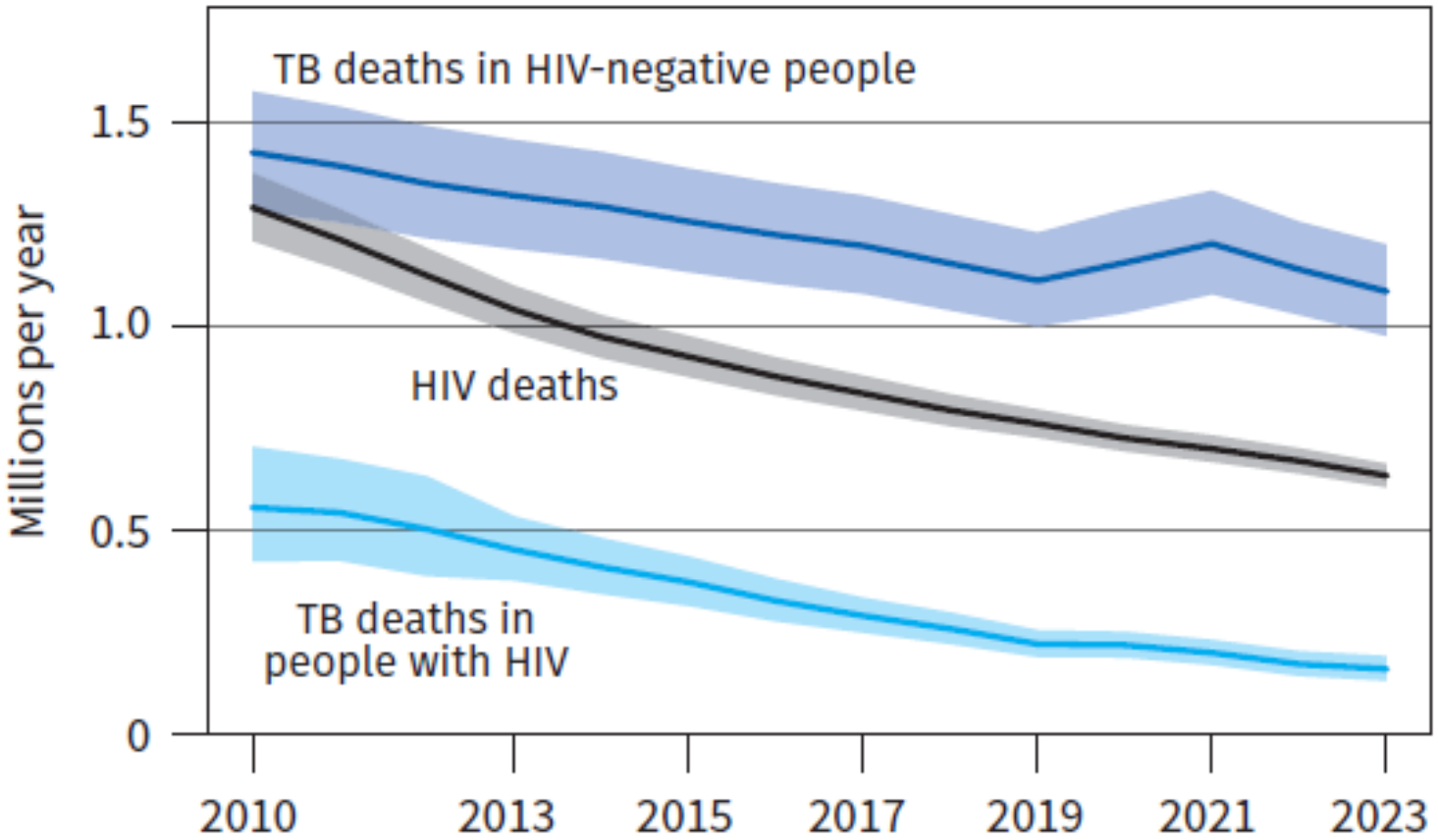
The horizontal dashed line shows the 2025 milestone of the End TB strategy, which is a 50% reduction in the TB incidence rate between 2015 and 2025. Shaded areas represent 95% uncertainty intervals.





WHO. Global TB Report, 2024.

Deaths due to TB, HIV, and TB/HIV



WHO. Global TB Report, 2024.

January 30, 2020

WHO Director-General's statement on IHR Emergency Committee on Novel Coronavirus (2019-nCoV)

العربية | 中文 | Français | Русский | Español

30 January 2020

Good evening to everyone in the room, and to everyone online.

Over the past few weeks, we have witnessed the emergence of a previously unknown pathogen, which has escalated into an unprecedented outbreak, and which has been met by an unprecedented response.

As I have said repeatedly since my return from Beijing, the Chinese government is to be congratulated for the extraordinary measures it has taken to contain the outbreak, despite the severe social and economic impact those measures are having on the Chinese people.

We would have seen many more cases outside China by now – and probably deaths – if it were not for the government's efforts, and the progress they have made to protect their own people and the people of the world.

The speed with which China detected the outbreak, isolated the virus, sequenced the genome and shared it with WHO and the world are very impressive, and beyond words. So is China's commitment to transparency and to supporting other countries.

Related

Statement on the second meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV)

COVID-19 pandemic

INT J TUBERC LUNG DIS 26(3):186–189

http://dx.doi.org/10.5588/ijtld.21.0734

EDITORIAL

The scientific response to TB – the other deadly global health emergency

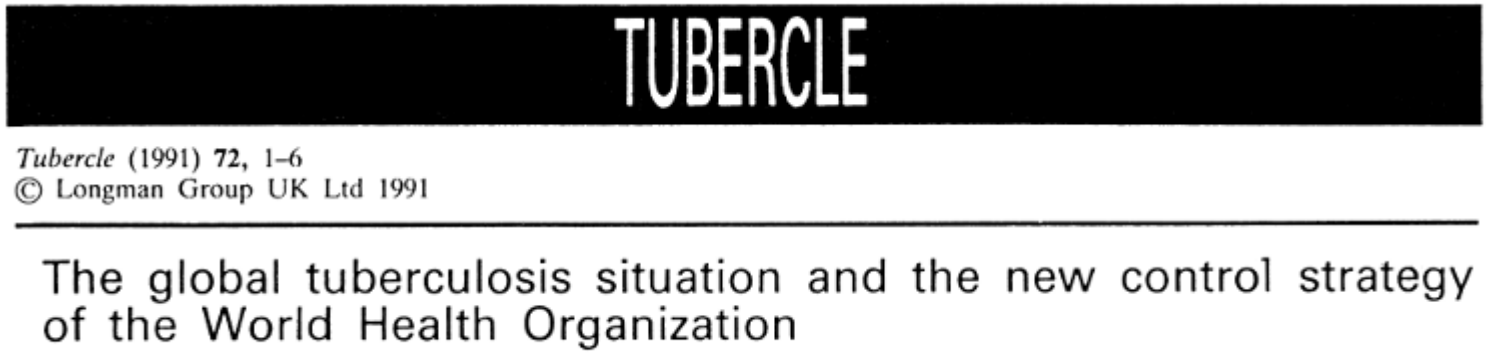
Table 2 A comparison of government funding for research on TB and two estimates for COVID-19 therapeutics and vaccines, 2020

	TB* US$	COVID-19† US$	COVID-19‡ US$
Total research funding	915 million (all areas)	53 billion (vaccines only)	104 billion (vaccines + therapeutics)
Funding for vaccine research	118.6 million	53.5 billion	98.9 billion
Public funding for vaccine research	77.5 million (65%)	51.4 billion (96%)	98.9 billion (100%)
Percentage of public funding committed via advanced purchase agreements	0%	88%	98%
Philanthropic funding for vaccine research	38.7 million	85.4 million	—
Private sector funding for vaccine research	2.4 million	517.8 million	—
Multilateral funding for vaccine research	0	1.4 billion (CEPI)	—
Funding for long-term consequences of disease (post-TB lung disease[15] and long COVID)	No estimate, but minimal	1.15 billion (US only)	—

* TB funding data comes from the Treatment Action Group and Stop TB Partnership report Tuberculosis Research Funding Trends, 2005–2020[8] which tracks research expenditures (actual disbursements) across six areas of TB research: basic science, diagnostics, drugs, vaccines, operational research/epidemiology, and infrastructure/unspecified projects.
† The Knowledge Network on Innovation and Access to Medicines published estimates of COVID-19 vaccine funding (disbursements and commitments) with data drawn from the Policy Cures Research COVID-19 R&D trackers and ACT-Accelerator Tracker; last updated July 8, 2021.
‡ The kENUP Foundation published estimates of public funding for COVID-19 vaccines and therapeutics (disbursements and commitments) in the first 11 months of the pandemic in January 2021.

Chaisson, Frick, Nahid. IJTLD 2022

Global Strategies for TB Control Through the Years - 1990s



TUBERCLE

Tubercle (1991) **72**, 1–6
© Longman Group UK Ltd 1991

The global tuberculosis situation and the new control strategy of the World Health Organization

DOTS: a breakthrough in TB control

- DOTS and World Health Assembly Targets:
  - By 2005, at least 70% of smear-positive TB cases will be detected and 85% cured
  - Use sputum smears (~50% sensitivity)
  - Passive case-finding
  - Other components: governmental commitment, registry of cases, supervision of initial therapy

Kochi, Tubercle 1991

INT J TUBERC LUNG DIS 2(9):S4–S8

THE PITTSFIELD LECTURE

The challenge of eradication: lessons from past eradication campaigns

D. A. Henderson

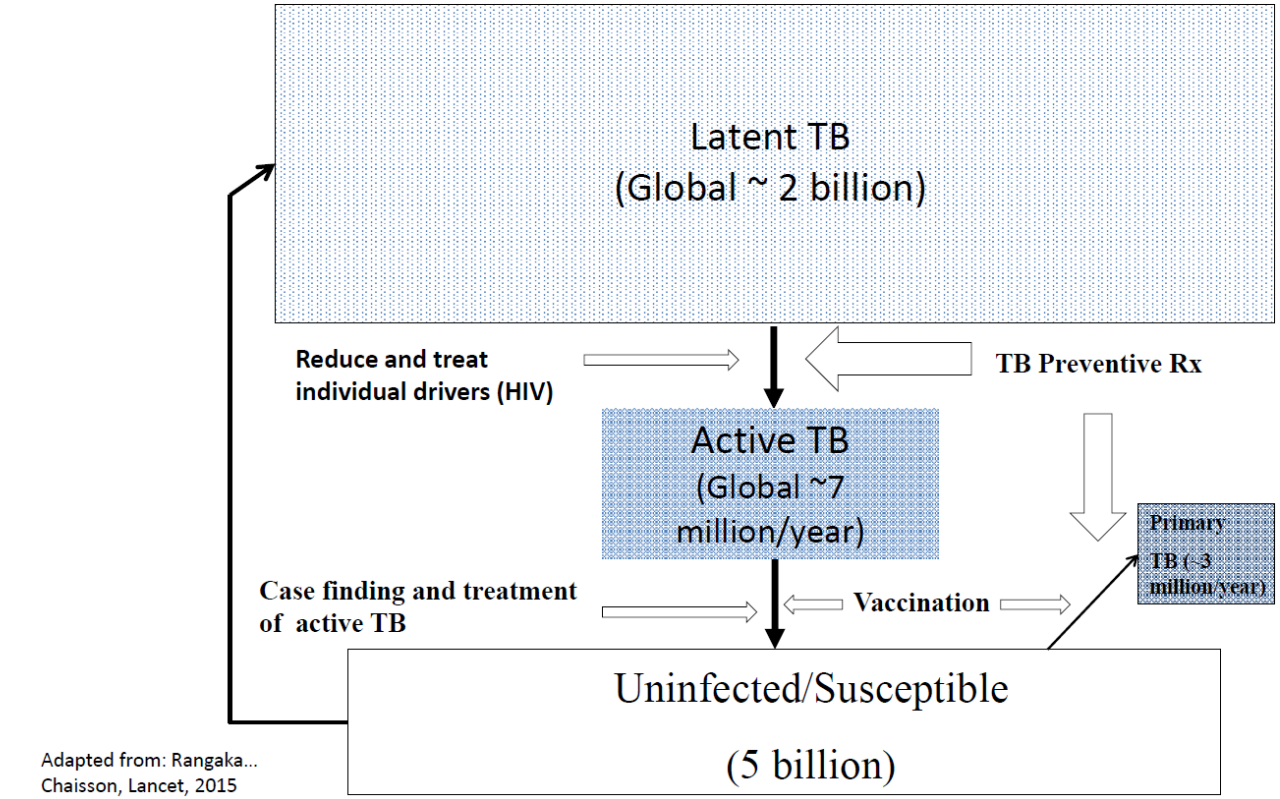
The Johns Hopkins University, Baltimore, Maryland, USA

Strange as it may seem, the earliest eradication programs began with an evangelistic fervor, an incomplete knowledge of the disease's ecology, unrealistic expectations, less than optimal technology, and with field experience that was minimal and uncritically evaluated.

Limitations of DOTS Strategy and 70/85 Benchmarks

- Fundamental misunderstanding of TB epidemiology
- Ignored seedbeds of TB
- Used passive case finding
- Relied on smear for diagnosis
- Assumed smear-negative TB is non-infectious
- Ignored HIV/TB
- Ignored MDR-TB
- Spurned research

Population Dynamics of Tuberculosis



Adapted from: Rangaka... Chaisson, Lancet, 2015

"A major area which has been neglected in most public health programs, with disastrous consequences, is research." DA Henderson

INT J TUBERC LUNG DIS 3(6):457–465

COUNTERPOINT

Will DOTS do it? A reappraisal of tuberculosis control in countries with high rates of HIV infection

K. M. De Cock,*† R. E. Chaisson‡

* London School of Hygiene and Tropical Medicine, Keppel Street, London, †Division of HIV/AIDS Prevention—Surveillance and Epidemiology, Centers for Disease Control and Prevention, Atlanta, Georgia, USA, ‡Johns Hopkins University, Baltimore, Maryland, USA

- TB incidence rising rapidly in countries with high HIV prevalence
- “Good” DOTS programs failing to contain TB
- TB control strategies need to be rethought in setting of HIV epidemic
- Novel approaches urgently needed
  - Active or mass case-finding
  - TB preventive therapy
  - Integration of TB/HIV services
  - Infection control

Setting Goals for Disease Control Strategies

1. *Specific*—the goals should be stated with specific numerical expectations;

2. *Measurable*—they must be measured without undue effort;

3. *Adaptable* and *adjusted to need*—the goals should be regularly reviewed for relevance and, as necessary, altered to address unforeseen circumstances;

4. *Reasonable*—staff who use these yard sticks should perceive them as being achievable within reason.

5. *Time limited*—without a reference point in time, the goal is meaningless.

6. *Epidemiologically-based to have impact.*

D.A. Henderson, The challenge of eradication: lessons from past eradication campaigns. IJTLD 1998; 2(9):S4–S8

Targets for TB Control Through the Years

- 2000s – Millennium Development Goals
- Target 6C. Have halted by 2015 and begun to reverse the incidence of malaria and other major diseases
- WHO Strategy: At least 70% of smear-positive TB cases will be detected and 85% cured

Vision, goal, targets, milestones

Vision:

A world free of TB

Zero TB deaths,
Zero TB disease, and
Zero TB suffering

Goal:

End the Global TB epidemic

	MILESTONES		TARGETS	
			SDG*	END TB
	2020	2025	2030	2035
Reduction in number of TB deaths compared with 2015 (%)	35%	75%	90%	95%
Reduction in TB incidence rate compared with 2015 (%)	20%	50%	80%	90%
TB-affected families facing catastrophic costs due to TB (%)	0%	0%	0%	0%

GLOBAL TB PROGRAMME

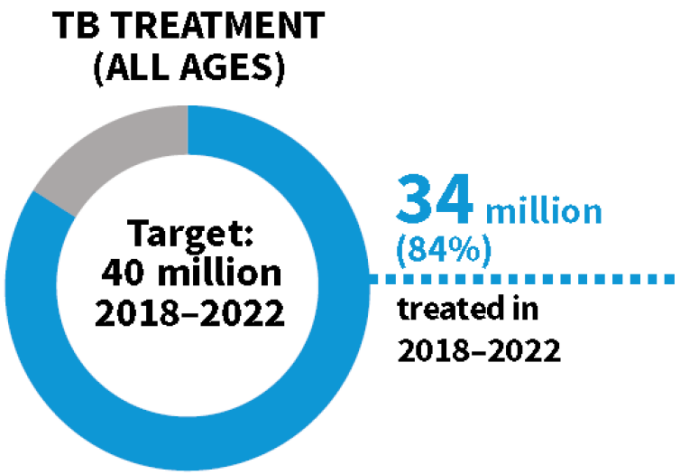
World Health Organization

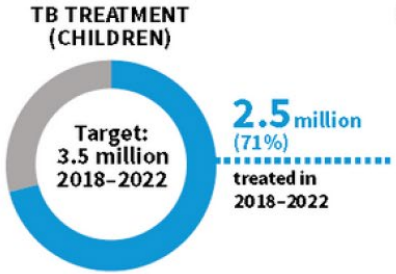
UN High-Level Meeting, September 26, 2018 General Assembly Declaration Commitments

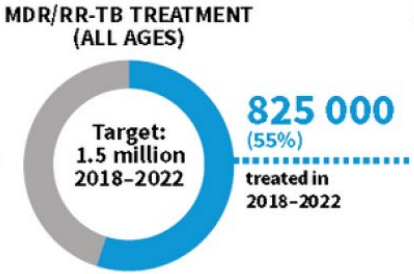
- End the TB epidemic globally by 2030
- Treat 40 million people with TB from 2018-2022, including:
  - 3.5 million children
  - 1.5 million people with MDR-TB (including 115,000 children)
- Provide **TB preventive therapy** to 30 million people by 2022, including:
  - 4 million children <5
  - 20 million household contacts
  - 6 million PLHIV
- Increase global investments in TB prevention and care to $13 billion/year by 2022
- Increase global investment in TB research to $2 billion/year
  - Close $1.3 billion funding gap

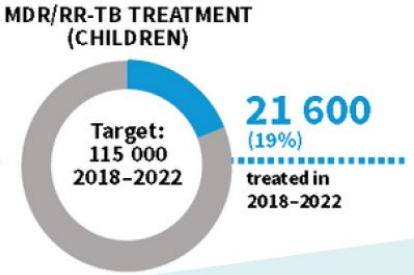
http://www.un.org/en/ga/73/resolutions.shtml

Progress towards the 2018 HLM Treatment Targets



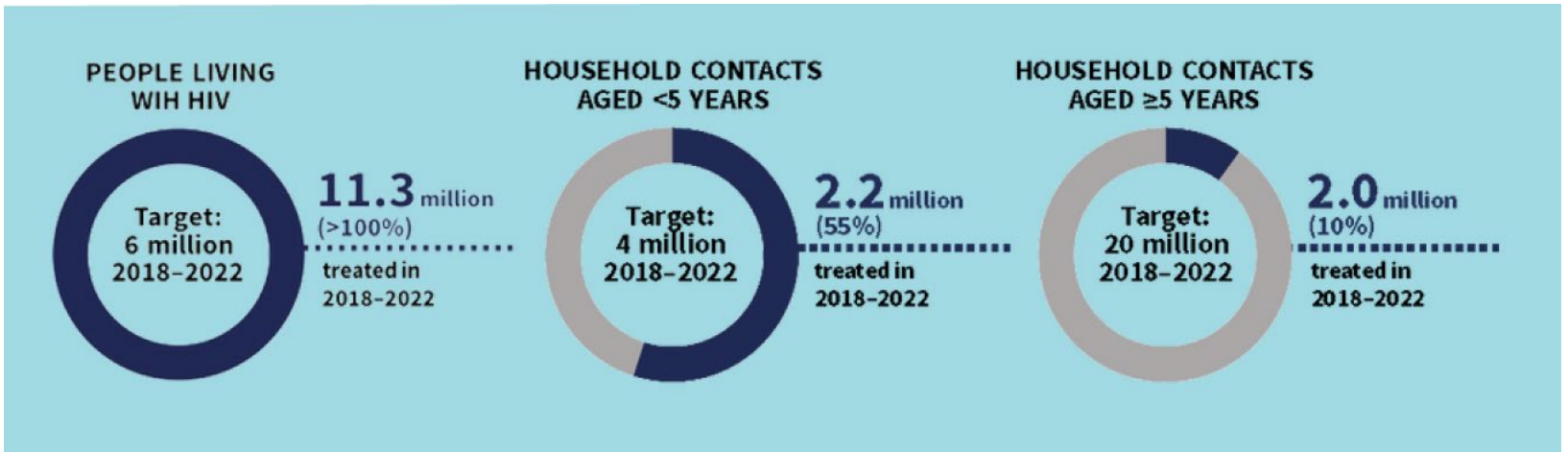




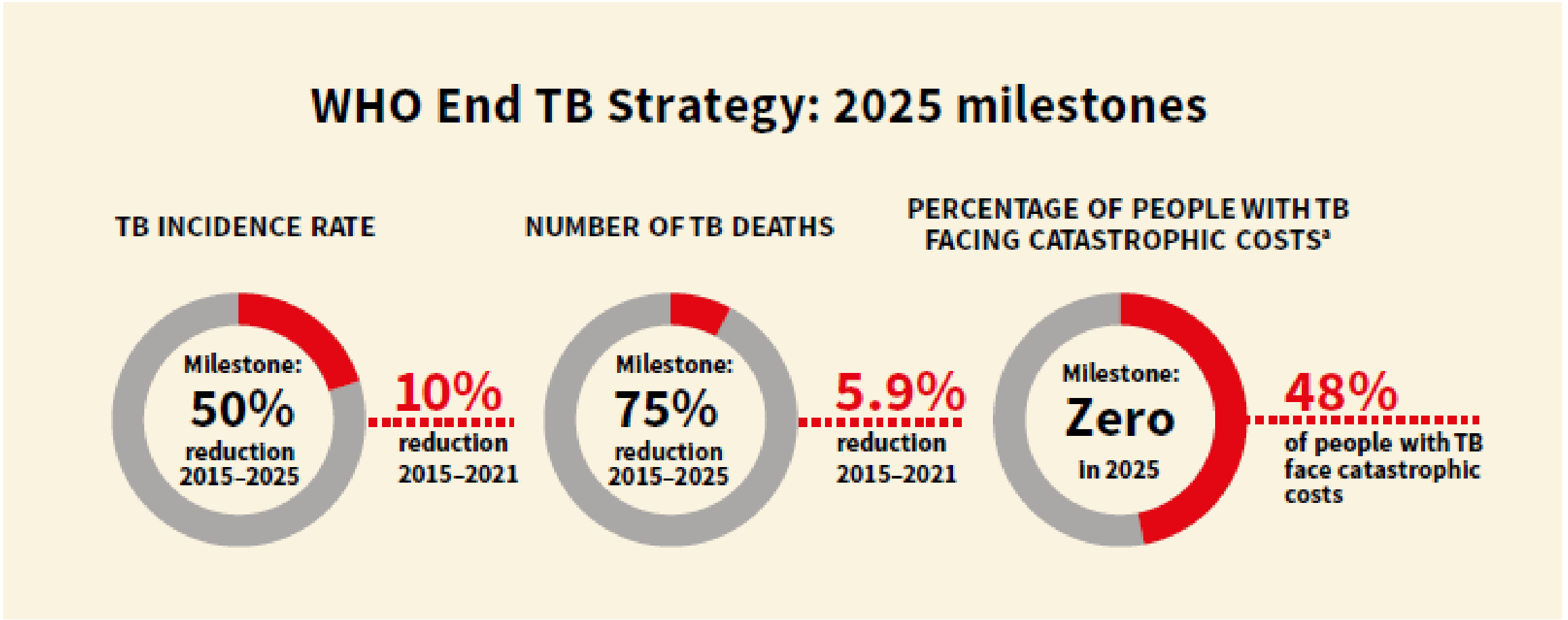


WHO. Status Update, September 2023

Progress towards the 2018 HLM Prevention Targets



WHO. Status Update, September 2023



WHO. Global TB Report, 2022

Another High-Level Meeting – September 20, 2023

High (and low)lights of 2023 UN HLM

"Right to science”

TRIPS flexibilities

US $22 billion per year for implementation

US $5 billion per year for research

Treat 45 million by 2027

Preventive treatment for 45 million by 2027

Lack of measurable, time-bound commitments

No accountability mechanisms

Weakened language on R&D investment -- "up to"

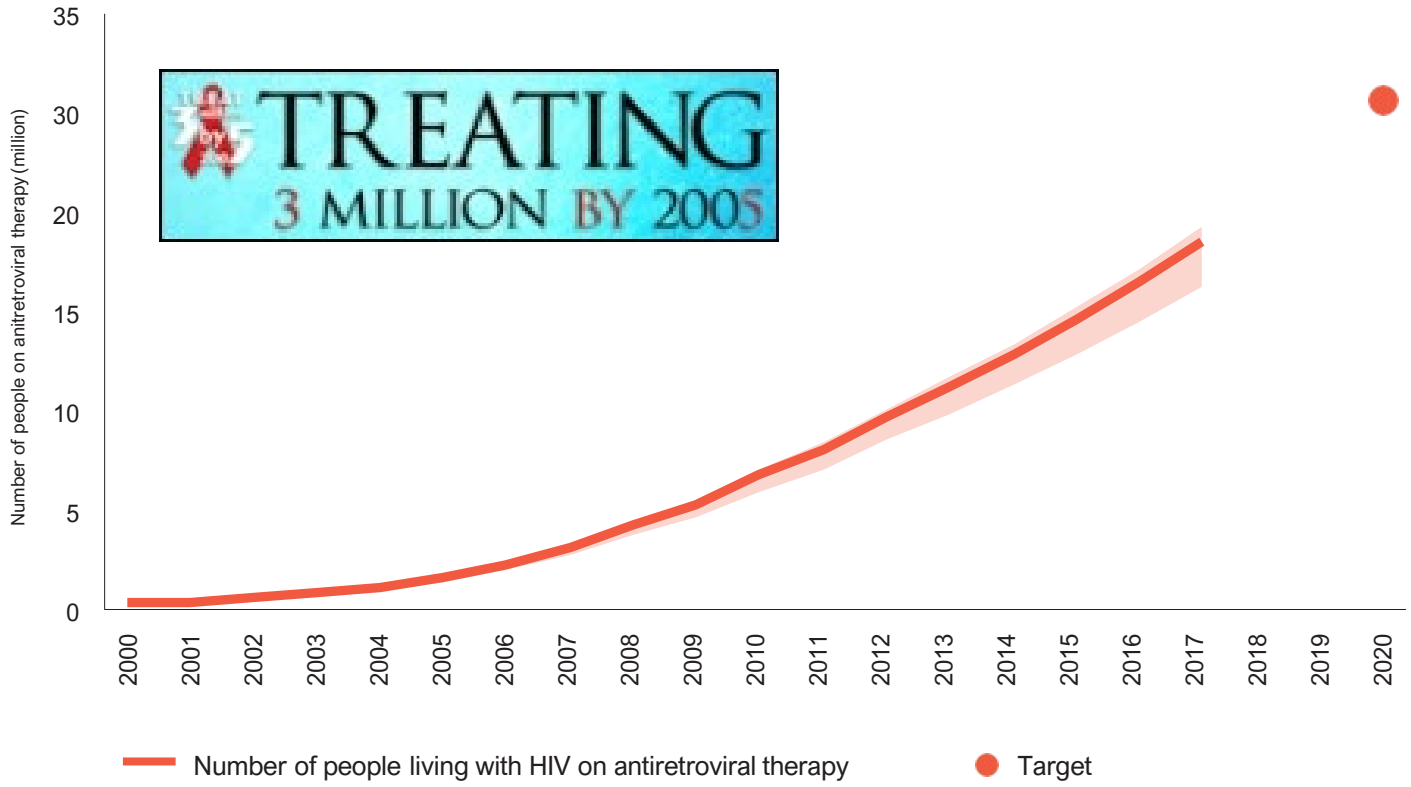
No commitment regarding access to the outputs of publicly funded research

Salvador Dali, Tilting at Windmills

End TB and UNHLM targets: Aspirations or delusions?

Global ART Scale-Up – A Delusion Realized

Number of people living with HIV accessing antiretroviral therapy, global, 2000–2017 and 2020 target



UNAIDS 2018

Is HIV epidemic control by 2030 realistic?

Chris Beyrer, Georgia D Tomaras, Huub C Gelderblom, Glenda E Gray, Holly E Janes, Linda-Gail Bekker, Gregorio Millett, Giuseppe Pantaleo, Susan Buchbinder, Lawrence Corey

Although epidemic control remains a crucial goal in HIV response, the findings from recent trials argue for increased scepticism about the current policy goal of achieving epidemic control by 2030. Goals are useful for mobilising stakeholders, but… we are not on track to reach current targets of epidemic control.

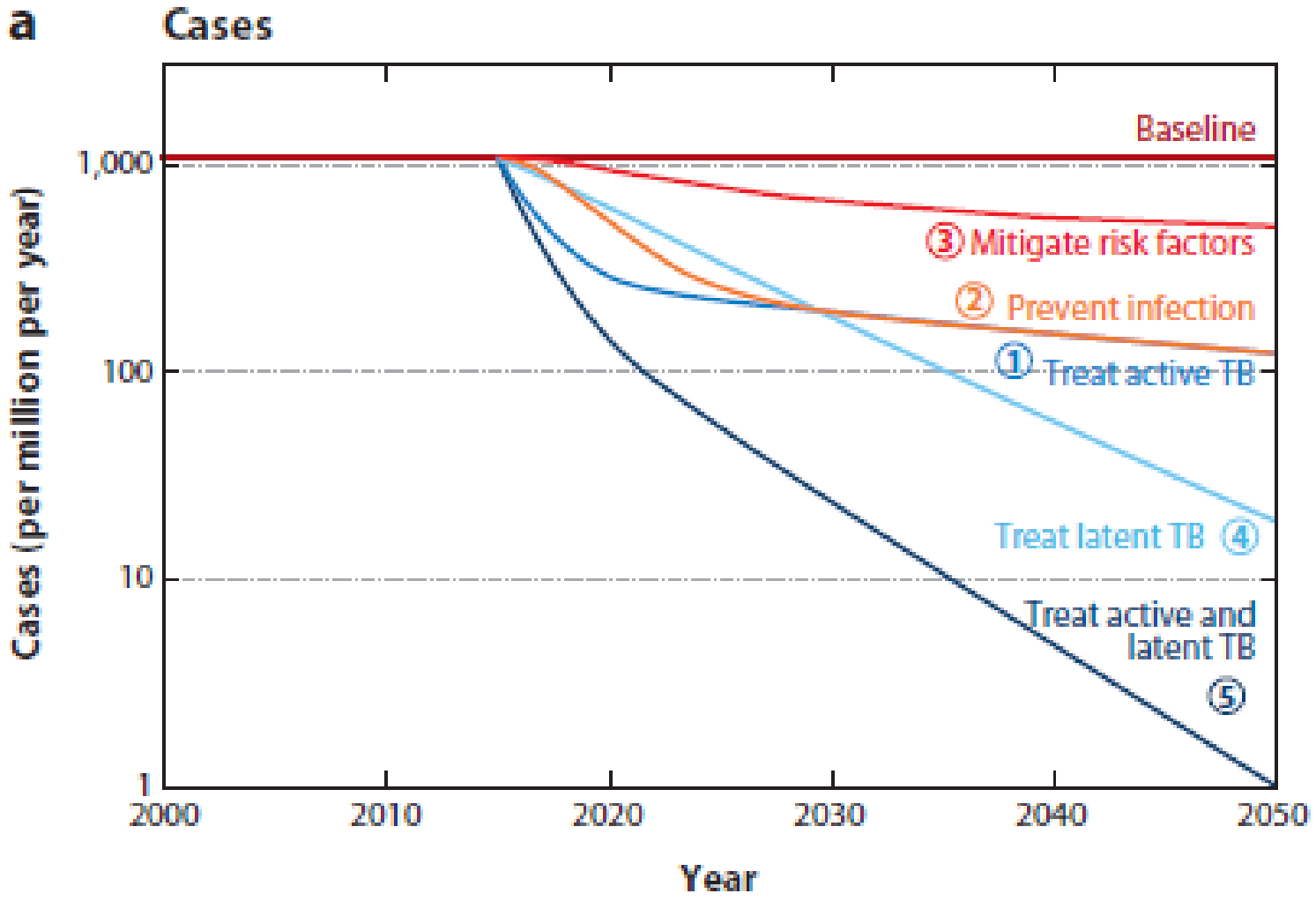
Lancet HIV 2024; 11: e489–94

Duke Global Health Institute (Prof C Beyrer MD) **and Duke Center for AIDS Research** (Prof C Beyrer, Prof G D Tomaras PhD), **Duke University, Durham, NC, USA; Department of Surgery and Department of Integrative Immunobiology, Duke University, Durham, NC, USA** (Prof G D Tomaras); **Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Center, Seattle, WA, USA** (H C Gelderblom MD, Prof H E Janes PhD, Prof L Corey MD); **Desmond Tutu HIV Centre, University of Cape Town, Cape Town, South Africa** (Prof L-G Bekker MD); **amfAR, Washington, DC, USA** (G Millett MPH); **Laboratory of AIDS Immunopathogenesis at the Centre Hospitalier Universitaire Vaudois, University of Lausanne, Lausanne, Switzerland** (Prof G Pantaleo MD); **South African Medical Research Council, Cape Town, South Africa** (Prof G E Gray MBBCH); **San Francisco Department of Health, San Francisco, CA, USA** (Prof S Buchbinder MD)

Correspondence to:
Prof Chris Beyrer, Duke Global Health Institute, Duke University, Durham, NC 27701, USA
chris.beyrer@duke.edu

See Online for appendix

Modeled approaches to reaching TB elimination



Dye, et al., Ann Rev Publ Health 2013

A Platform for Controlling Global Tuberculosis: Tools and Implementation

- **FIND** the TB that is there
  - Improved diagnostic technologies, including POC, essential
  - Better case-finding strategies in facilities and community

- **TREAT** the TB that is found
  - Improved treatment outcomes for all forms of TB
  - Shorter duration of treatment
  - New drugs and treatment strategies still urgently needed

- **PREVENT** the TB that hasn't occurred yet
  - New preventive therapies (e.g, long-acting injectables)
  - Infection (transmission) control through social network tracing
  - New vaccines

CREATE
Consortium to Respond Effectively to the AIDS TB Epidemic

SMART4TB Leadership

Richard Chaisson
Johns Hopkins University

Kelly Curran
Johns Hopkins University

Carrie Tudor
Johns Hopkins University

Appolinaire Tiam
Elizabeth Glaser Pediatric AIDS Foundation

Erica Lessem
Johns Hopkins University

Payam Nahid
University of California, San Francisco

Lindsay McKenna
Treatment Action Group

Laura Guay
Elizabeth Glaser Pediatric AIDS Foundation

Gidado Mustapha
KNCV Tuberculosis Foundation

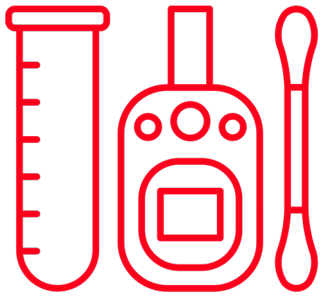
Laurence Borand
Johns Hopkins University

USAID
FROM THE AMERICAN PEOPLE

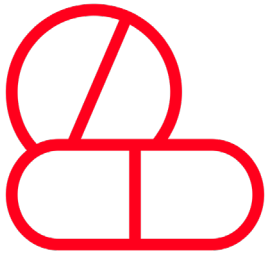
Supporting, Mobilizing, and Accelerating Research for Tuberculosis Elimination

SMART4TB Consortium

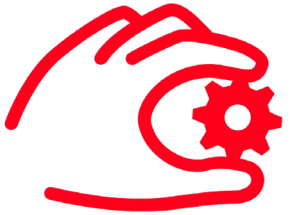
SMART4TB – USAID-funded Consortium to Advance END-TB Goals



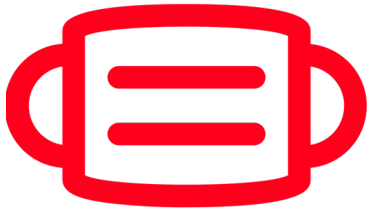
Diagnostics



Therapeutics



Operational Research



Interrupting Transmission

Vaccine Preparedness

Capacity Strengthening

Policy Translation

USAID FROM THE AMERICAN PEOPLE

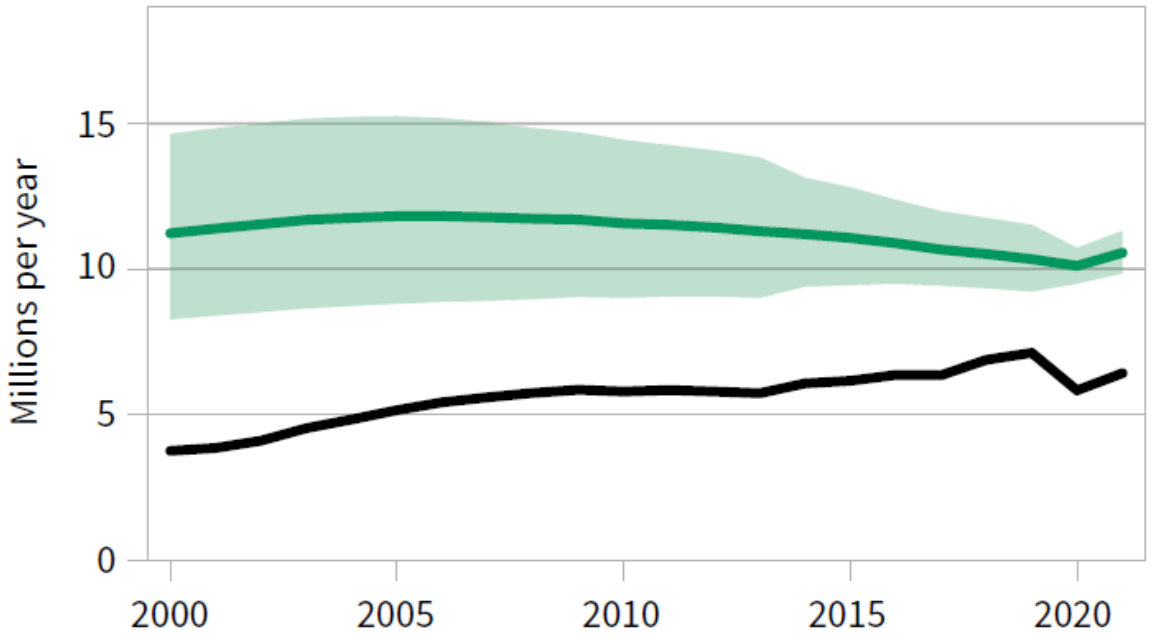
Supporting, Mobilizing, and Accelerating Research for Tuberculosis Elimination

SMART4TB Consortium

Gaps in TB Diagnosis

Global trends in notifications of people newly diagnosed with TB (black) and the estimated number of incident TB cases (green), 2000–2021

The shaded area represents the 95% uncertainty interval.



WHO. Global TB Report, 2022.

INT J TUBERC LUNG DIS 19(11):1320–1325

http://dx.doi.org/10.5588/ijtld.15.0222

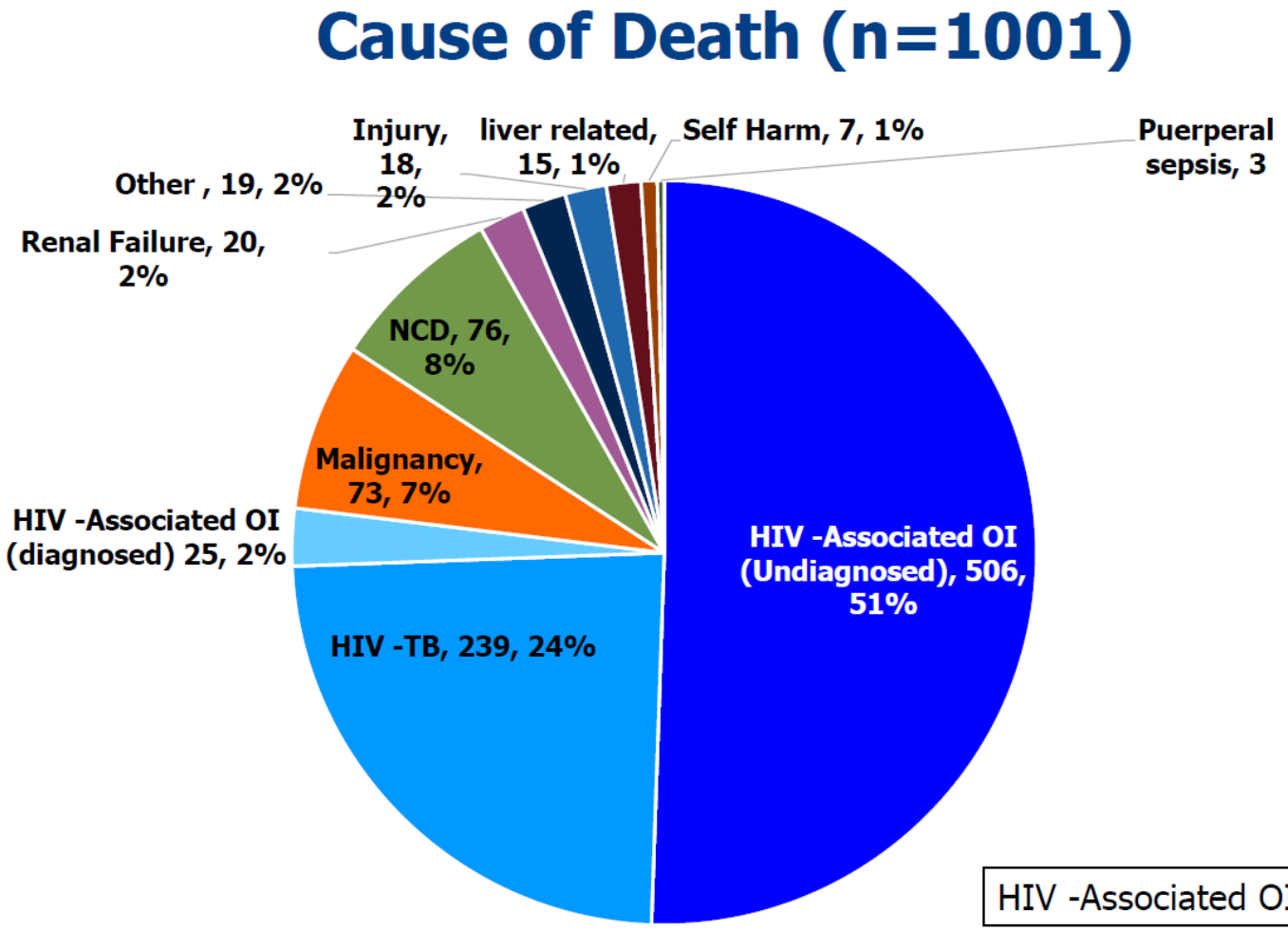
Undiagnosed TB in adults dying at home from natural causes in a high TB burden setting: a post-mortem study

T. Omar,* E. Variava,† E. Moroe,‡ A. Billioux,§ R. E. Chaisson,§ L. Lebina,‡ N. Martinson‡§¶

- Adults dying at home, no specific diagnosis
- (18% excluded, known to have TB)
- Consent from family
- Bilateral axillary lung biopsy
- Modified BAL
- 32% with TB at death

PHRU
IMPROVING LIFE THROUGH RESEARCH

Verbal Autopsy Study of PWHIV Dying in India, 1/2019 – 3/2020

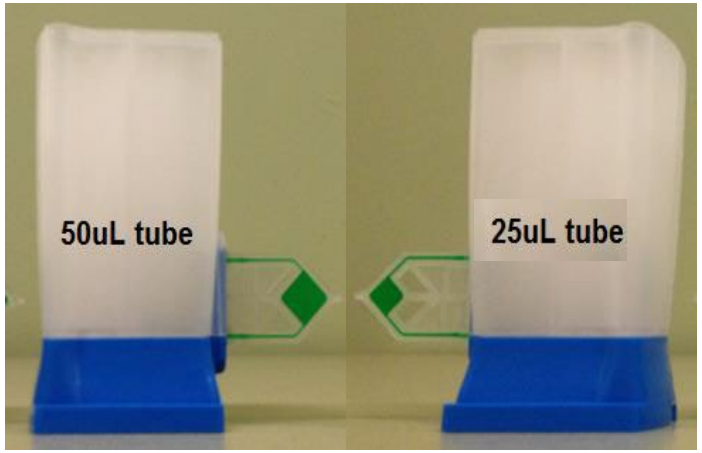


- 49% had a history of TB
- Male:Female = 1

HIV -Associated OI – 770 (77%)

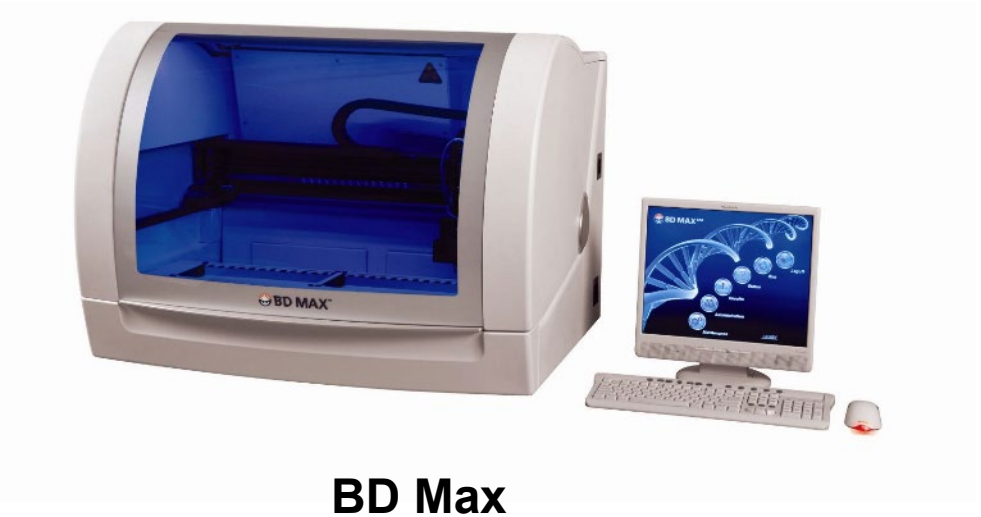
Slide courtesy of Sunil Solomon, MBBS, PhD

New Tools for Diagnosing TB



Xpert MTB/RIF Ultra

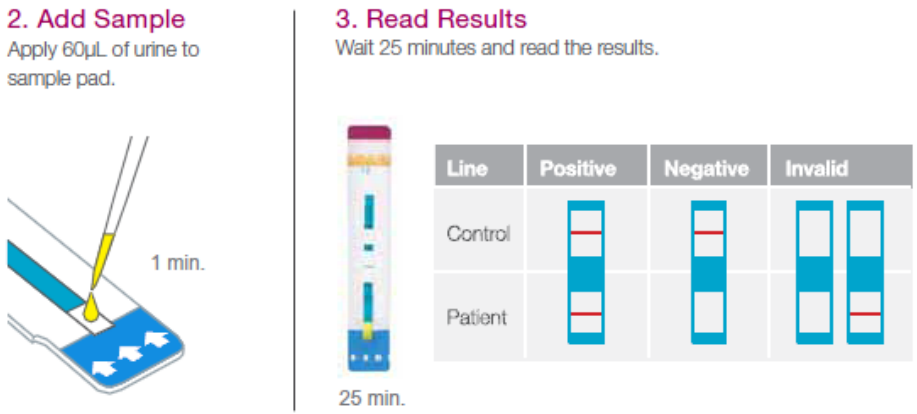
Omni Xpert Platform



BD Max

Abbott

Truenat



LAM

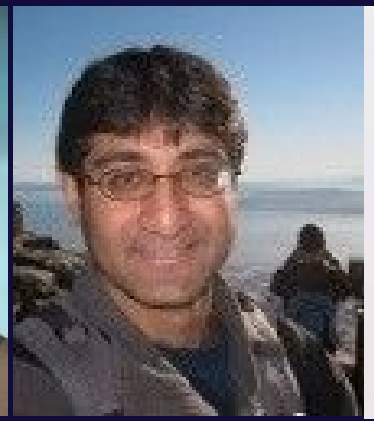
Technical Area 1: Diagnostics

Adithya Cattamanchi
University of California, San Francisco

Claudia Denkinger
Heidelberg University

Devan Jaganath
University of California, San Francisco

Yuka Manabe
Johns Hopkins University



Maunank Shah
Johns Hopkins University

Nilesh Bhatt
Elizabeth Glaser Pediatric AIDS Foundation

Kristin Kremer
KNCV Tuberculosis Foundation

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SMART4TB Consortium

Swab-based TB assay on fully-integrated, POC molecular platform

Sherlock Biosciences, Veros

Boditech Med, IsoAmplar

Co-Diagnostics, Co-Dx PCR Pro

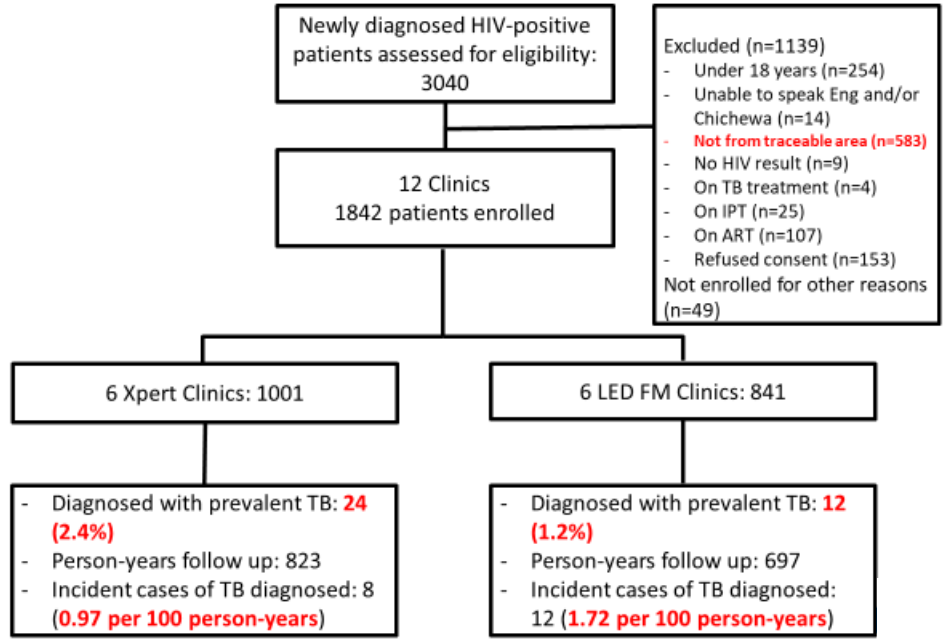
Molbio Diagnostics, Truenat

Minute Molecular Diagnostics, DASH

Screening for tuberculosis with Xpert MTB/RIF versus fluorescent microscopy among people newly diagnosed with HIV in rural Malawi: A cluster-randomized trial

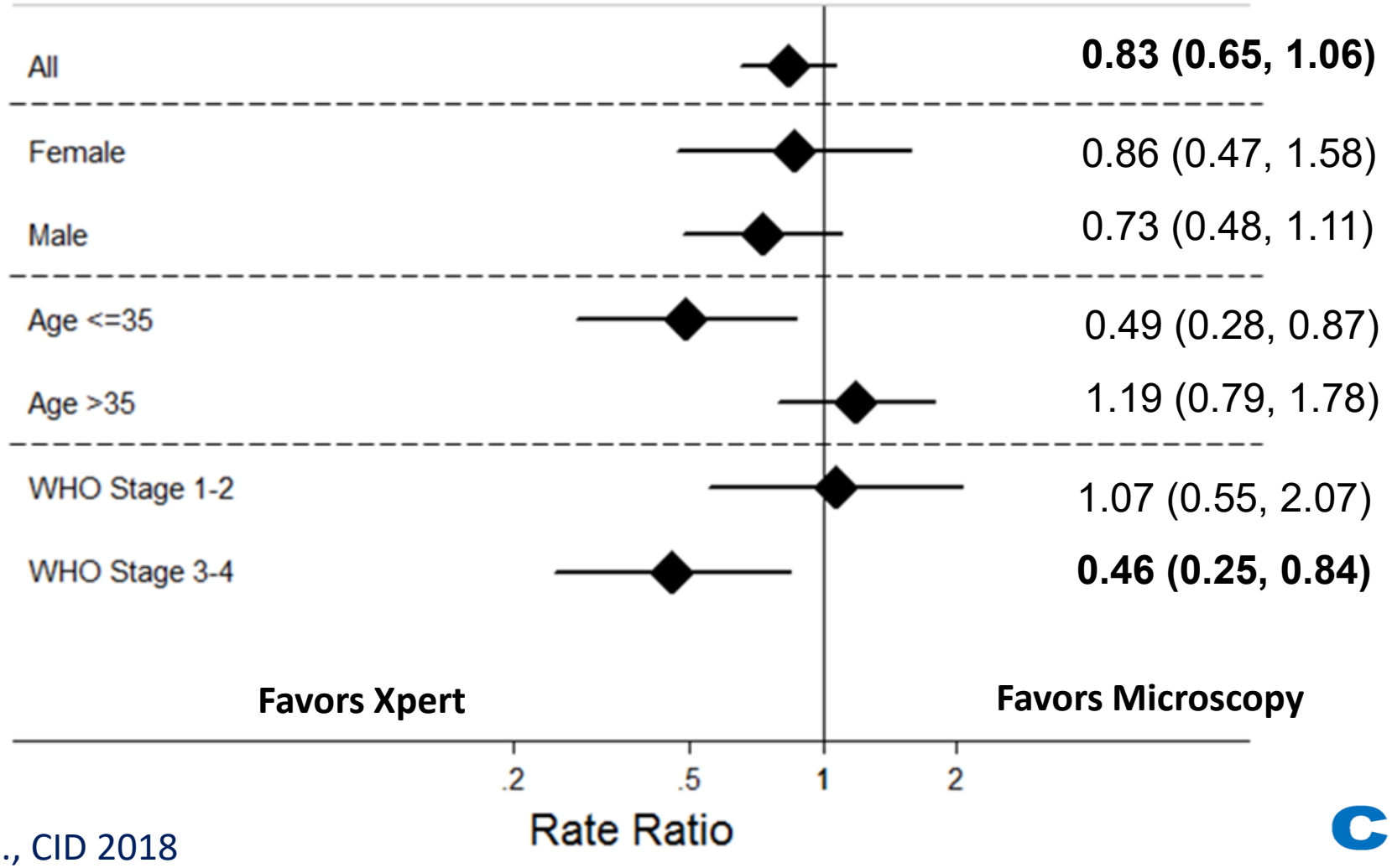
Lucky G. Ngwira, McEwen Khundi, Grace L. Barnes, Austin Nkhoma, Michael Murowa, Silvia Cohn, Larry Moulton, Richard E. Chaisson, Elizabeth L. Corbett, David W. Dowdy

CONSORT flowchart



Cluster-randomized Trial of Xpert vs. LED Fluorescent Microscopy as Point of Care Test in HIV Clinics

Rate ratio for all-cause mortality at 1 year



Ngwira et al., CID 2018

Universal vs. Symptom-based TB Screening of Pregnant Women with HIV– A Cluster-randomized Trial in South Africa

Baseline Characteristics by Arm		
	Universal Clinics (8) N=941	**Symptom Clinics (8)** N=1,100
Age	30.2 yrs	29.5 yrs
Gestational age	24.6 wks	24.4 wks
TB Symptoms	17.3%	22.1%
Prior TB	9.8%	7.8%
On ART	99.5%	98.6%
CD4 count	426 cells/mm^3	451 cells/mm^3
Hb	11.4 g/dl	10.8 g/dl

Yield of TB diagnoses by Arm		
Study Arm	TB Cases n/N	**Cluster-adjusted MTb Yield (95%CI)**
Universal Testing	34/941	**3.6% (1.2-6.0)**
Symptom Testing	4/1100	**0.36% (0.0-1.1)**

P = 0.01

Martinson, et al. IAS 2017

Targeted Universal Test for TB (TUTT)

Martinson, et al. PLoS Medicine, 2023, 20(5): e1004237

Cluster-randomized trial in 62 South African primary care clinics

Universal testing of ‘high-risk’ patients attending intervention clinics

- Primary analysis: TB diagnoses in control clinics decreased over time, intervention clinics had a 17% increase in TB diagnoses, interaction IRR 1.17 (95% CI 1.14, 1.19, $p < 0.001$).

Yield of Targeted Testing (% with TB)

- Overall 8.1%
- HIV+ 7.2%
- Close contact 9.6%
- Prior TB (2 yrs) 16.3%

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis

S.E. Dorman, P. Nahid, E.V. Kurbatova, P.P.J. Phillips, K. Bryant, K.E. Dooley, M. Engle, S.V. Goldberg, H.T.T. Phan, J. Hakim, J.L. Johnson, M. Lourens, N.A. Martinson, G. Muzanyi, K. Narunsky, S. Nerette, N.V. Nguyen, T.H. Pham, S. Pierre, A.E. Purfield, W. Samaneka, R.M. Savic, I. Sanne, N.A. Scott, J. Shenje, E. Sizemore, A. Vernon, Z. Waja, M. Weiner, S. Swindells, and R.E. Chaisson, for the AIDS Clinical Trials Group and the Tuberculosis Trials Consortium

N ENGL J MED 384;18 NEJM.ORG MAY 6, 2021

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bedaquiline–Pretomanid–Linezolid Regimens for Drug-Resistant Tuberculosis

F. Conradie, T.R. Bagdasaryan, S. Borisov, P. Howell, L. Mikiashvili, N. Ngubane, A. Samoilova, S. Skornykova, E. Tudor, E. Variava, P. Yablonskiy, D. Everitt, G.H. Wills, E. Sun, M. Olugbosi, E. Egizi, M. Li, A. Holsta, J. Timm, A. Bateson, A.M. Crook, S.M. Fabiane, R. Hunt, T.D. McHugh, C.D. Tweed, S. Foraida, C.M. Mendel, and M. Spigelman, for the ZeNix Trial Team*

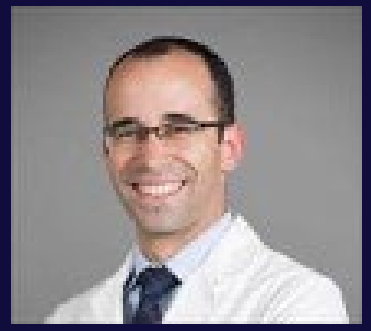
N ENGL J MED 387;9 NEJM.ORG SEPTEMBER 1, 2022

Impacts of new short-course regimens for DS- and DR- TB

Faster cure for patients
Decreased costs of supervision
Increased capacity for treatment
Higher drug costs

Faster cure for patients
Improved clinical outcomes
Fewer side effects/AEs
Decreased costs of supervision
Increased capacity for treatment

Technical Area 2: Therapeutics



Gustavo Velásquez
University of California, San Francisco

Nicole Salazar-Austin
Johns Hopkins University

Eric Nuermberger
Johns Hopkins University

Sonya Krishnan
Johns Hopkins University

Rada Savic
University of California, San Francisco

Patrick Phillips
University of California, San Francisco

Ethel Weld
Johns Hopkins University

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SMART4TB Consortium

Shortened Regi**M**en for Drug-suscept**I**b**LE TB** in Children (SMILE-TB)

Open-label, Randomized, Controlled, Treatment-shortening Noninferiority Trial

Children < 10 years with presumed DS-TB

N=860

Randomization (1:1)

8w HRZ(E) + 8-16w HR
(per severity disease & local SOC)

H – Isoniazid
R – Rifampicin
Z – Pyrazinamide
E – Ethambutol

RHZ & RH dispersible **FDC**

8w HPZM

H – Isoniazid
P – Rifapentine
Z – Pyrazinamide
M – Moxifloxacin

Standalone dispersible tablets

Follow up 12 months post randomization

PK sub studies for RPT & MFX dose confirmation/optimization and drug-drug interaction between RPT and DTG in CLHIV

Early DSMB assessment by risk strata

SMART4TB Consortium

PRISM-TB

Randomization of regimens (1:1:1)

Control

‘Preferred’ WHO Control (26-39w)

Intervention

Stratification

Duration

Eligible persons with FQ-S RR-TB (N=690)

BPaLM → 17w

BPaLM

- **Harder-to-treat TB** → 26w
- **Easier-to-treat TB** → 13w

All participants followed up to 18 months post-randomization

Assuming approximately 75% easier-to-treat TB, 25% harder-to-treat TB

B – Bedaquiline
Pa – Pretomanid
L – Linezolid
M – Moxifloxacin

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SMART4TB Consortium

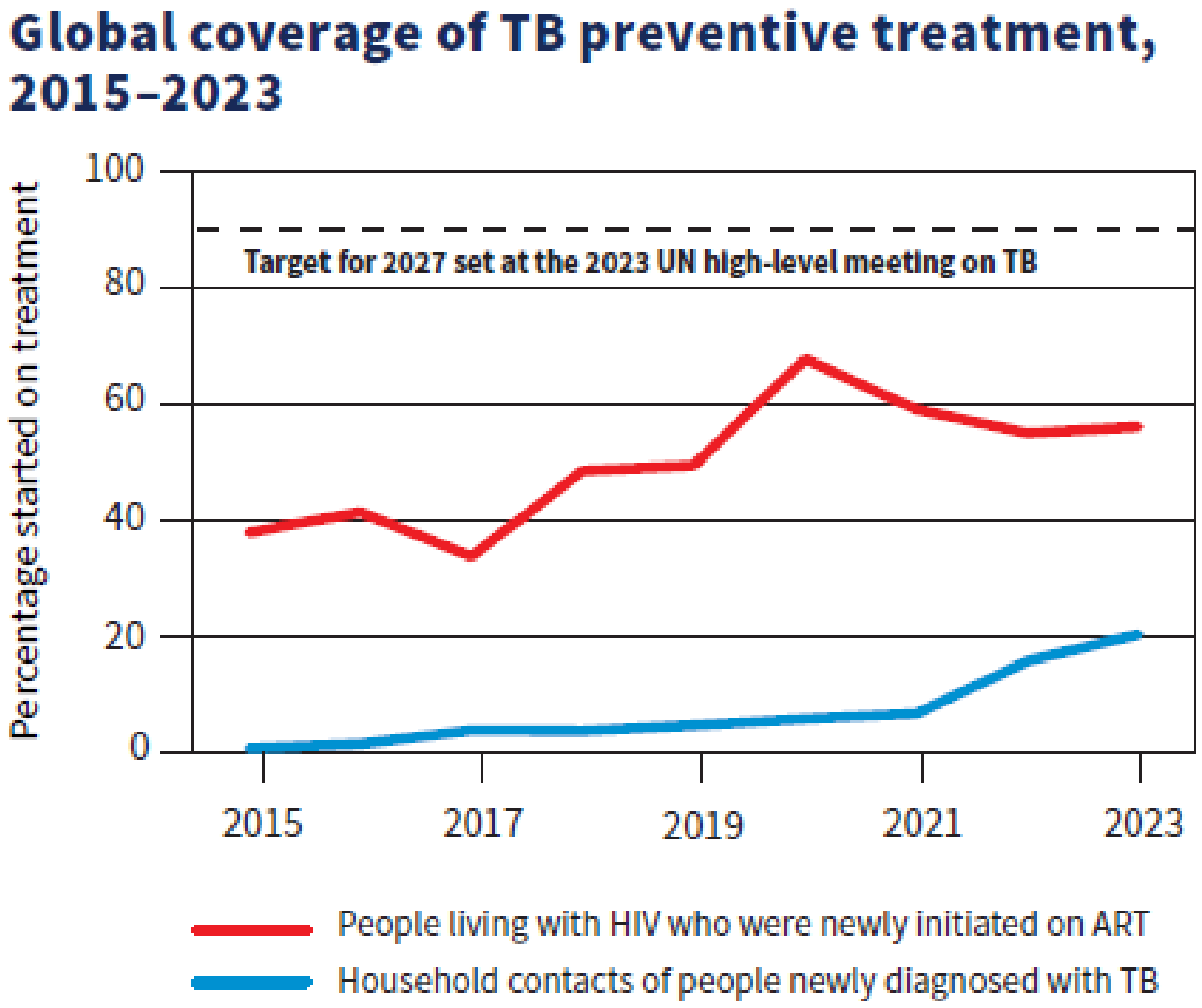
Columbia | Mailman School of Public Health

Prevention of TB: Underappreciated and Poorly Implemented

‘In most situations, something that is prevented is a nonevent… As a consequence, the benefits of prevention are more likely to appeal to our intellect than to our emotions.’

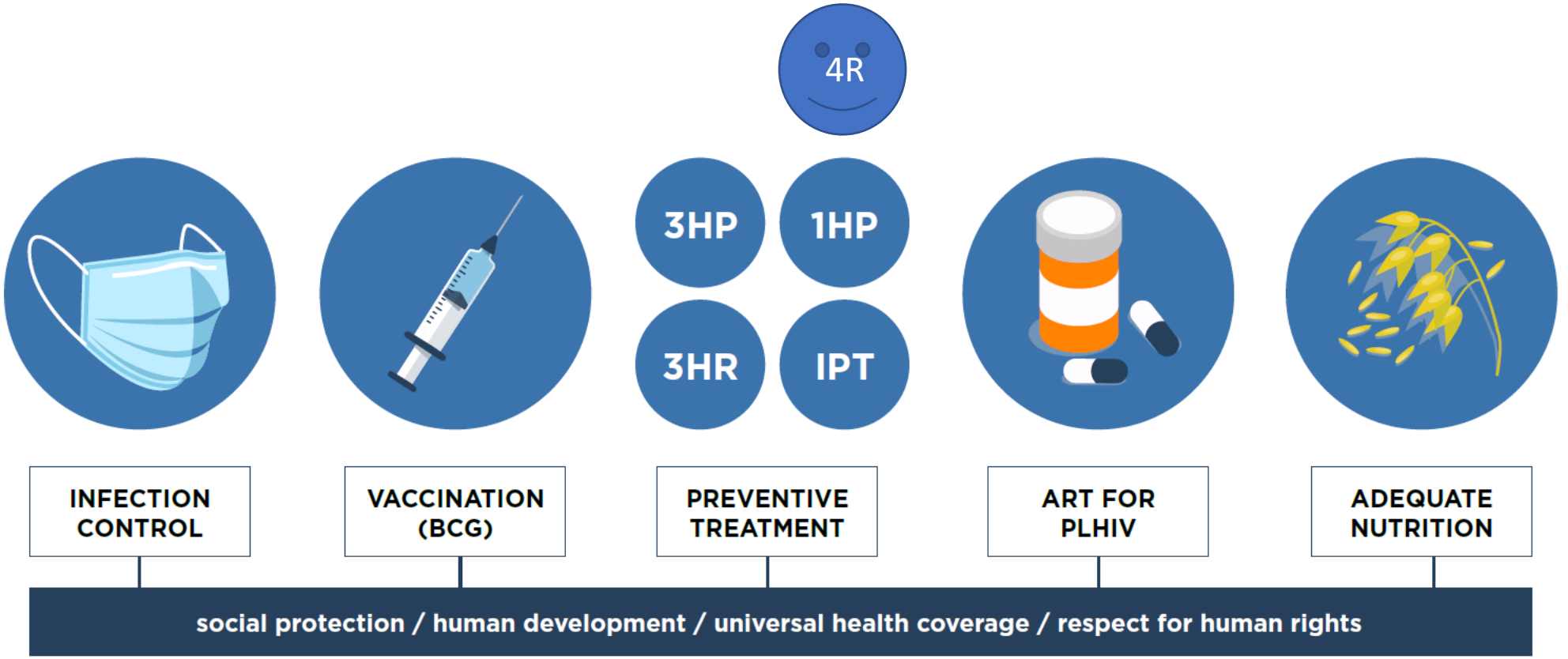
George W. Comstock. JAMA 1986.215:2729

How Are We Doing with Global Targets?



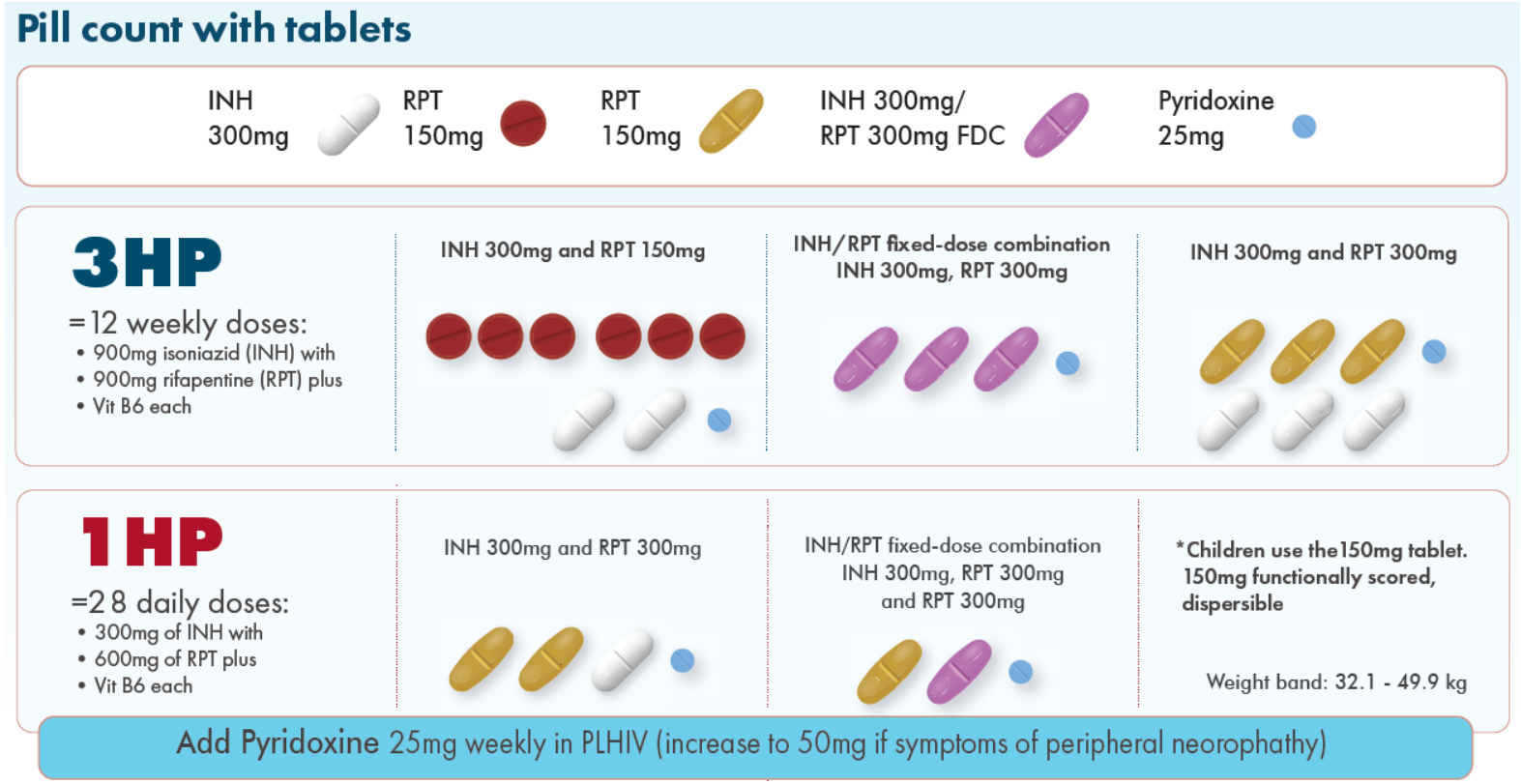
WHO. Global TB Report, 2024

What are our tools for TB prevention?

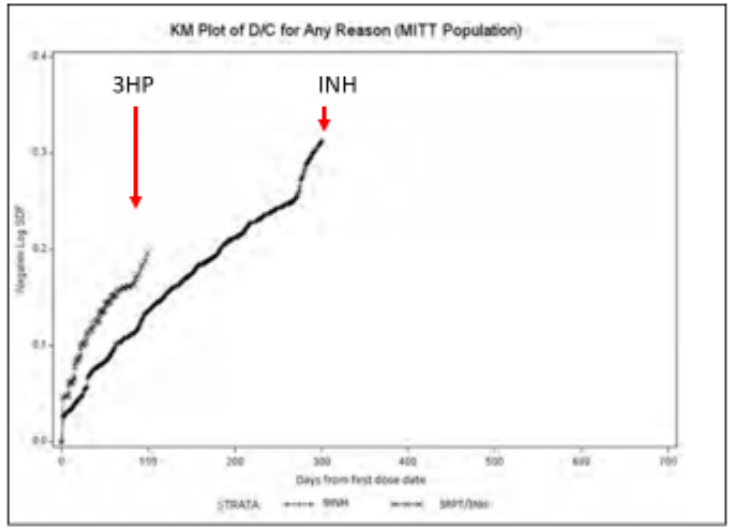


Treatment Action Group. AN ACTIVIST'S GUIDE TO Rifapentine TB PREVENTIVE TREATMENT: 3HP AND 1HP. April 2024

Benefit of Short-course TPT



Rates of Early Discontinuation of TPT in Study 26
Longer Duration = More Opportunity to Stop



TBTC Study 26, unpublished

Barriers to short-course TPT

- Price/cost to patients
- Lack of generic manufacturing
- Regimen choice
- Drug-drug interactions
- Drug-resistant TB

- Clinician reluctance to prescribe TPT
- Implementation challenges

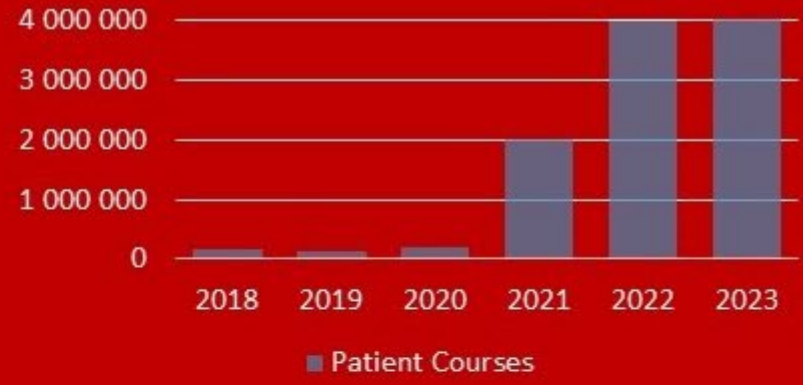
Promoting uptake of TB preventive therapy with 3HP

Price of 3HP

The price dropped from $72 in 2017 to $14,25 in 2022 and $9,99 in 2023 for the FDC. 1HP is available at $17- $18.

Rifapentine Manufacturing Capacity

Increased from 180k patient courses in 2018 to over 4,5 million in 2023.

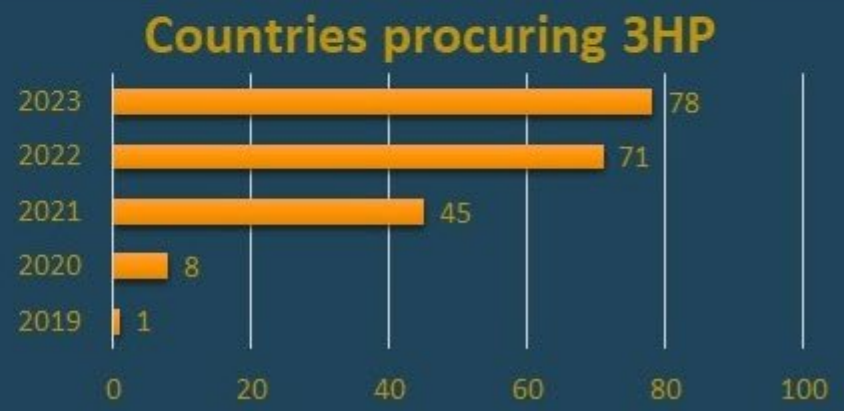


3HP Global procurement expansion

Over 4,2 million patient courses of rifapentine-based TB preventive treatments have purchased across 78 countries. In total, 138 countries now have access to purchase 3HP.

Countries procuring 3HP

From one (1) country in 2018 to over seventy-eight (78) countries procuring 3HP in 2023.



>1 million additional courses of 3HP catalyzed

IMPAACT4TB
PREVENTING TB TO END TB

ULTRA CURTO – 1 V 3 HP IN BRAZIL

STUDY DESIGN

500 HIV-uninfected individuals ≥15 years old and no evidence of active TB who:

Have tuberculin skin test (TST) reactivity ≥ 10 mm and/or a positive Interferon Gamma Release Assay (IGRA), **AND**

- Are a contact of confirmed pulmonary TB case within past 90 days, or
- Have a documented conversion of TST or IGRA within 2 years

STUDY REGIMENS

All treatment self-administered.

	Arm A	Arm B
Rifapentine	600 mg once daily for 4 weeks	900 mg weekly for 12 weeks
Isoniazid	300 mg once daily for 4 weeks	900 mg weekly for 12 weeks

Durovni, et al. World Conf Lung Health, Bali, 2024

STUDY OUTCOMES / PRIMARY OUTCOMES

Treatment success: Successful completion of TPT with **>90% adherence** documented by **self-report, pill count, and pharmacologic monitoring**.

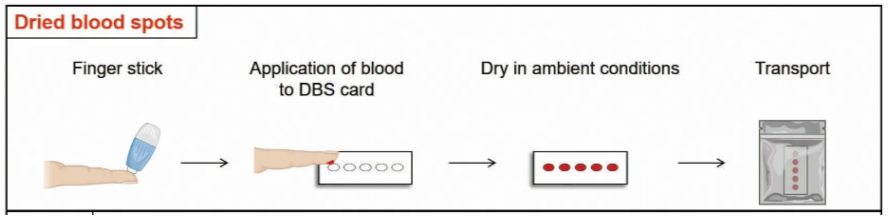
1HP: having taken **at least 25 doses** of medication **within 8 weeks**

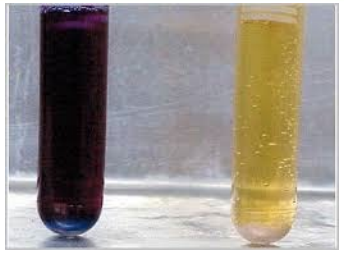
3HP: having taken **at least 11 doses** of medication **within 16 weeks**

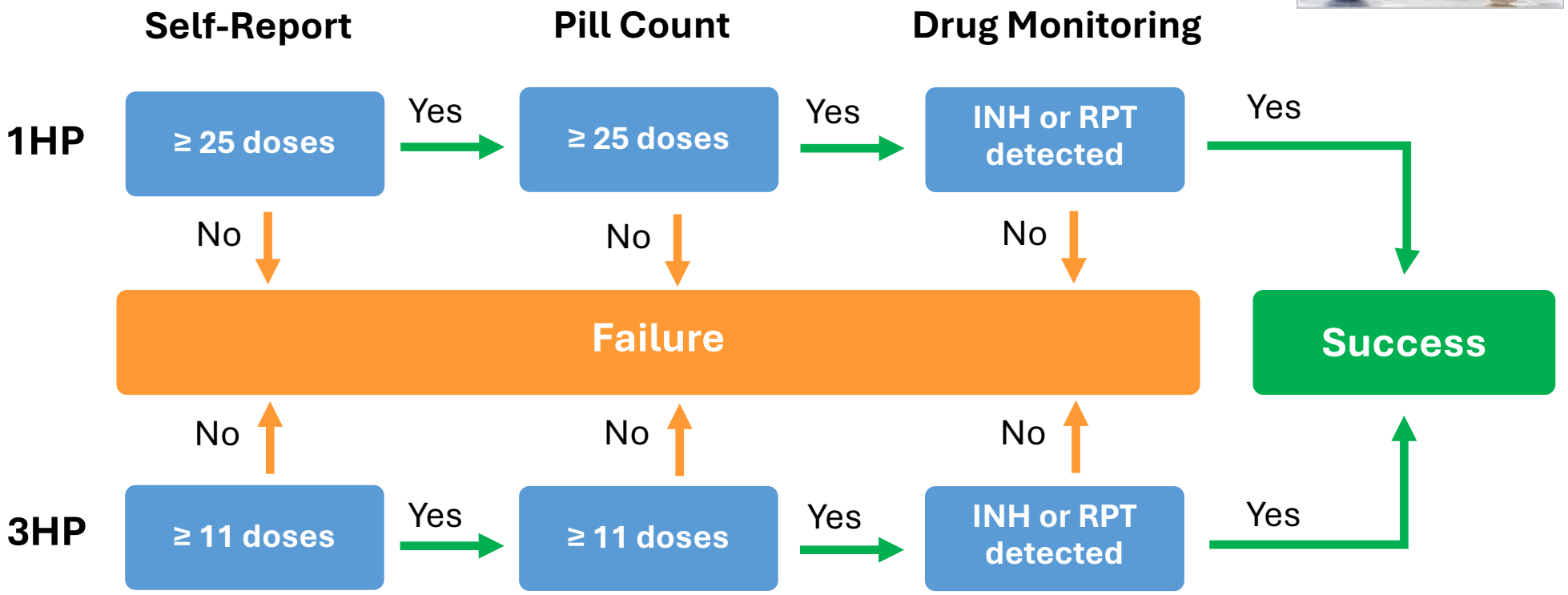
Targeted safety events: Defined as Grade ≥2 (DAIDS) hypersensitivity syndrome, rash, tolerability*: peripheral neuropathy, hepatotoxicity, nausea and vomiting, and drug-related fever, or discontinuation of medication for any side effect.

*Interim safety analysis after 25 participants in both arms have completed 4 weeks of treatment to ensure that 1HP is safe and well tolerated by HIV-negative participants, as compared with 3HP.

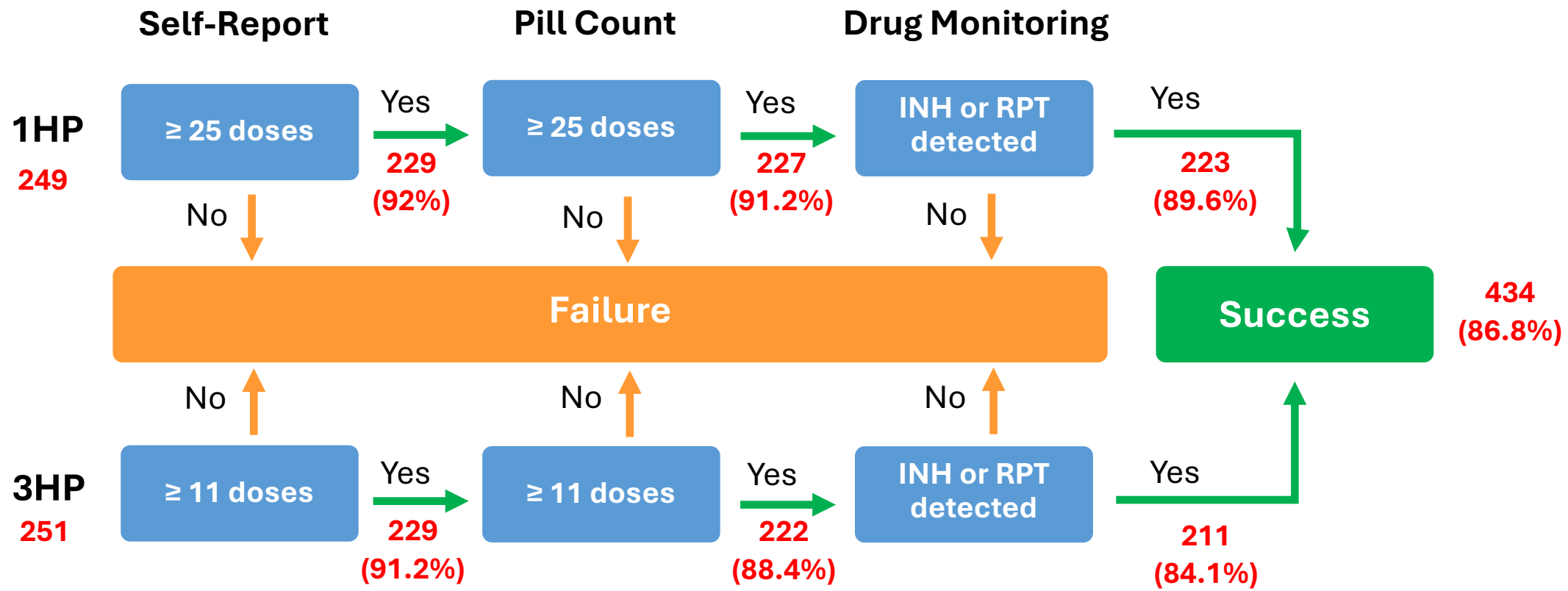
ANALYTIC APPROACH







RESULTS


Self-Report
Pill Count
Drug Monitoring
1HP
249
≥ 25 doses
Yes
229
(92%)
≥ 25 doses
Yes
227
(91.2%)
INH or RPT detected
Yes
223
(89.6%)
No
No
No
Failure
Success
434
(86.8%)
No
No
No
3HP
251
≥ 11 doses
Yes
229
(91.2%)
≥ 11 doses
Yes
222
(88.4%)
INH or RPT detected
Yes
211
(84.1%)

RESULTS

Outcomes	**1HP** (n=249)	**3HP** (n=251)	**P value**
Primary Outcome #1: Successful completion	223 (89.6%)	211 (84.1%)	0.07
Primary Outcome #2: Targeted AE or discontinuation for AE (Grade 2+)	40 (16.1%)	26 (10.4%)	0.06
Targeted AE (Grade 2+)	36 (14.5%)	23 (9.2%)	0.07
Targeted AE without discontinuation	22	15	
Targeted AE with discontinuation	14	8	
Discontinued treatment due to AE (Grade 2+)	18 (7.2%)	11 (4.4%)	0.17
Grade 3+ targeted AE	9 (3.6%)	7 (2.8%)	0.72

* Targeted safety events: Defined as Grade ≥2 hypersensitivity syndrome, rash, peripheral neuropathy, hepatotoxicity, nausea and vomiting, and drug-related fever

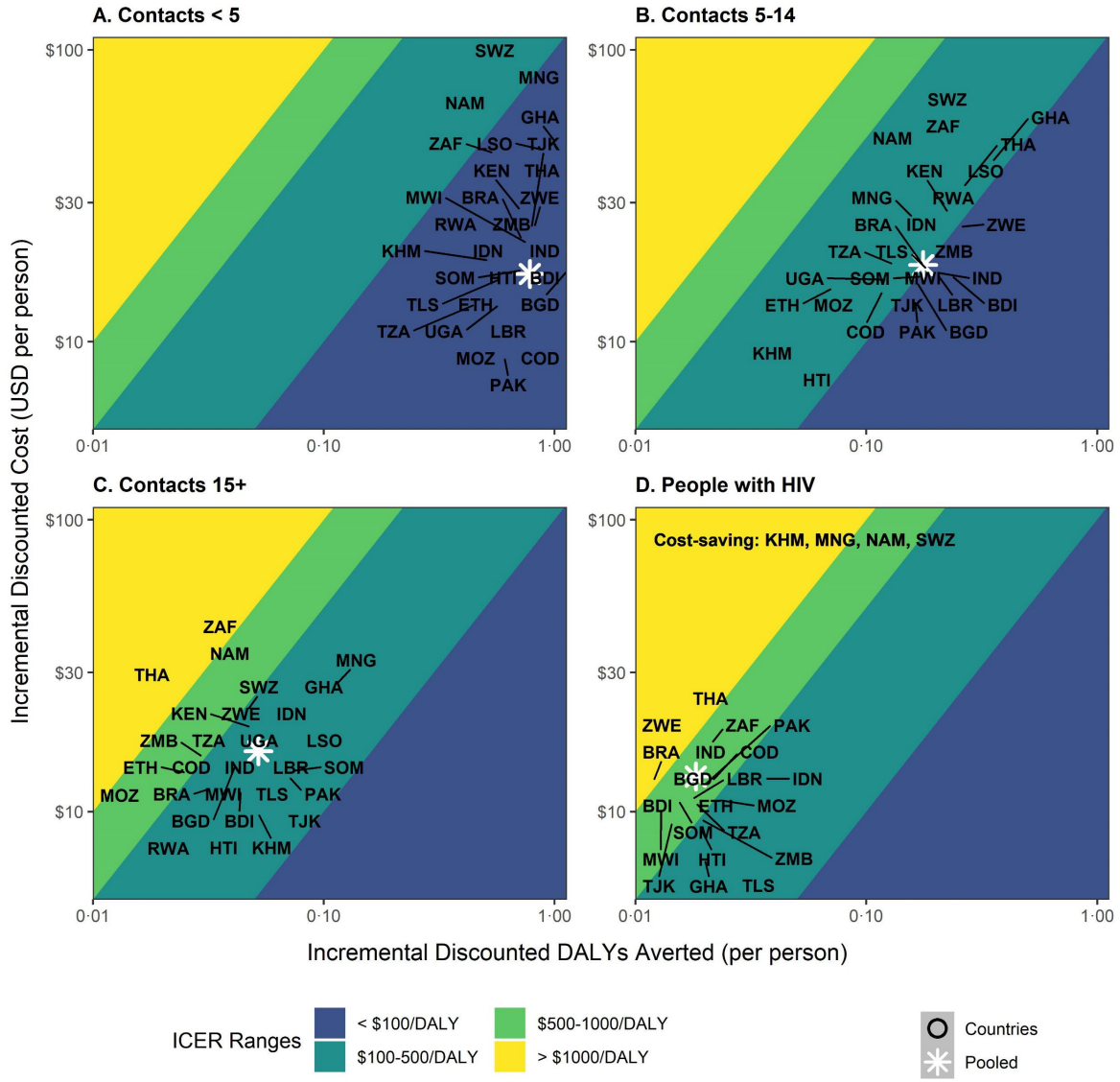
ULTRA CURTO COSTS BY INTERVENTION

	Doses	Medication Cost	No. Clinic Visits	Total Clinic Costs	Total Patient Costs	Estimated Total Cost
6H (literature)	180	$3.54	6	$203.22	$88.92	$295.68
3HP	12	$12.91	4	$135.48	$17.80	$166.19
1HP	28	$19.54	2	$67.74	$11.47	$98.75

	1HP vs 3HP	1HP vs 6H	3HP vs 6H
Cost ($)	$-13,323.09	$-88,896.77	$-75,573.68
DALY	-3.75	-119.02	-115.28
ICER ($ per DALY averted)	$3,556.89	$746.89	$655.58

Baille, Salazar-Austin, Dowdy, preliminary data

Impact and cost-effectiveness of short-course TB preventive treatment for household contacts and people with HIV in 29 high-incidence countries: a modeling analysis



Ryckman, et al., Lancet Global Health, 2023;11:e1205-e1216.

3HP and 1HP in Priority Populations (PHIV)

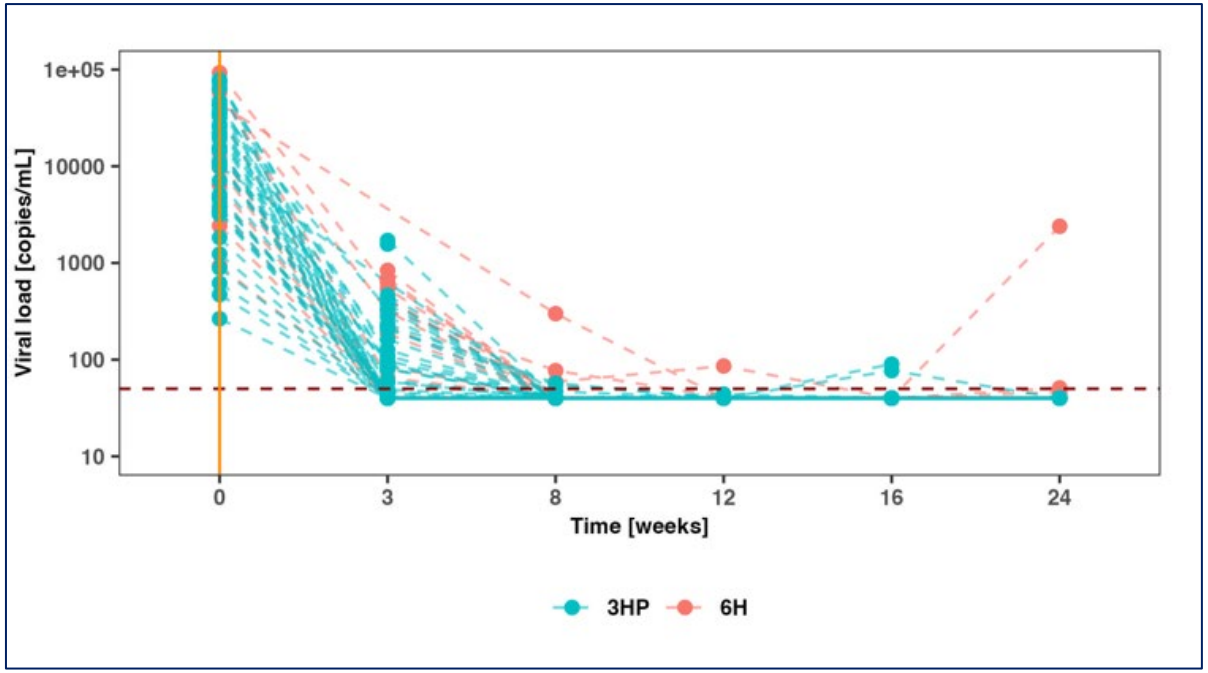
DOLPHIN Trials

- DOLPHIN – 3HP and DTG safe and effective in PHIV with suppressed VL

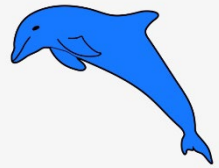
Viral load < 40 copies/mL at Baseline and Week 9 in all 60 participants

Dooley et al., Lancet HIV 2020

- DOLPHIN TOO – 3HP safe and effective in PHIV starting DTG



Weld et al., Lancet HIV, in press



DOLPHIN Trials

3HP and 1HP in Priority Populations (PHIV)

- DOLPHIN-KIDS – 3HP in Children HIV on DTG
  - First PK milestone passed, recruitment continues with daily DTG

    Salazar-Austin, Union 2024

- DOLPHIN-MOMS – 1HP and 3HP in pregnant WHIV on TLD
  - First PK cohort analysis completed, study continues

    Mathad, LaCourse, et al., in progress

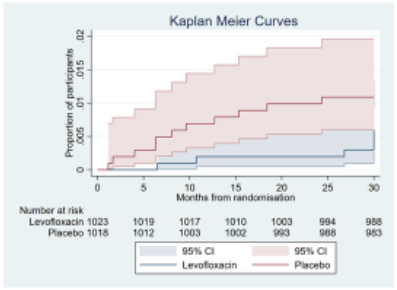
- DOLPHIN 1 to 3 Study – 1HP vs 3HP in PHIV and HHCs
  - PHIV arms fully enrolled, HHC continue to recruit

    Churchyard, Chaisson et al. in progress

The Union WORLD CONFERENCE ON LUNG HEALTH 2023
TRANSFORMING EVIDENCE INTO PRACTICE
Paris, November 15-18

The effectiveness of levofloxacin for the treatment of latent TB infection among household contacts of patients with multidrug-resistant TB: The VQUIN trial, by Fox et al (LB02-106-16)

- 2041 children and adults in Vietnam were enrolled: 1023 in LFX arm and 1018 in placebo arm.
- 6 months LFX was associated with a 45% reduction in microbiologically-confirmed incident TB at 30 months.
- LFX was well-tolerated among adults and children and no acquired drug resistance.

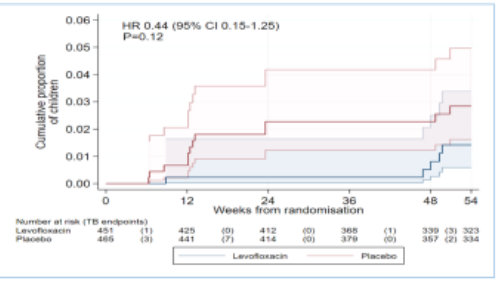


@UNIONCONFERENCE #UNIONCONF worldlunghealth.org

The Union WORLD CONFERENCE ON LUNG HEALTH 2023
TRANSFORMING EVIDENCE INTO PRACTICE
Paris, November 15-18

A phase III cluster randomised placebo-controlled trial to assess the efficacy of preventive treatment in child contacts of multidrug-resistant TB: The TB-CHAMP Trial, by Hesseling et al (LB02-107-16)

- 922 children in South Africa were enrolled: 453 in LFX arm and 469 in placebo arm.
- Evidence of LFX efficacy with substantial effect size: 1.1% in LFX-arm vs 2.6% in placebo-arm (HR 0.44 [95% CI 0.15-1.25])
- LFX was extremely safe in children
- **Data of VQUIN and TB-CHAMP are shared with WHO.**



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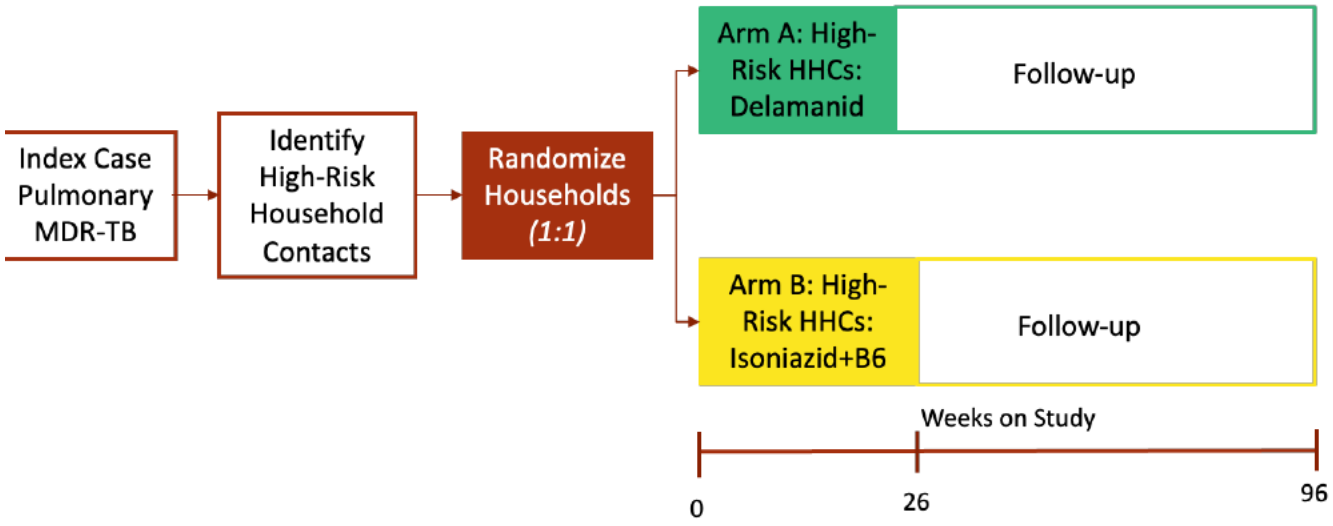
Analysis	Levo event rate	Placebo event rate	HR (95% CI)
Overall: IPD meta-analysis	8/1474 (0.54%)	21/1483 (1.42%)	0.40 [0.17-0.90]
V-QUIN std analysis	3/1023 (0.29%)	9/1018 (0.88%)	0.34 [0.09-1.25]
TB-CHAMP std analysis	5/451 (1.11%)	12/465 (2.58%)	0.44 [0.15-1.26]

PHOENIX Rising

Protecting Households On Exposure to Newly Diagnosed Index Multidrug-Resistant Tuberculosis Patients (A5300B/I2003B/PHOENIx)



Phase III open-label, multi-center, cluster-randomized, superiority trial

High-Risk Household Contacts

- Children <5 years old
- ≥5 years of age who are
  - HIV-infected or non-HIV immunosuppressed
  - TST positive (≥5mm) and/or IGRA positive

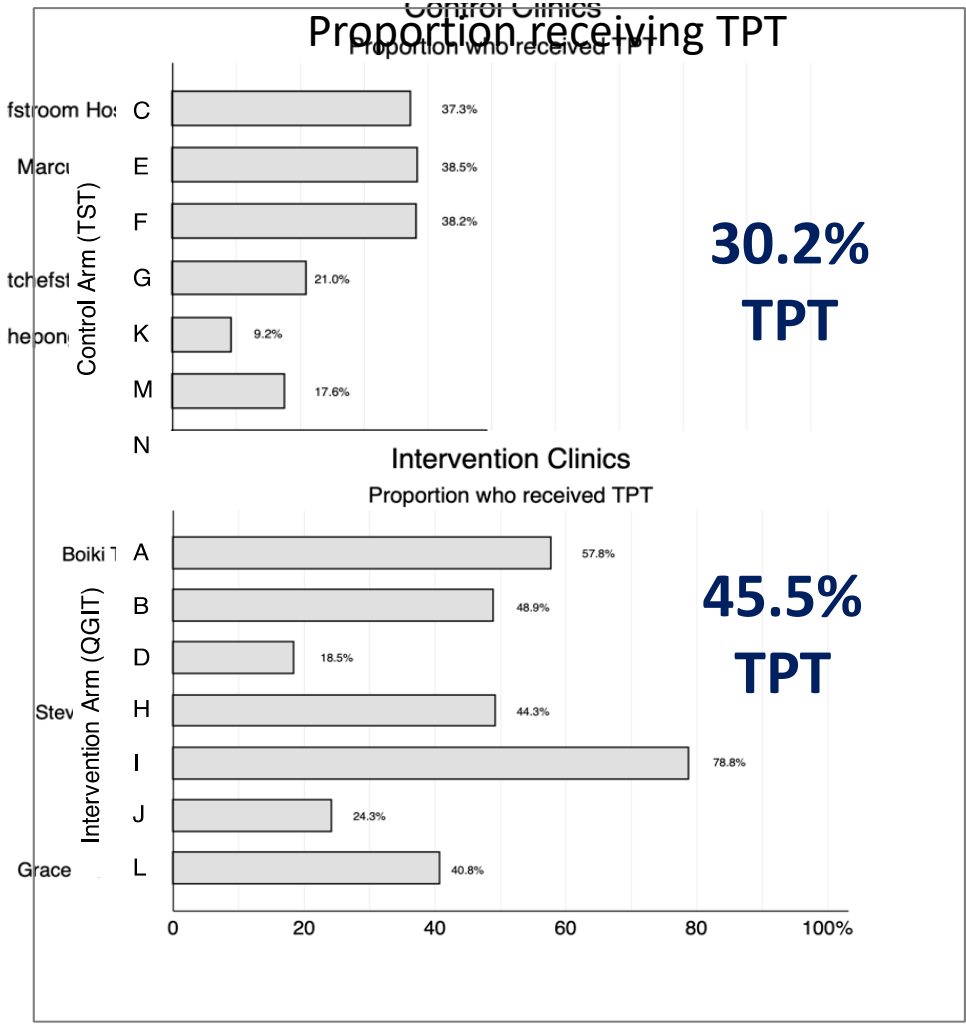
1,695 Index Cases and 3,885/3,834 (101%) Contacts enrolled

ACTG AIDS CLINICAL TRIALS GROUP

IMPAACT International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Clinician Reluctance to Prescribe TPT
TEKO Study

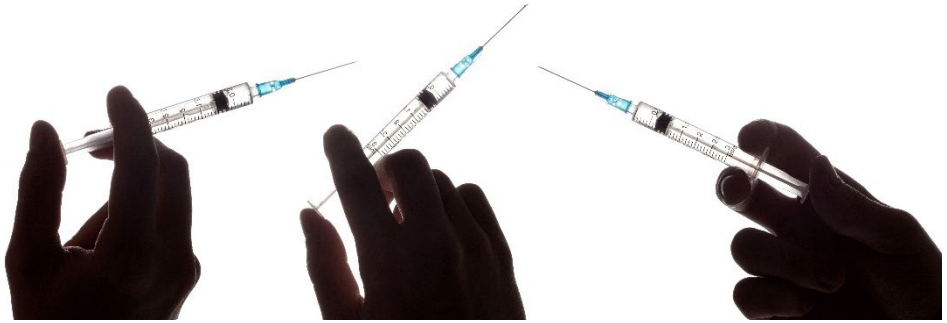
- Cluster-randomized trial of IGRA linked to CD4/VL testing in PHIV in 14 clinics in South Africa
- South African guidelines recommend TPT for all PHIV with no evidence of active TB
- Intervention: 516/1,284 (45.5%) received TPT prescription
- Control: 271/948 (30.2%) received TPT prescription
- Majority in both arms not prescribed TPT despite guidelines



Jarrett, et al., Clin Infect Dis. 2024;79:751

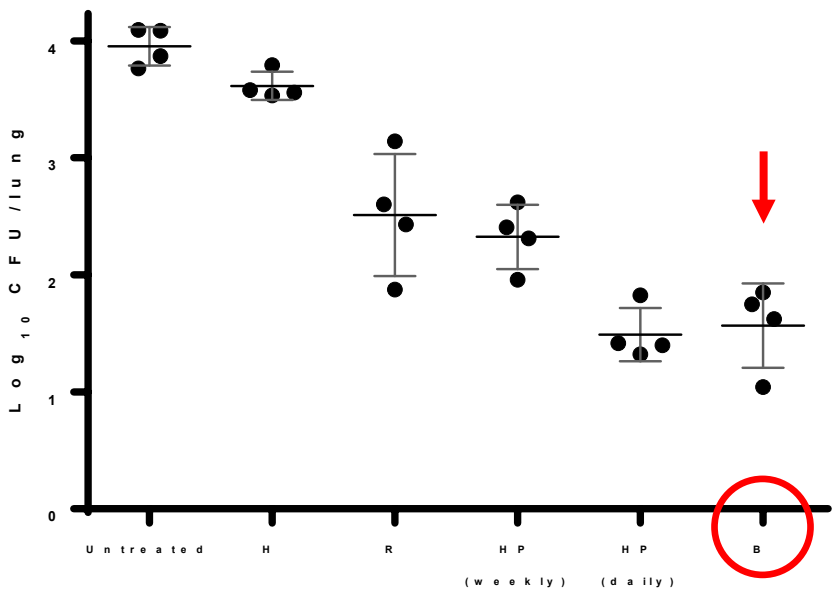
Potential Game-Changers

- Pan-TB short-course preventive therapy
- Long-acting injectables/implants
- Vaccines



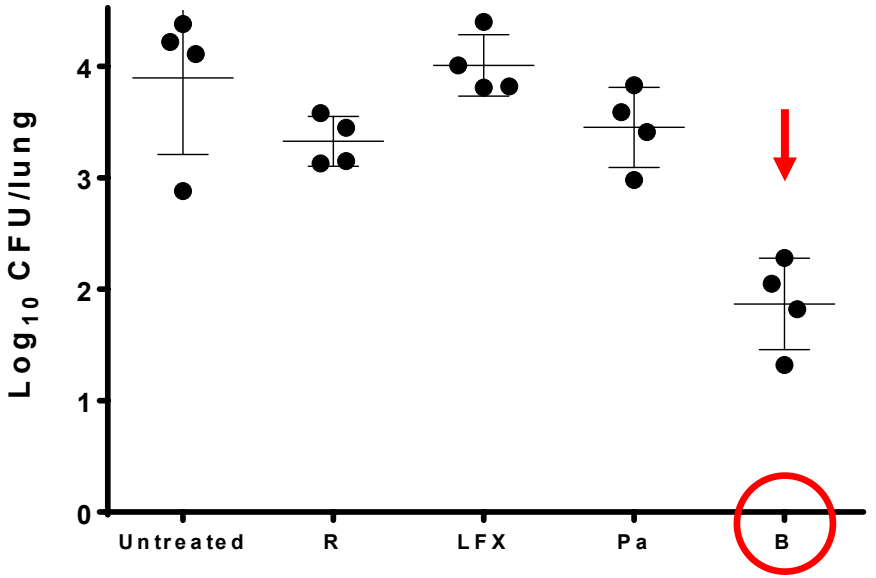
Efficacy of BDQ in a paucibacillary mouse model of TPT

Lung bacterial counts after 1 month of treatment



Zhang *et al. AJRCCM* 2011;184:732

Lung bacterial counts after 1 month of treatment



Lanoix *et al. AAC* 2014; 58:2316

Oral BDQ x 1 month has efficacy similar to 1HP and superior to LFX, Pa

2-drug combinations of BDQ with LFX, Pa, sutezolid were no better than BDQ alone

Courtesy of Eric Nuermberger

Clinical simulation of oral BDQ for TPT from translational model

Translational model incorporating BDQ and M2 metabolite PK-PD predicts oral BDQ 200 mg x 4 weeks to be at least as effective as 3HP

Courtesy of Eric Nuermberger and Rada Savic

R. Savic et al, OA44-449-15 and OA44-450-15, Bali 2024

Eric
Nuermberger

Sonya
Krishnan

Bedaquiline Roll-out Evidence in Contacts and People Living with HIV to prevent TB

(BREACH-TB)

An open-label, randomized, controlled, Phase 3 clinical trial of bedaquiline for prevention of TB disease in PLHIV and contacts of drug-susceptible and rifampin-resistant TB

COLUMBIA | MAILMAN SCHOOL OF PUBLIC HEALTH

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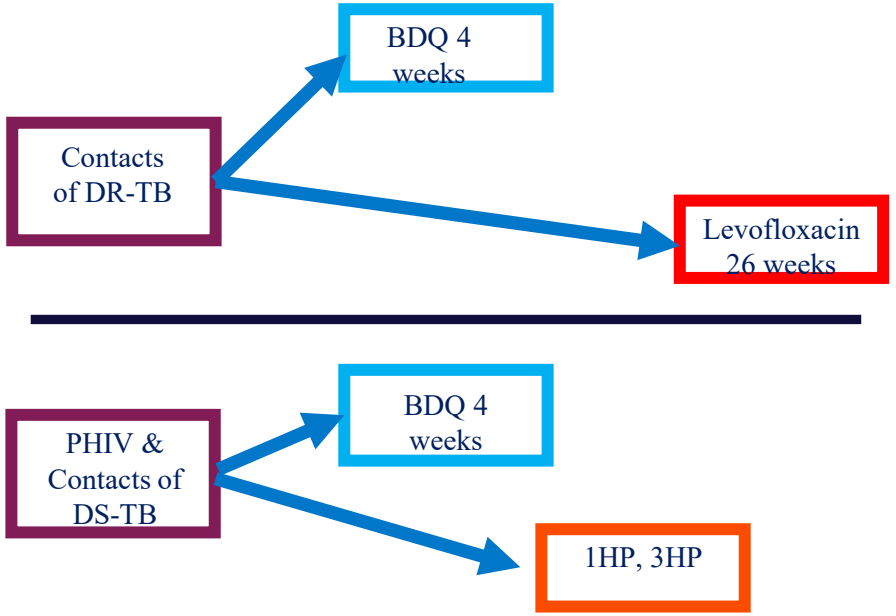
Supporting, Mobilizing, and Accelerating Research for Tuberculosis Elimination

SMART4TB Consortium

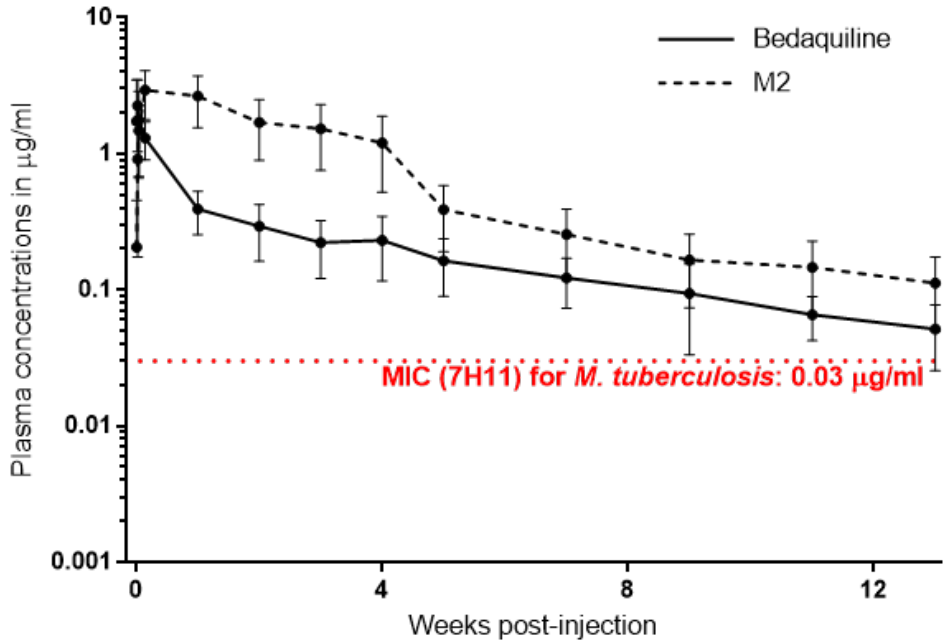
BREACH-TB: Study Overview

- Phase 3, open-label, multicenter, randomized, controlled trial
- 2 primary indications:
  - Adults & children close contacts of RR-TB
  - PHIV and Adults & Children close contacts of DS-TB
- Non-inferiority design comparing efficacy & safety of BDQ vs. Comparator
- Followed up to 96 weeks post-randomization
  – **<u>Primary endpoint 72 weeks</u>**

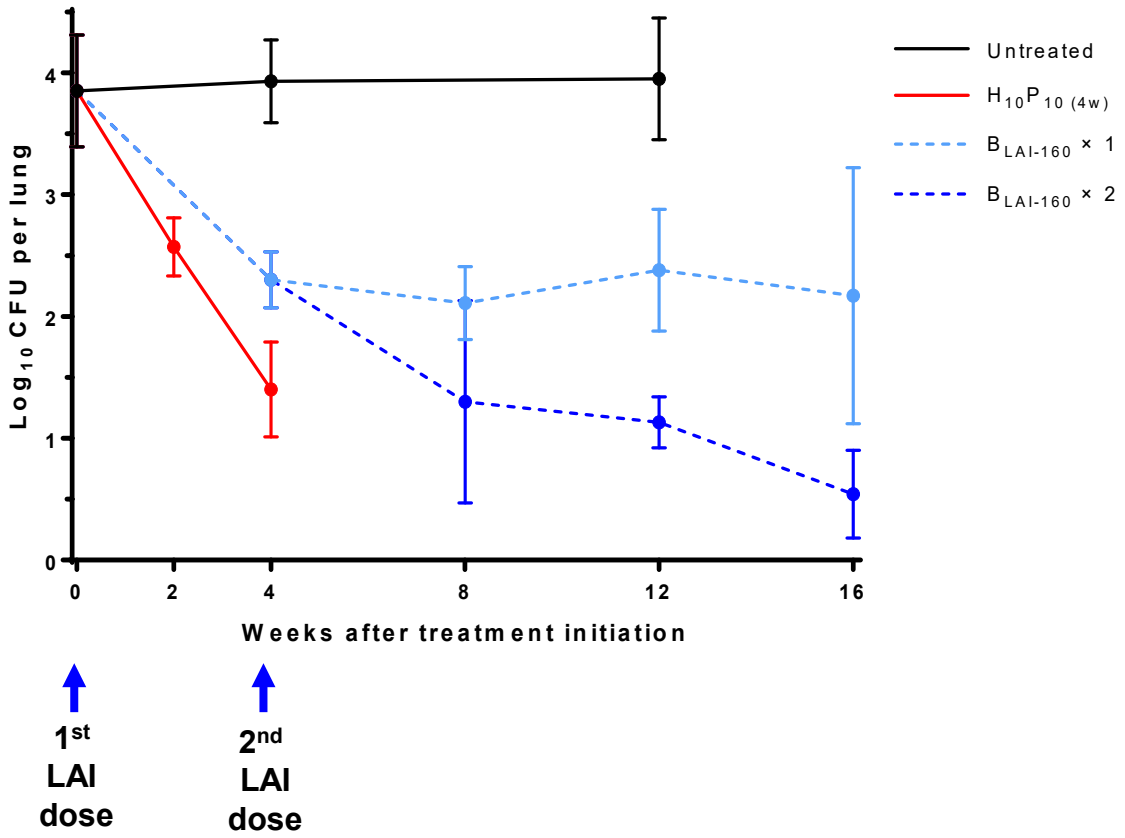


Efficacy of LAI bedaquiline in a mouse model of TPT

Plasma concentrations of BDQ and M2 metabolite after single IM injection to mice



Efficacy of 1 or 2 monthly $B_{LAI-160}$ doses vs. 1HP

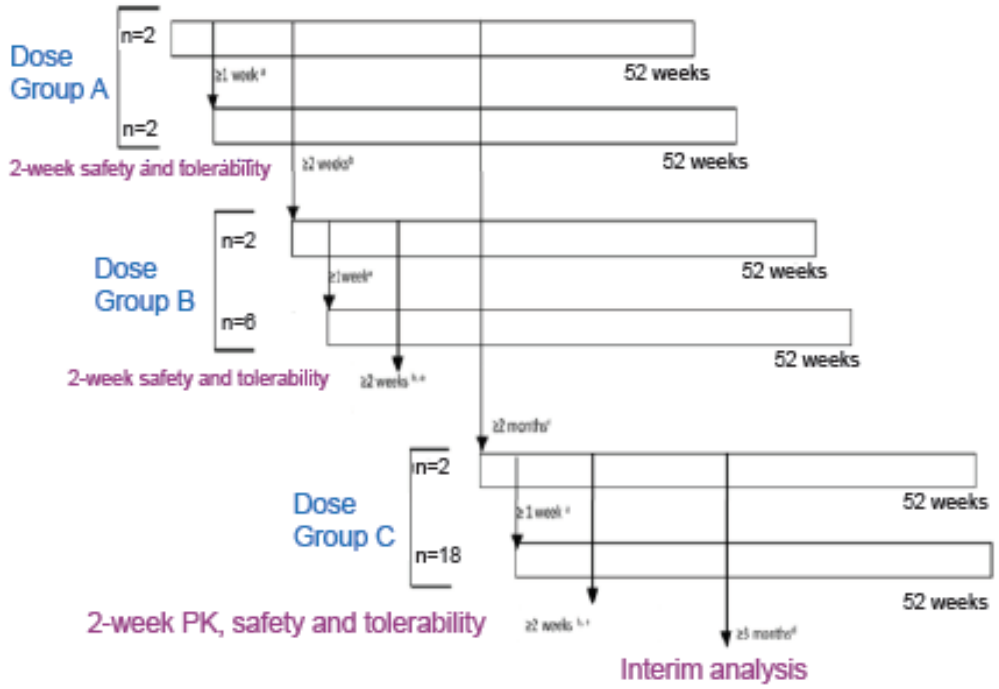


Kaushik et al. *Antimicrob Agents Chemother* 2019; pii: AAC.00007-19
Kaushik et al, *Am J Respir Crit Care Med* 2022

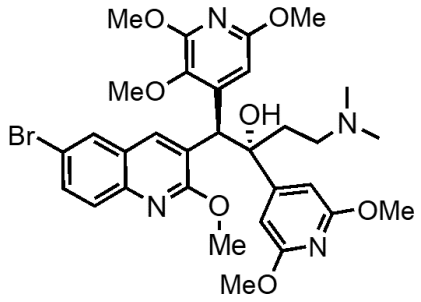
Courtesy of Eric Nuermberger

Phase 1 trial of LAI bedaquiline (initiated July, 2024)

- **Single ascending dose (SAD) study**
  - PK, safety, & tolerability of IM dosing in 32 healthy volunteers
  - Lower-dose PK assessed before proceeding with the ascending dosing strategy
  - Planned interim analysis at Group C enrollment to inform next steps



Vivian Cox, LEAP-TB Workshop, Baltimore, April 2024



TBAJ-876, a next-generation diarylquinoline

Potency and safety parameters

	BDQ	TBAJ-876
MIC v. *Mtb* H37Rv (μg/ml)	0.03	0.006
MIC v. Rv0678 variant (μg/ml)	0.25	0.025
hERG IC_{50} (μM)	0.37	>30
28-Day Rat NOAEL (mg/kg/day)	6	40
Safety Margin Rat (Male)	0.2	15

Superior potency vs. BDQ

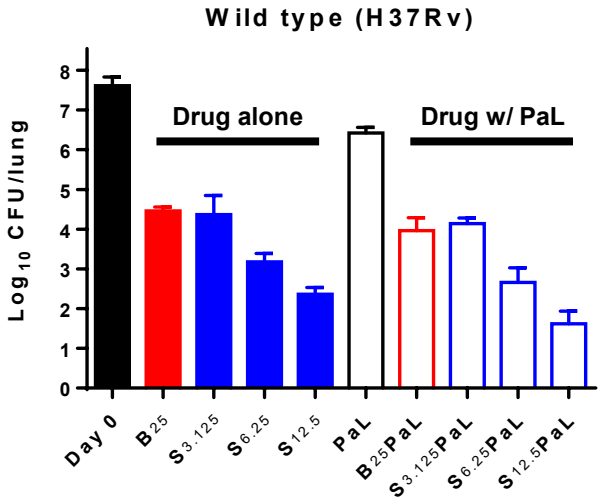
(1) superior efficacy *in vitro* and in murine TB models
(2) superior potency against BDQ-resistant *Rv0678* variant

Improved safety vs. BDQ

(1) reduced cardiovascular liability (eg, hERG inhibition)
(2) larger pre-clinical safety margin
(3) ΔQTc no different from placebo in Phase I MAD study

Phase 2b NC-009 trial is underway to evaluate oral TBAJ-876 with PaL to treat TB disease

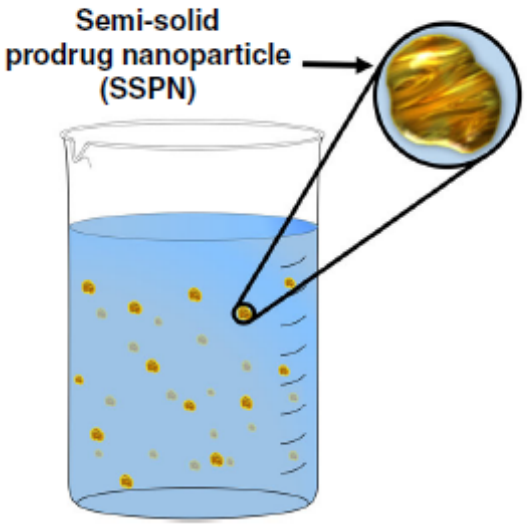
In vivo potency of TBAJ-876 (S) vs. BDQ (B)



C. Cooper et al, World Microbe Forum 2021
A. Lombardi et al, AAC 2024
D. Almeida et al, AAC 2021

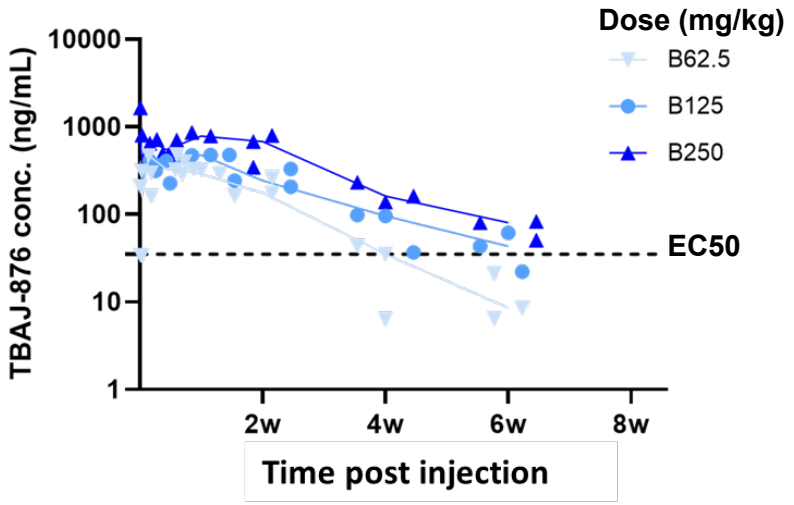
Courtesy of Eric Nuermberger

Superior efficacy of TBAJ-876 LAI in mouse model of TPT



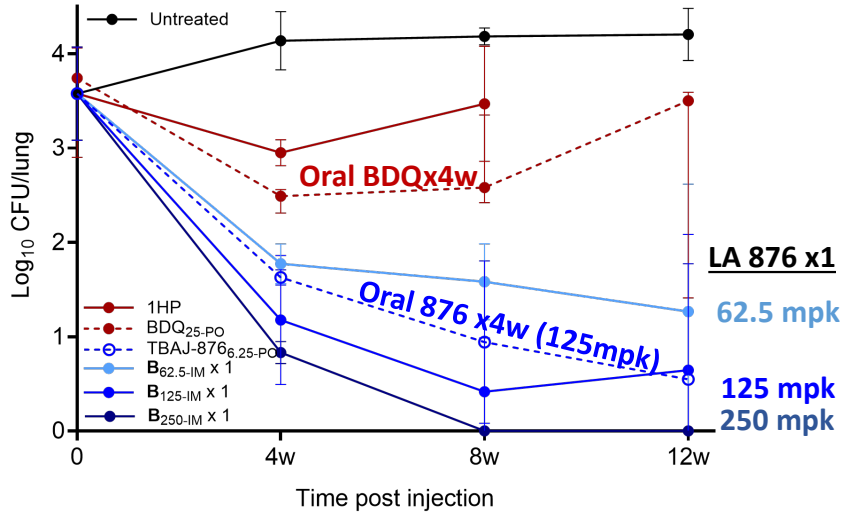
25g needle
API loading = 80 wt%
API conc = 300 mg/ml

Median plasma conc. after IM injection



- Single IM doses ≥125 mg/kg produced sustained plasma exposures above EC_{50} for 6 weeks.
- All dose levels had superior bactericidal activity compared to 1HP and 4 weeks of oral BDQ (500 mg/kg total dose).
- 23 of 25 mice receiving doses ≥125 mg/kg had no recoverable CFU at Week 12 post-dose.
- These data provide POC for a highly efficacious pan-TPT regimen comprised of a single IM dose of a TBAJ-876 LAI formulation.

Dose-ranging bactericidal activity of LAI TBAJ-876

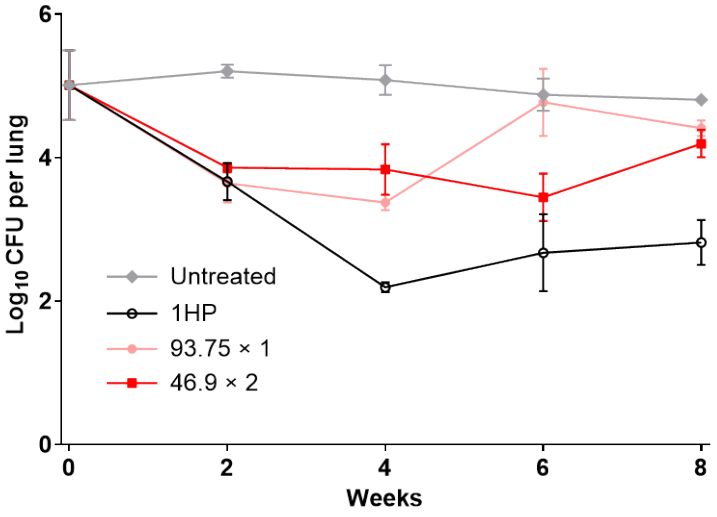


Courtesy of Eric Nuermberger

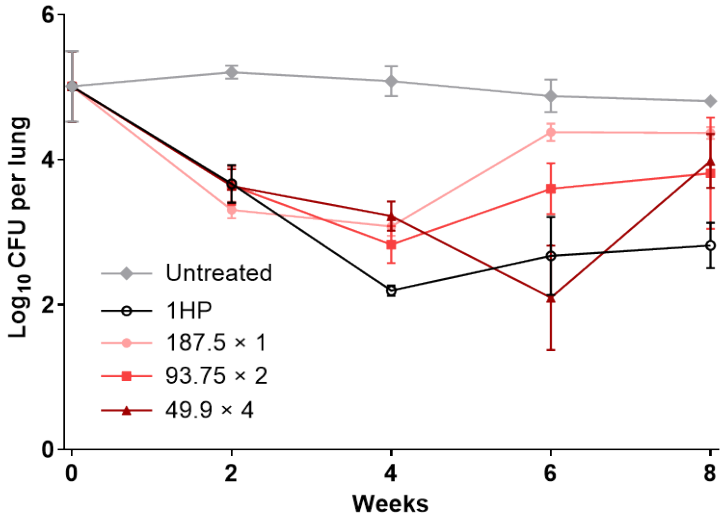
Hobson et al, CROI 2024, Poster 00881

Efficacy of Rifapentine-LAI in mouse TPT model

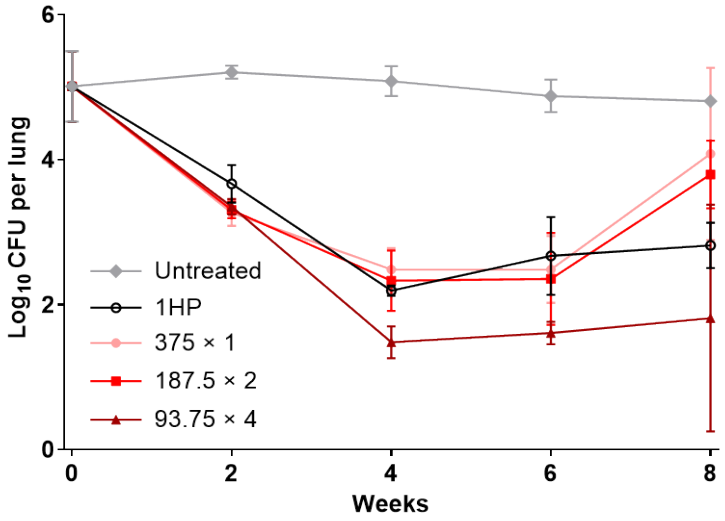
Total dose: 93.75 mg/kg



Total dose: 187.5 mg/kg



Total dose: 375 mg/kg



- RPT-LAI exhibited dose-dependent bactericidal activity
- A trend towards superior efficacy with divided dosing was observed (x4 > x2 > x1)
- The 4-dose schedule for 187.5 mg/kg and the 1- or 2-dose schedules for 375 mg/kg achieved an E_{max} similar to 1HP

Courtesy of Eric Nuermberger

Pertinez et al, CROI 2024, abstract 880

Improved Detection of Tuberculosis and Multidrug-Resistant Tuberculosis among Tibetan Refugees, India

Kerry L. Dierberg, Kunchok Dorjee, Fulvio Salvo, Wendy A. Cronin, J'Belle Boddy, Daniela Cirillo, Tsetan Sadutshang, Richard E. Chaisson

- Survey of 28,000 Tibetan refugees in India

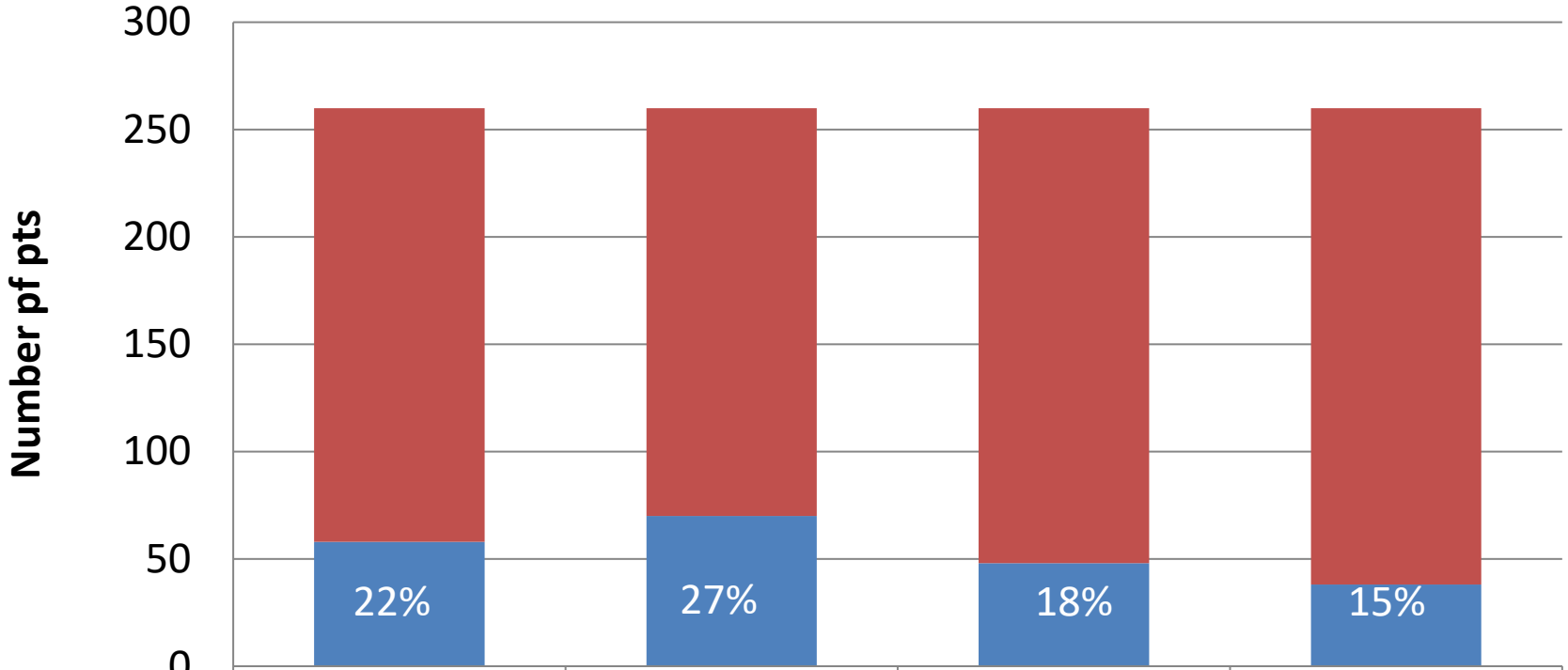
- TB Prevalence: 346/100,000
- Prevalence in schoolchildren: 391/100,000
- 5% MDR TB

DELEK HOSPITAL

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 22, No. 3, March 2016


DELEK HOSPITAL

TB Drug Resistance Survey in the Tibetan Community in India
Overall Results



	Streptomicin	Isoniazid	Rifampicin	Ethambutol
Sensitive	202	190	212	222
Resistant	58	70	48	38

Salvo et al., . Int J Tuberc Lung Dis 2014;18:655-62.

Kunchok Dorjee, MBBS, MPH, PhD

Tuberculosis Manual

Tibetan TB Program

Tibetan TB Control Programme

- Standardized diagnostic criteria
- Routine susceptibility testing
- WHO-approved treatment regimens
- Community-based DOT
- Contact evaluation and treatment

Outcomes

- >90% treatment success
- ~50% reduction in MDR-TB

Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America

hivma hiv medicine association

OXFORD

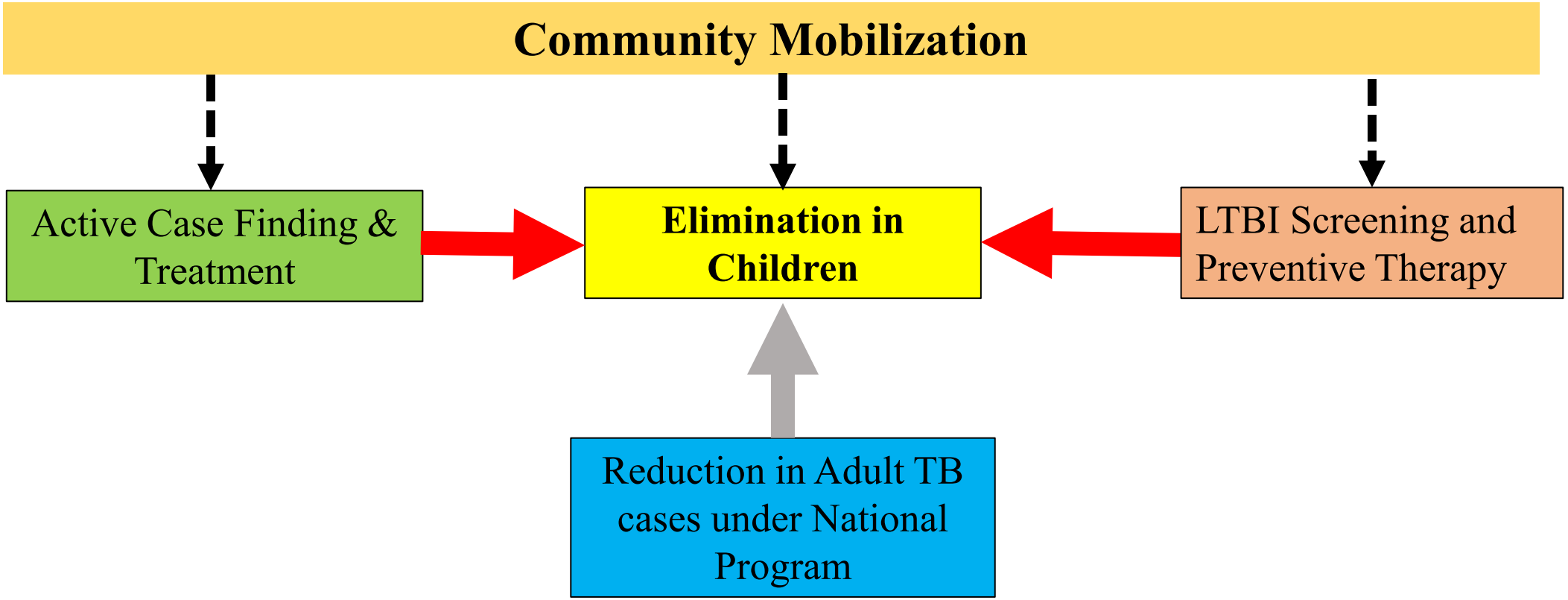
High Prevalence of Active and Latent Tuberculosis in Children and Adolescents in Tibetan Schools in India: The Zero TB Kids Initiative in Tibetan Refugee Children

Kunchok Dorjee,[1] Sonam Topgyal,[2] Chungdak Dorjee,[3] Tenzin Tsundue,[2] Tenzin Namdol,[2] Tenzin Tsewang,[2] Tenzin Nangsel,[2] Dekyi Lhadon,[2] Tsering Choetso,[2] Tenzin Dawa,[2] Tenzin Phentok,[2] Andrea N. DeLuca,[1] Lobsang Tsering,[4] Dawa Phunkyi,[2] Tsetan D. Sadutshang,[2] Elizabeth J. Bonomo,[1] Zorba Paster,[5] and Richard E. Chaisson[1]

[1]Center for Tuberculosis Research, Division of Infectious Diseases, Johns Hopkins University School of Medicine, Baltimore, Maryland; [2]Division of Tuberculosis, Tibetan Delek Hospital, [3]Tibetan Children's Village School, and [4]Department of Health, Central Tibetan Administration, Dharamsala, India; and [5]Department of Family Medicine and Community Health, University of Wisconsin–Madison

Zero TB Kids: Comprehensive mobile community-based screening and treatment program for active and latent TB that brings TB care to doorsteps of the schools and monasteries

Zero TB Kids Framework for TB Control and Elimination in Children



Community Mobilization

"Unlike many…diseases, TB is curable so it must be eliminated…. We should never let down our guard in the goal to eliminate TB."

- His Holiness The 14th Dalai Lama


NEVER GIVE UP.
TEAM UP TO DEFEAT TB.


A man may die, nations
may rise and fall, but
an idea lives on.


ZERO TB

Transformative technologies for Zero TB Kids

GeneXpert system at school

Electronic Adherence Monitor Device (https://www.wisepill.com/evrimed)

Zero TB Facebook, Twitter, and Instagram pages

Zero TB Kids WhatsApp Hotline for communication

Latent TB Infection screening in kids

Preparing TB Preventive Therapy medicine boxes separately for each child.

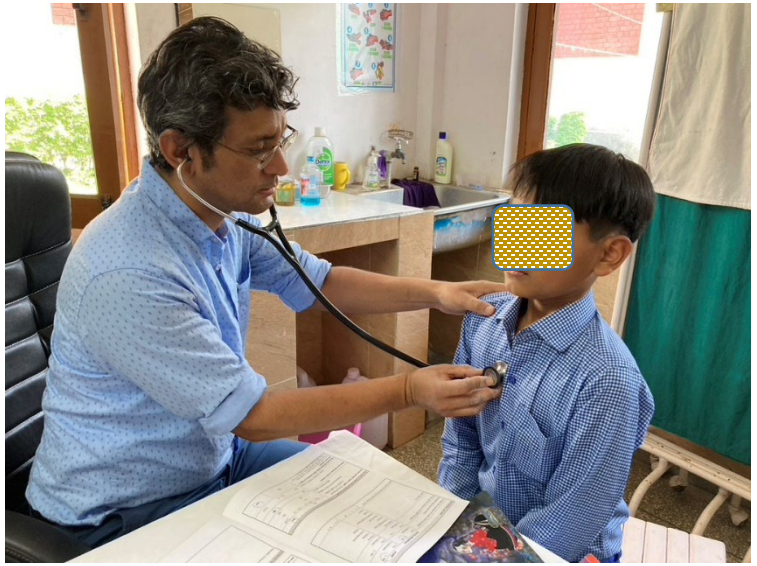
Year-wise Prevalence of Active TB in Schoolchildren

Year	Student population	TB Disease	Prevalence
2017	5013	42	838/100,000
2018	5015	22	439/100,000
2019	4995	7	139/100,000

Year-wise Prevalence of Latent TBI in Schoolchildren

Year	Students screened	Latent TBI	Prevalence
2017	4860	913	19%
2018	827	124	15%
2019	3608	383	11%

2022 Follow-up Prevalence Survey with additional technologies



Near point-of-care Quantiferon testing

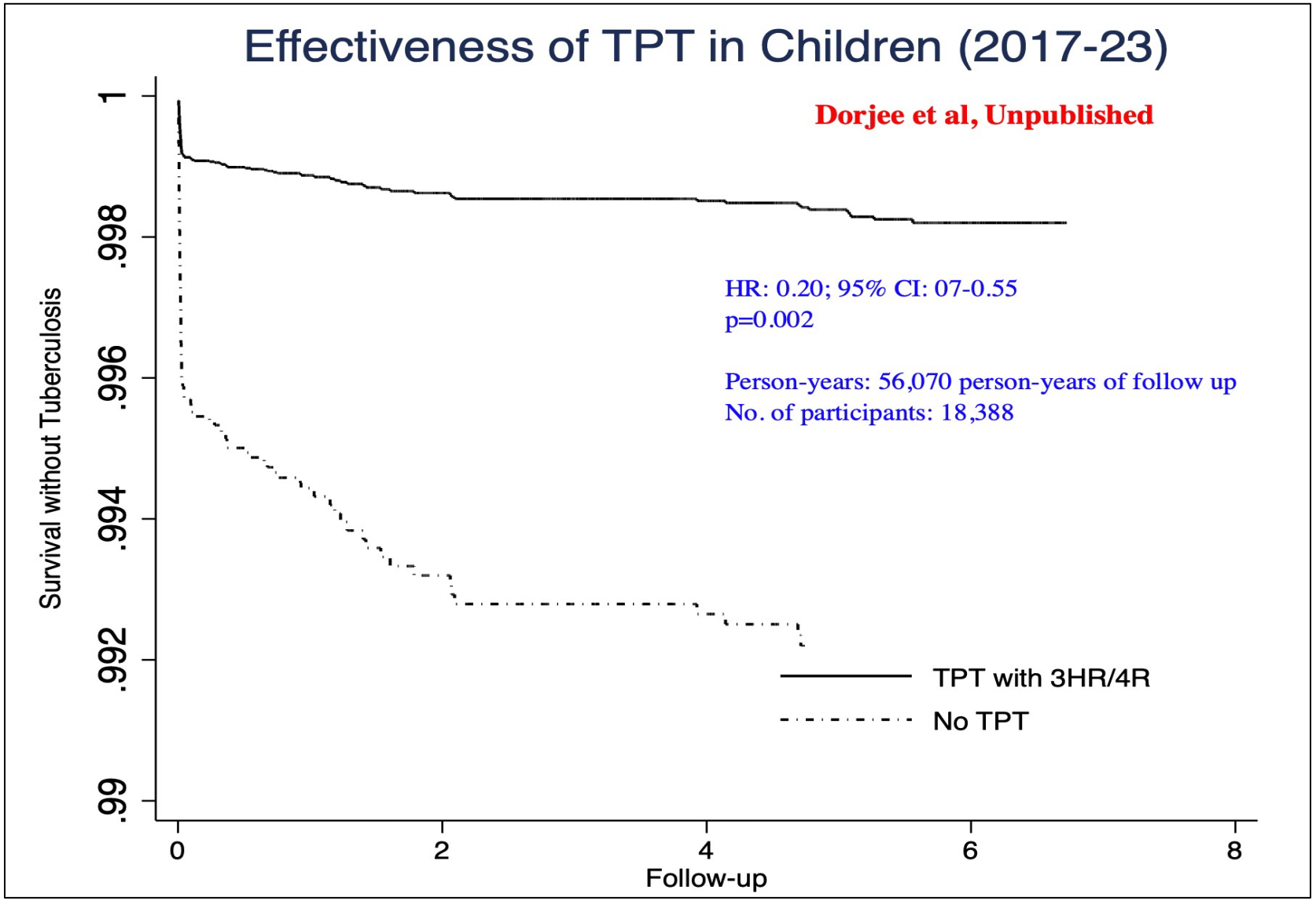
Portable digital CXR with Computer-Assisted Diagnosis

Zero TB Kids 2022-3 Results

Population	No. Screened	Active TB	TB Prevalence	TB Infection	Given TPT
Students	3093	4	129/100,000	433 (13%)	397 (91%)
Teachers/ Staff	140	0	0	61 (44%)	38 (62%)

Kunchok Dorjee, unpublished

Seven Years of Zero TB in Kids - Impact



PLOS MEDICINE

RESEARCH ARTICLE

Risk of developing active tuberculosis following tuberculosis screening and preventive therapy for Tibetan refugee children and adolescents in India: An impact assessment

Kunchok Dorjee[1]*, Sonam Topgyal[2], Tenzin Tsewang[2], Tenzin Tsundue[2], Tenzin Namdon[2], Elizabeth Bonomo[1], Caroline Kensler[1], Dekyi Lhadon[2], Tsering Choetso[2], Tenzin Nangsel[2], Tsering Dolkar[2], Thupten Tsekyi[2], Chungdak Dorjee[3], Dawa Phunkyi[2], Tsetan D. Sadutshang[2], Zorba Paster[4], Richard E. Chaisson[1]

1 Center for TB Research, Division of Infectious Diseases, School of Medicine, Johns Hopkins University, Baltimore, Maryland, United States of America, 2 Division of Tuberculosis, Delek Hospital, Department of Health, Central Tibetan Administration, Dharamsala, India, 3 Tibetan Children's Village School, Dharamsala, India, 4 Department of Family Medicine, University of Wisconsin, Madison, Wisconsin, United States of America

'For the first time, …the TB epidemic curve is bent for this vulnerable refugee children population, setting the community on a path to TB elimination, and presenting a model for communities nationally and globally.'

Dorjee, et al., PLoS Med 18(1):e1003502. https://doi.org/10.1371/journal.pmed.1003502

Achieving TB Control: Aspirations, Delusions, and Reality

Pablo Picasso, Ciencia y caridad

"Remember that if a man seeks the impossible, the possible may be justly denied him; a poet said it better…

'if the impossible I demand,
for me the possible is banned.'"

Miguel de Cervantes, "Don Quixote"

Acknowledgements

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Kunchok Dorjee

Jonathan Golub

David Dowdy

Susan Dorman

Emily Kendall

Ethel Weld

Beatriz Kohler

Charlotte Baille

PHRU

Neil Martinson

ACTG

Sue Swindells

Rada Savic

TBTC

Tim Sterling

Andy Vernon

Payam Nahid

LSHTM/MLW Blantyre

Liz Corbett

Lucky Ngwira

Ultra Curto Team, Brazil

Betina Durovni

Marcelo Cordeiro Dos Santos

Solange Cavalcante

Aurum Institute

Gavin Churchyard

Zero TB in Tibetan Kids

Zorba Paster

Tsetan Sadutshang

Dawa Phunkyi

Daniela Cirillo

Funders:

NIAID/NICHD/FIC/NIH

CDC

UNITAID

FDA

USAID

STOP TB Partnership

Bill and Melinda Gates Foundation

JHU Alliance for a Healthier World

Private donors

thebmj

BMJ 2018;362:k2738 doi: 10.1136/bmj.k2738 (Published 23 August 2018)

ANALYSIS

Revisiting the timetable of tuberculosis

Tuberculosis has a much shorter incubation period than is widely thought, say **Marcel A Behr and colleagues**, and this has implications for prioritising research and public health strategies

Marcel A Behr *professor of medicine*[1], Paul H Edelstein *professor of pathology and laboratory medicine*[2 3], Lalita Ramakrishnan *professor of immunology and infectious diseases*[3]

Is there a late spike of TB disease?

Reactivation TB is thought to occur most frequently later in life when immunity wanes or intercurrent illness occurs. If this were the case, we would expect a rise in TB incidence decades after infection,

Key messages

- The current thought is that *Mycobacterium tuberculosis* frequently establishes a latent infection following which there is a reactivation process that leads to active TB disease, after a long and variable incubation period
- Rather, the incubation period of TB is typically several months to two years, and after that, disease is relatively infrequent
- There is no evidence for a bimodal distribution of TB that distinguishes primary progressive TB from reactivation TB
- Immunoreactivity to TB does not necessarily indicate the presence of live bacteria, as reactivity can persist after infection has been cleared
- Classifying two billion people with evidence of immunoreactivity as having latent TB infection may divert fundamental research and public health interventions away from transmissible active TB disease and newly infected people at highest risk of progression to disease

IJTLD OPEN 1(8):335–337
 http://dx.doi.org/10.5588/ijtldopen.24.0336

EDITORIAL

Rethinking latent TB? Think again

R.E. Chaisson,[1] P.C. Hopewell[2]
[1]*Johns Hopkins University Center for Tuberculosis Research, Baltimore, MD, USA;* [2]*University of California, San Francisco, CA, USA*
Correspondence to: Richard E Chaisson, Johns Hopkins University Center for Tuberculosis Research, Baltimore, MD, USA. E-mail: rchaiss@jhmi.edu

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

June 9, 2000 / Vol. 49 / No. RR-6

MMWR™
MORBIDITY AND MORTALITY
WEEKLY REPORT

Recommendations and Reports

Inside: Continuing Education Examination

Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection

U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Centers for Disease Control and Prevention (CDC)
Atlanta, GA 30333

Change in Nomenclature

Identification of persons with LTBI has previously been accomplished by widespread tuberculin skin testing of individuals or groups at variable risk for TB. In many situations, this screening was done with limited consideration of the risk for TB in the population(s) being tested. To focus on groups at the highest risk for TB, the term "targeted tuberculin testing" is used in these guidelines to encourage directed program activities.

SCIENTIFIC RATIONALE

Targeted Tuberculin Testing

Groups at Risk and Risk Factors for Infection with M. tuberculosis

AMERICAN JOURNAL OF EPIDEMIOLOGY
Vol. 99, No. 2

Printed in U.S.A.

THE PROGNOSIS OF A POSITIVE TUBERCULIN REACTION IN CHILDHOOD AND ADOLESCENCE

GEORGE W. COMSTOCK,[1, 2] VERNA T. LIVESAY[2] AND SHIRLEY F. WOOLPERT[2]

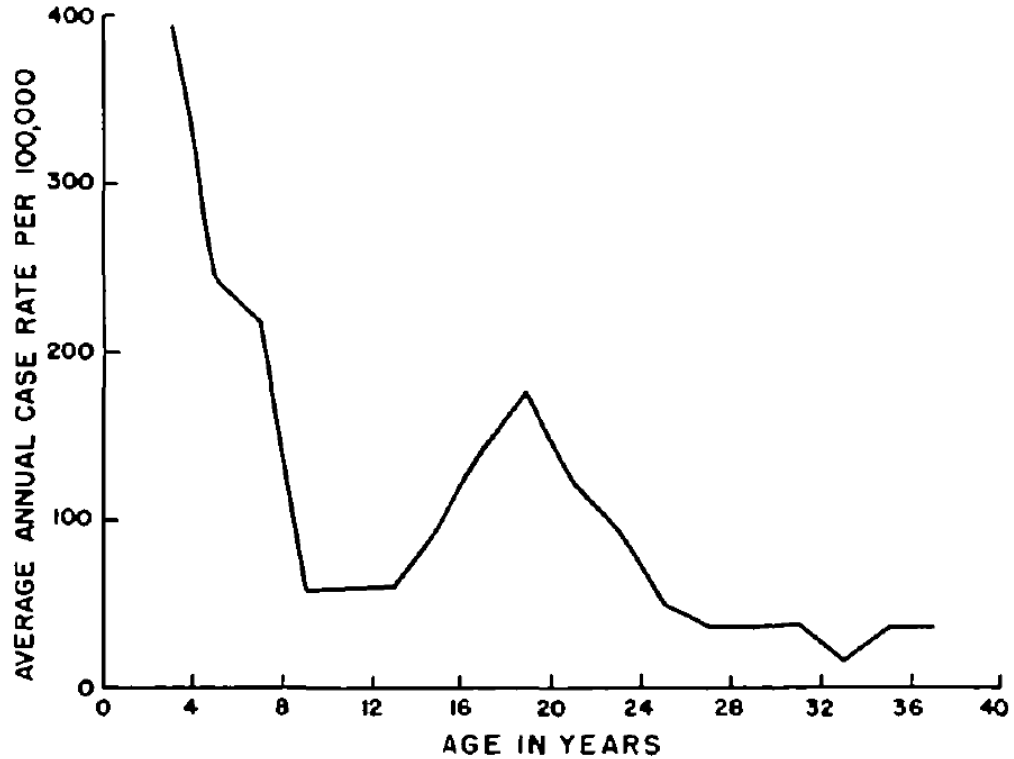
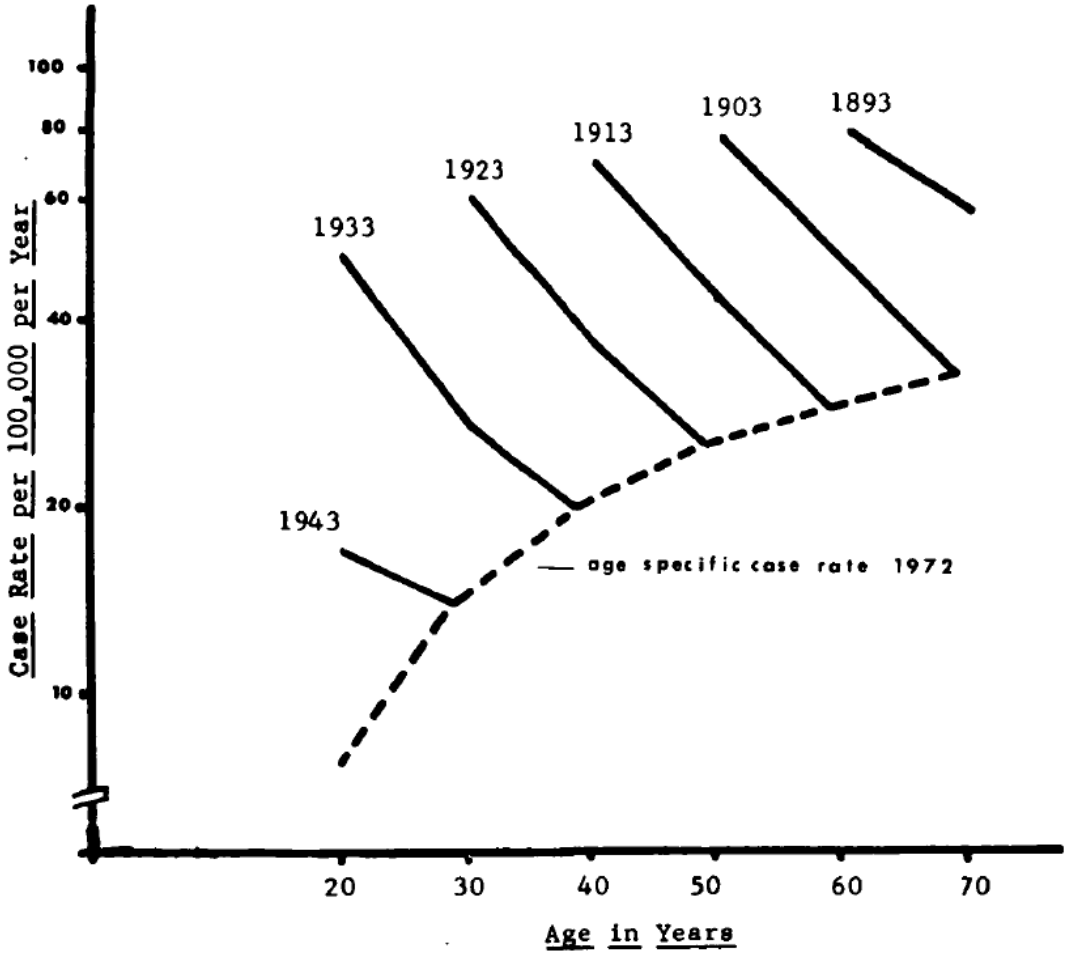


FIGURE 1. Incidence of tuberculosis among initial reactors to tuberculin, by age when tuberculosis was first diagnosed.

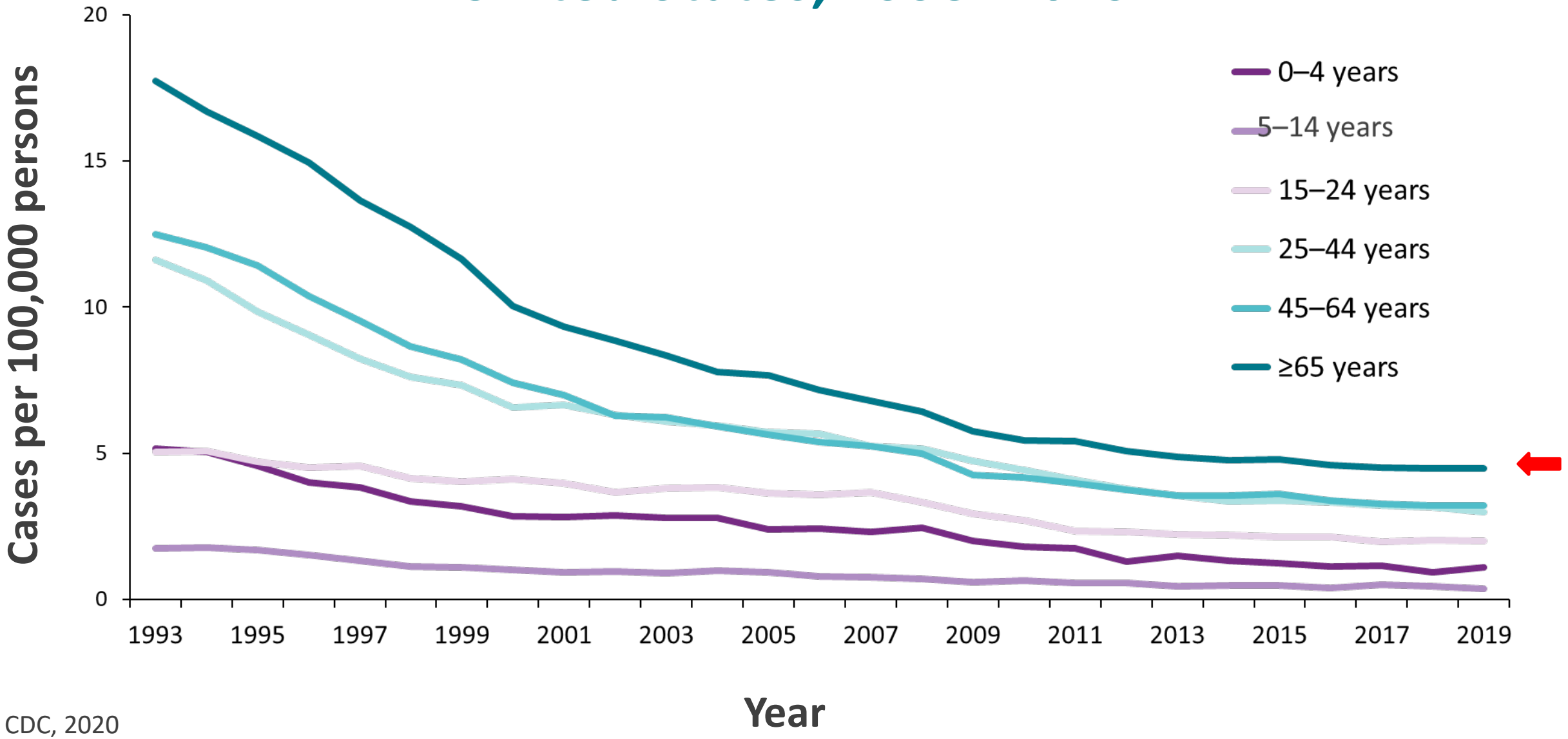
Increasing age is not associated with an increased risk of reactivation of latent TB



The risk of reactivation declines over time, but the higher prevalence of people with TB infection in older age groups contributes to higher case rates.

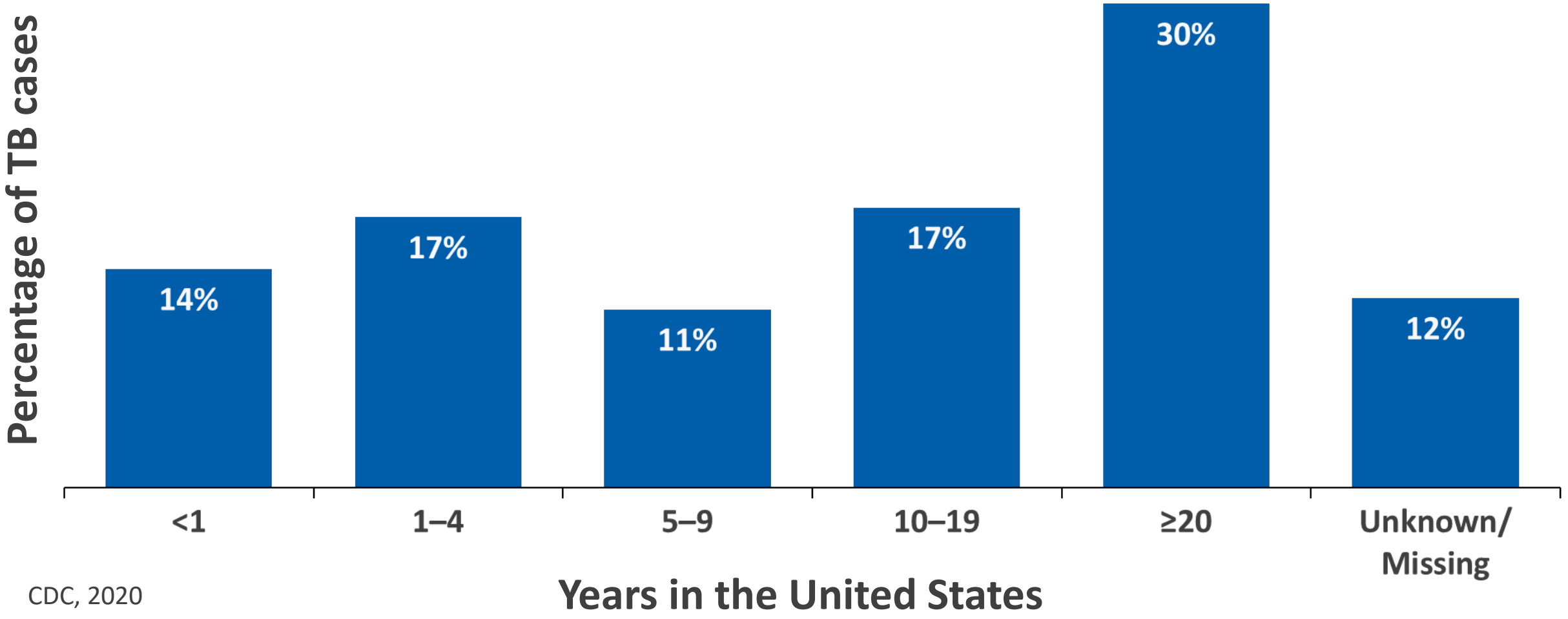
Comstock, Frost Revisited: The modern epidemiology of tuberculosis. Am J Epidemiol, 1975

TB Case Rates by Age Group, United States, 1993–2019

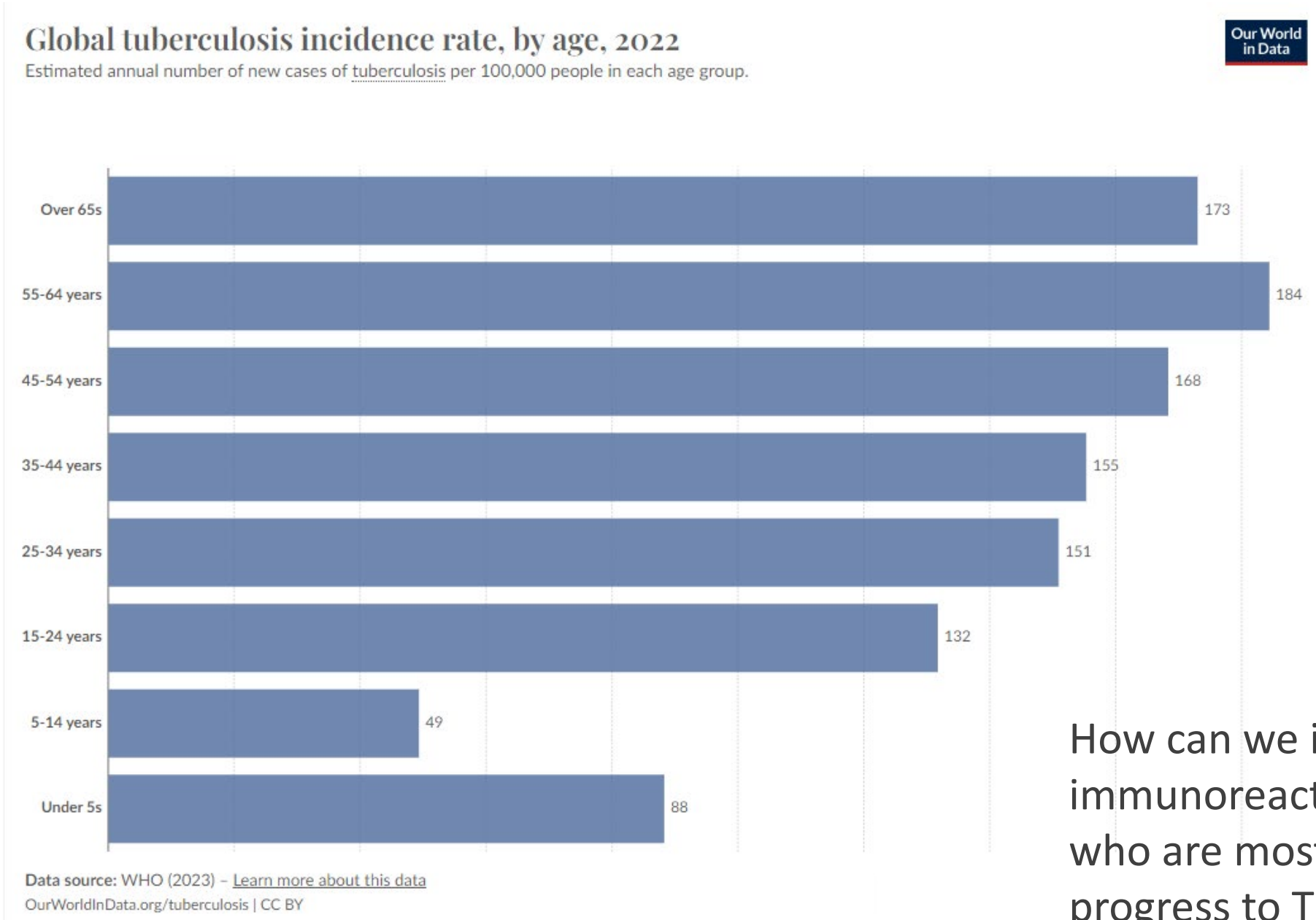


CDC, 2020

Percentage of TB Cases Among Non-U.S.–born Persons by Years Since Initial Arrival in the United States at Diagnosis, 2019 (N=6,364)



CDC, 2020



How can we identify immunoreactive people who are most likely to progress to TB disease?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Prevention of *M. tuberculosis* Infection with H4:IC31 Vaccine or BCG Revaccination

E. Nemes, H. Geldenhuys, V. Rozot, K.T. Rutkowski, F. Ratangee, N. Bilek, S. Mabwe, L. Makhethe, M. Erasmus, A. Toefy, H. Mulenga, W.A. Hanekom, S.G. Self, L.-G. Bekker, R. Ryall,* S. Gurunathan, C.A. DiazGranados, P. Andersen, I. Kromann, T. Evans, R.D. Ellis, B. Landry, D.A. Hokey, R. Hopkins, A.M. Ginsberg, T.J. Scriba, and M. Hatherill, for the C-040-404 Study Team†

- 2976 adolescents with neonatal BCG vaccination screened
- 48% IGRA-positive and ineligible
- 990 randomized to H4:IC31, BCG, or placebo
- No difference in initial IGRA conversion (13-16%)
- 'Sustained' IGRA conversion:
  - H4:IC31 8.1%
  - BCG 6.7%
  - Placebo 11.6%
- BCG revaccination efficacy for sustained conversion = 45%

N Engl J Med 2018;379:138-49.

Potential Impact of BCG Revaccination in Adolescents

- Population prevalence of TST/IGRA+ in adolescents ~50%
- Population = 100,000
- 10% of LTBI+ develop TB in follow up → 50,000 X .1 = 5,000

- 11% of placebo recipients become infected
- 10% develop TB in follow up → 5,500 X .1= 550

- 7% of BCG revaxed become infected
- 10% develop TB in follow up → 3,500 X .1 = 350

- Total TB burden with no vaccine (placebo) = 5,550
- Total TB burden with BCG revaccination = 5,350
- Impact of BCG revaccination = 5,550/5,350 ~ 3%
- Caveats:
  - Revax may protect in people who convert, but 100% efficacy unlikely
  - TB rates in IGRA+ people may be lower since some period of risk has passed

Can TB Vaccines Cause Harm?

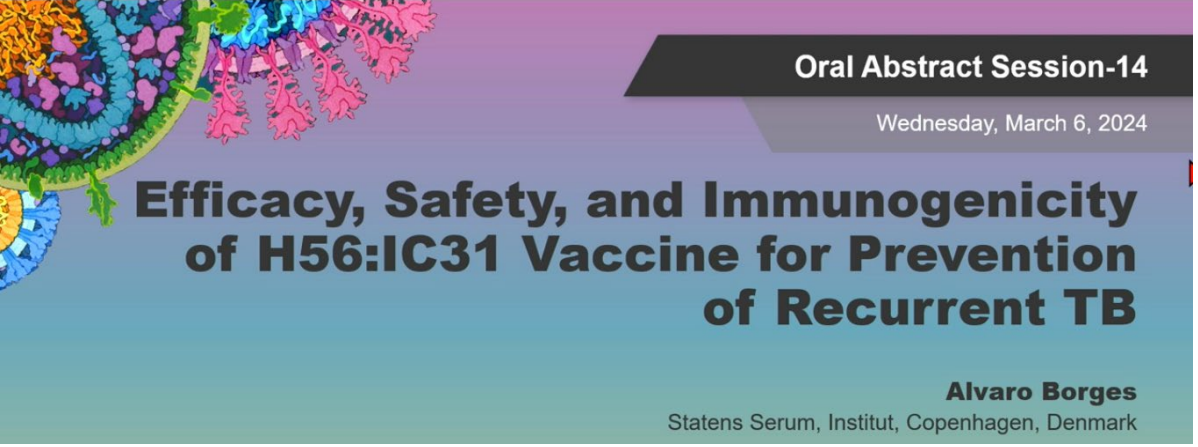
Table 4. Effectiveness of neonatal BCG vaccination in 2 programs in which vaccine was changed.

Location of study, variable	Early period	Recent period
Cali, Columbia		
No. of case-control pairs	191	191
OR	0.49	1.18
Program effectiveness, %	51	−18
Jakarta, Indonesia		
Vaccinated[a]	11/74	16/58
Not vaccinated[a]	25/70	6/30
OR	0.42	1.38
Program effectiveness, %	58	−38

NOTE. Data are from [14].

[a] No. of case patients/no. of control subjects.

Comstock, Clin Infect Dis, 2000;suppl



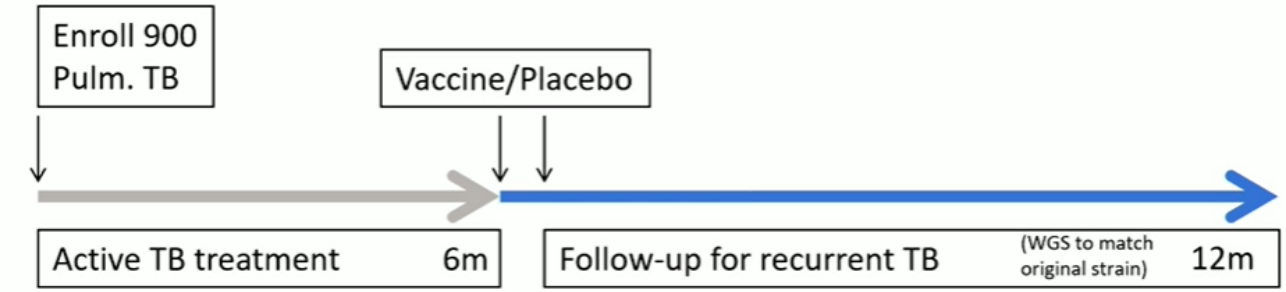
Oral Abstract Session-14

Wednesday, March 6, 2024

Efficacy, Safety, and Immunogenicity of H56:IC31 Vaccine for Prevention of Recurrent TB

Alvaro Borges
Statens Serum, Institut, Copenhagen, Denmark

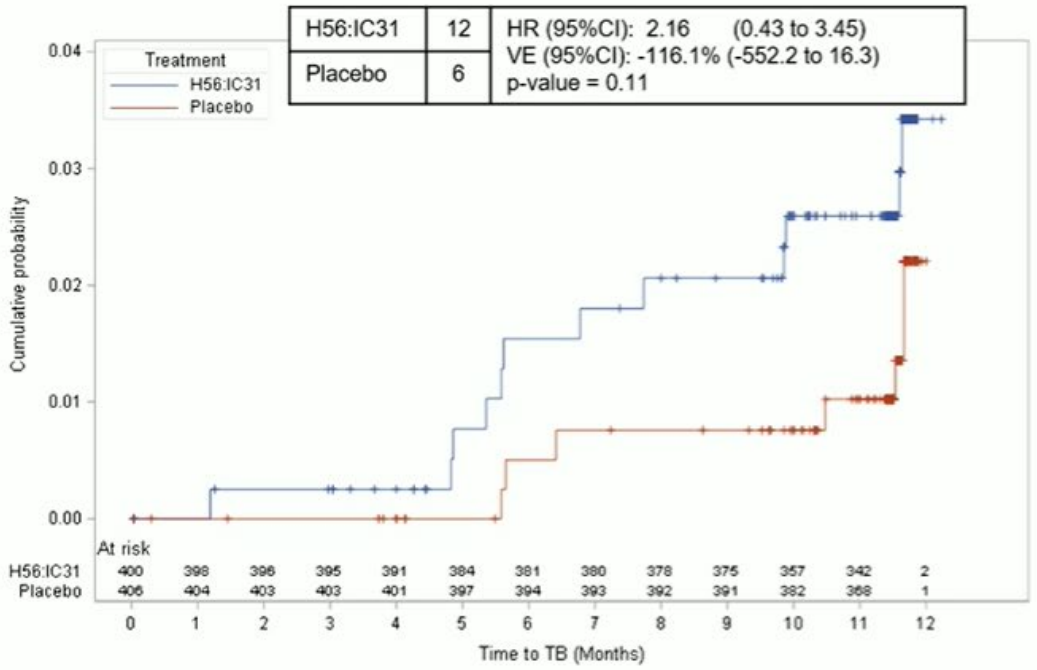
Phase II H56:IC31 POR trial design



Sites	Mbeya, Tanzania TASK, Aurum, SATVI, UCTLI, South Africa
Sponsor	IAVI/SSI
Trial duration	6+2+12 months
Vaccine efficacy	60%
Recurrence rate	4% / yr
Loss to follow up	10%
Power	80%
Type I error rate (two-sided)	20%
Sample size/arm	450
Expected prim. endpoints	23
Cost	13.8 million €

Time from d70 to TB relapses and reinfections

Relapses



Re-infections