Management of latent TB infection: gaps & opportunities

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Enhancing Adherence, Infection Control Capacities, and Cost-Effectiveness

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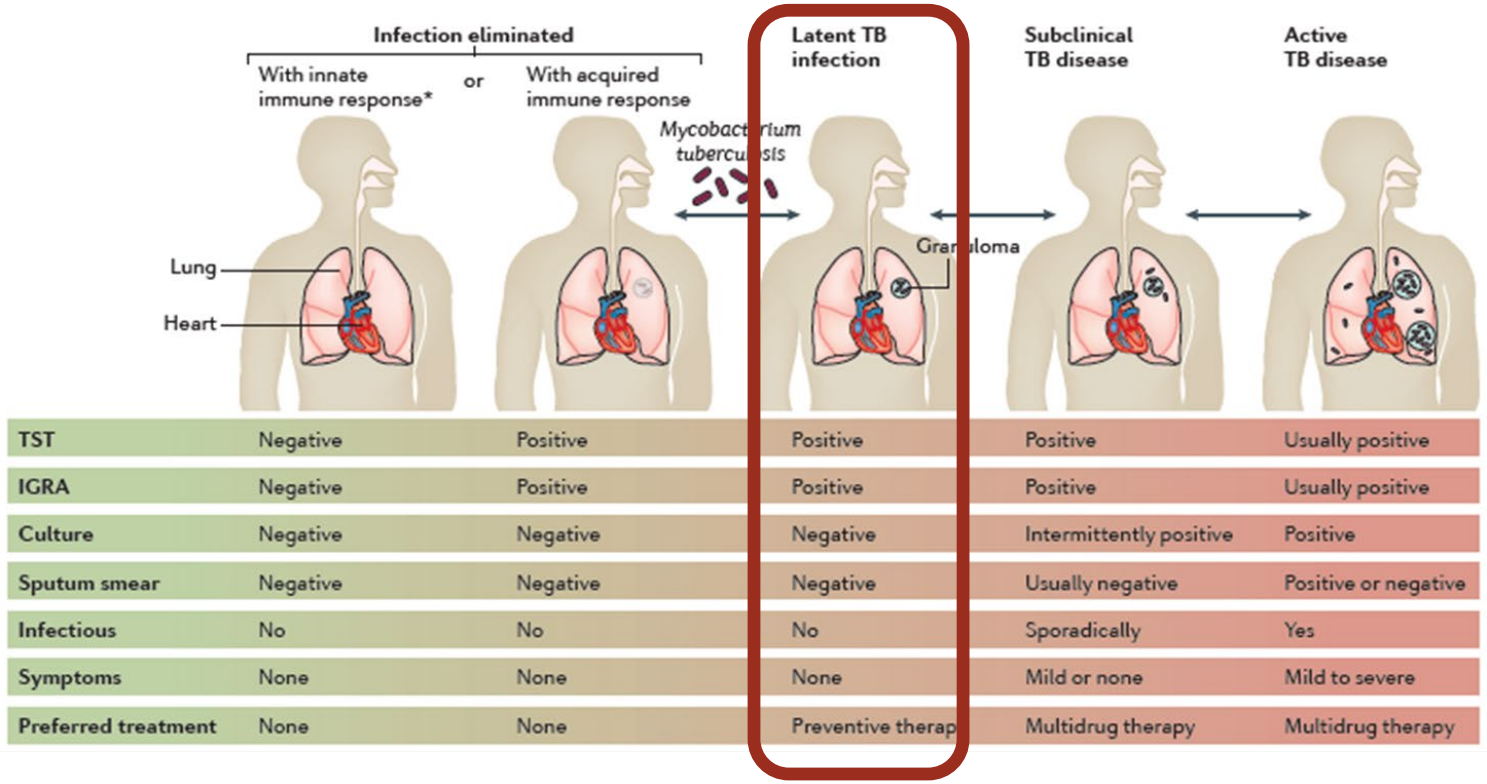
Overview

- Gaps & opportunities
  - Cascade of care
  - People living with HIV
  - Household contacts
- Future TPT regimens
- Conclusion

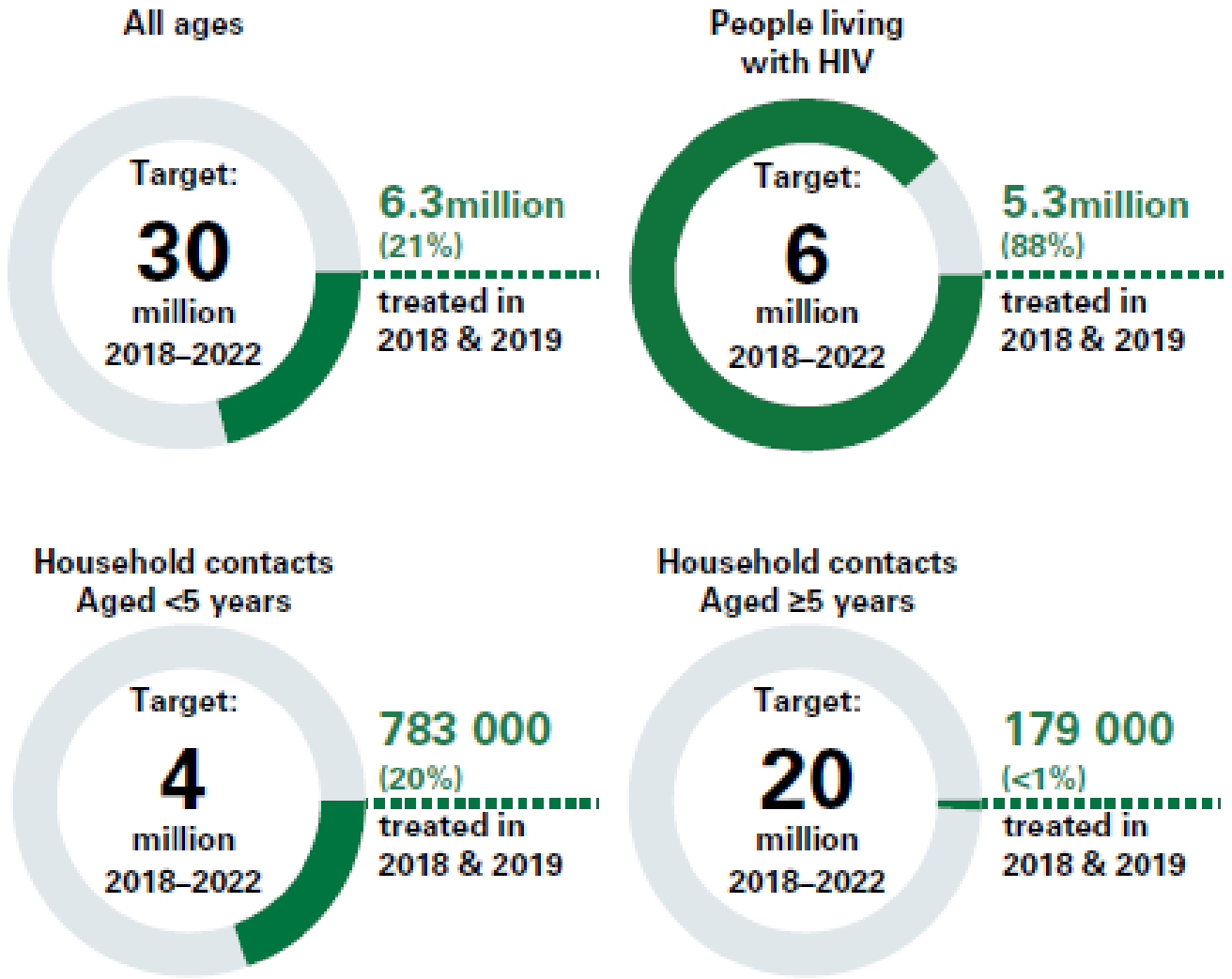


TST	Negative	Positive	Positive	Positive	Usually positive
IGRA	Negative	Positive	Positive	Positive	Usually positive
Culture	Negative	Negative	Negative	Intermittently positive	Positive
Sputum smear	Negative	Negative	Negative	Usually negative	Positive or negative
Infectious	No	No	No	Sporadically	Yes
Symptoms	None	None	None	Mild or none	Mild to severe
Preferred treatment	None	None	Preventive therap	Multidrug therapy	Multidrug therapy

Pai. Nature Reviews | Disease Primers. 2016)

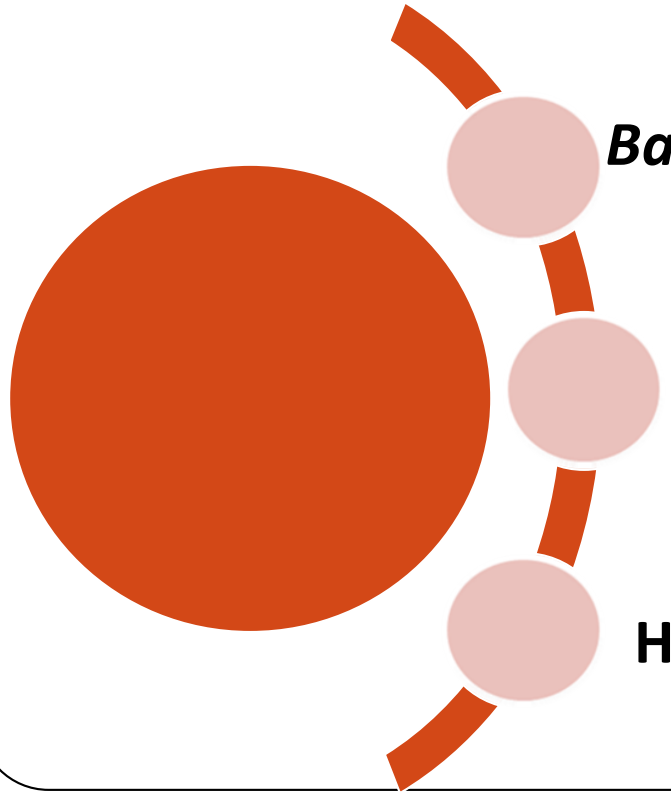
Global progress in scaling up TPT

2018-2019 vs. 2018–2022 targets



(Global TB Report, 2020)

Research gaps



Barriers in implementation

Cascade of prevention

High risk groups

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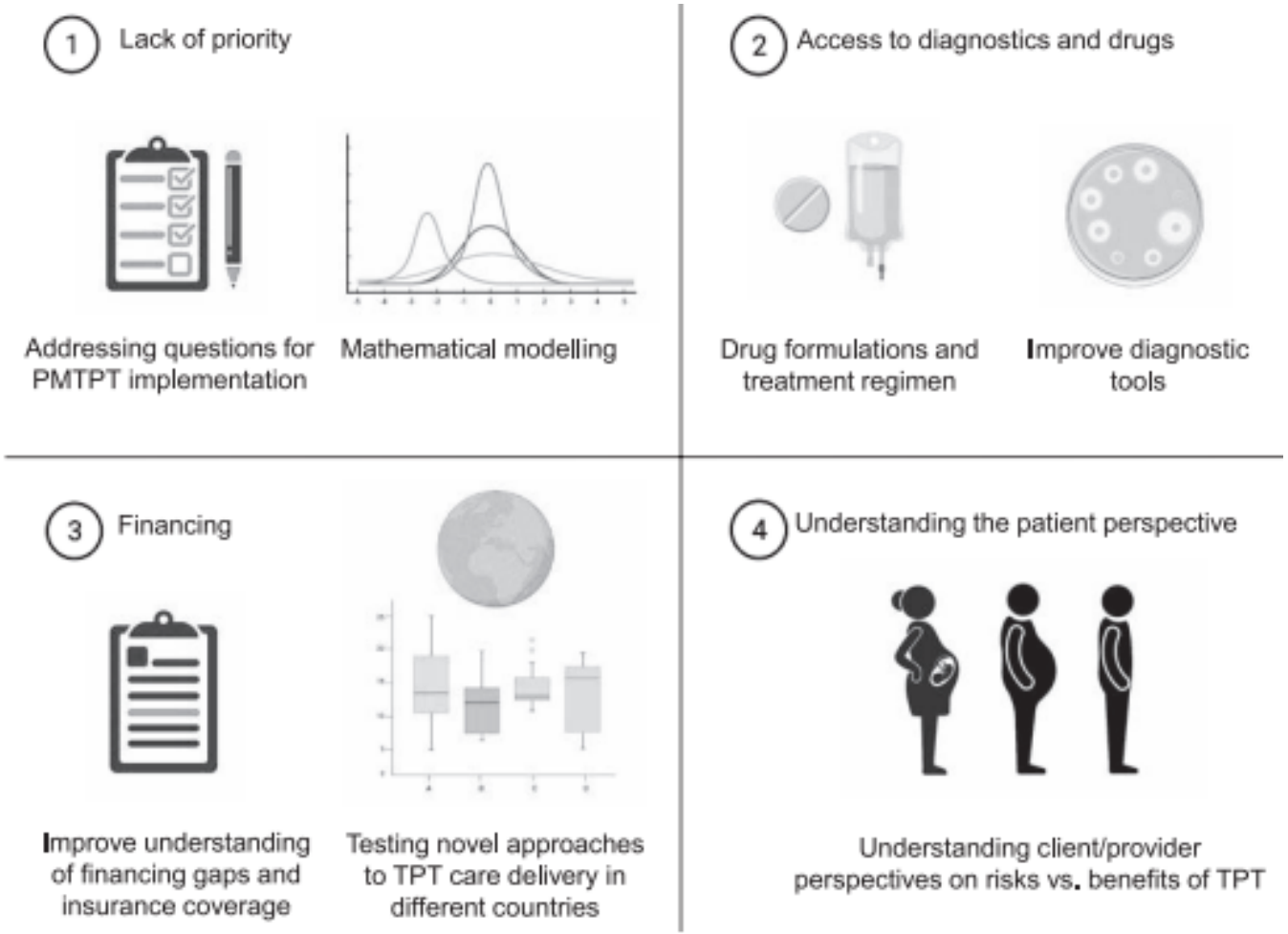
Research gaps

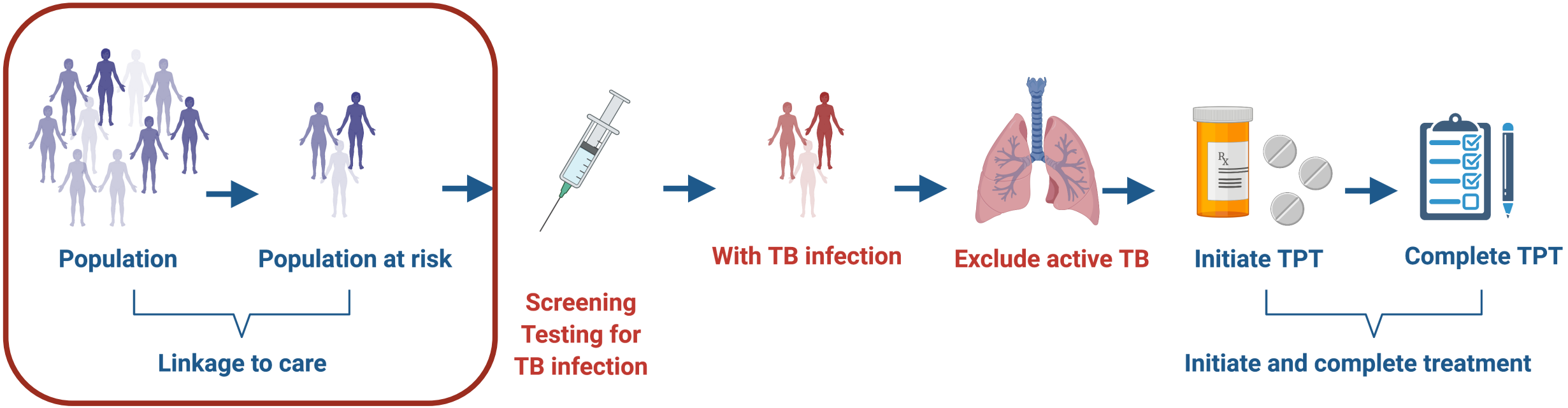
Barriers in implementation



(Oxlade et al. Int J Tuberc Lung Dis. 2021)

Research gaps

Cascade of prevention

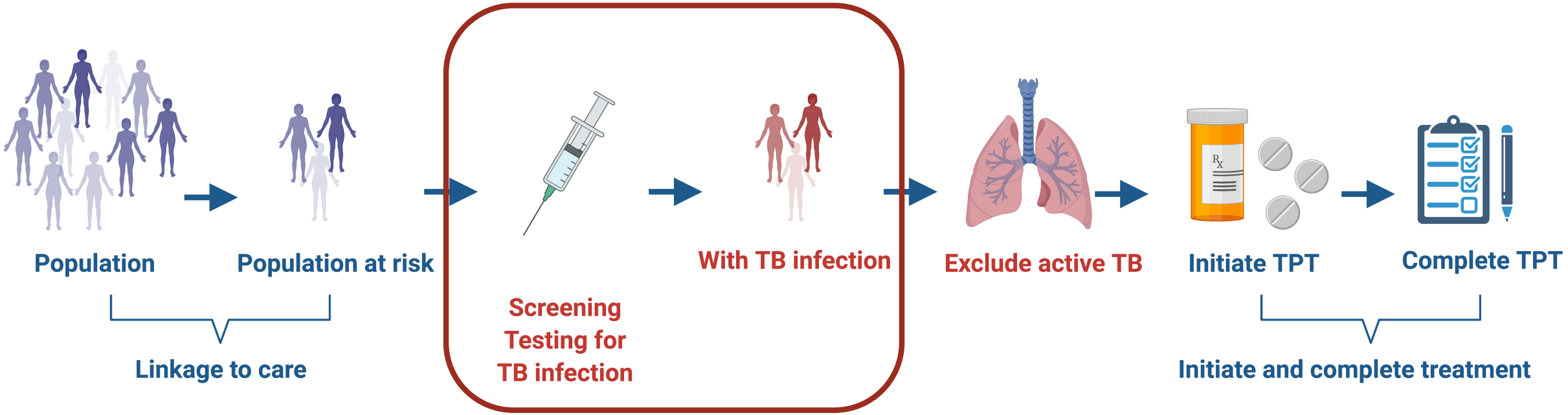


- Best approaches for linkage to care
- Characterise the impact of different strategies in different contexts (modeling studies)
- Identify acceptability and feasibility of different treatments and models of care

(Oxlade et al. Int J Tuberc Lung Dis. 2021)

Research gaps

Cascade of prevention

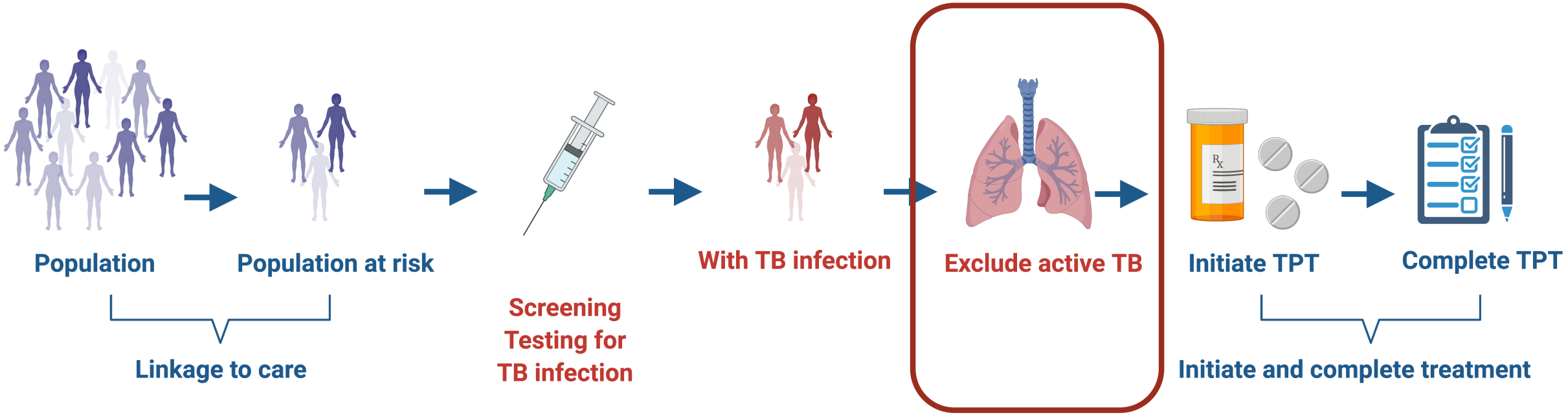


- Re-evaluation of cost, feasibility, yield and cost-effectiveness of testing for TB infection among household contacts aged ≥5 years
- Assessment of the benefit of tests for TB infection in PLHIV on ART and/or in low burden settings
- Evaluation of more specific TB skin tests and point-of-care IGRA tests
- Deeper understanding of mechanisms of latency to identify biomarkers of progression

(Oxlade et al. Int J Tuberc Lung Dis. 2021)

Research gaps

Cascade of prevention

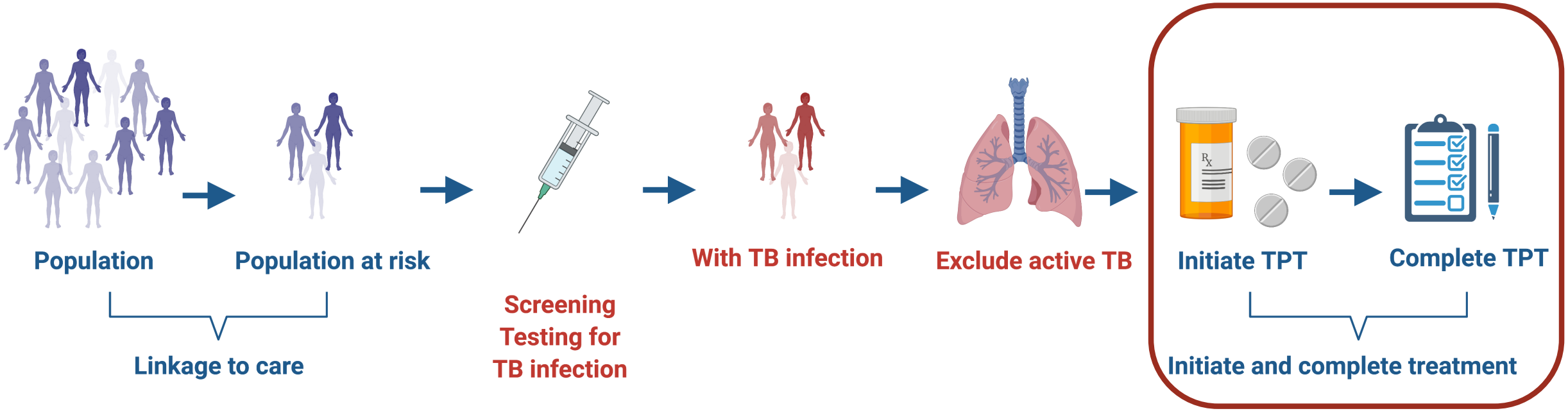


- Evaluation of computer-aided detection of TB on digital CXR
- Cost-effectiveness and feasibility of expanding digital CXR in primary care settings in high & intermediate incidence countries
- Cost-effectiveness of expanded CXR access
- Development and assessment of alternative methods to exclude TB disease

(Oxlade et al. Int J Tuberc Lung Dis. 2021)

Research gaps

Cascade of prevention



- Evaluation of regimens of 1–2 months' duration for efficacy, safety, tolerability and Acceptability
- Patient and provider attitudes to TPT and ways to overcome barriers to acceptance of treatment
- How to accurately monitor and track adverse events related all TPT regimens in programmatic settings
- Evaluation of safety of all TPT regimens in pregnant and breastfeeding women
- Shorter regimens and/or long-acting single-dose regimens ('depot' injections of a long-acting agents)

(Oxlade et al. Int J Tuberc Lung Dis. 2021)

Research gaps

High risk groups

People living with HIV

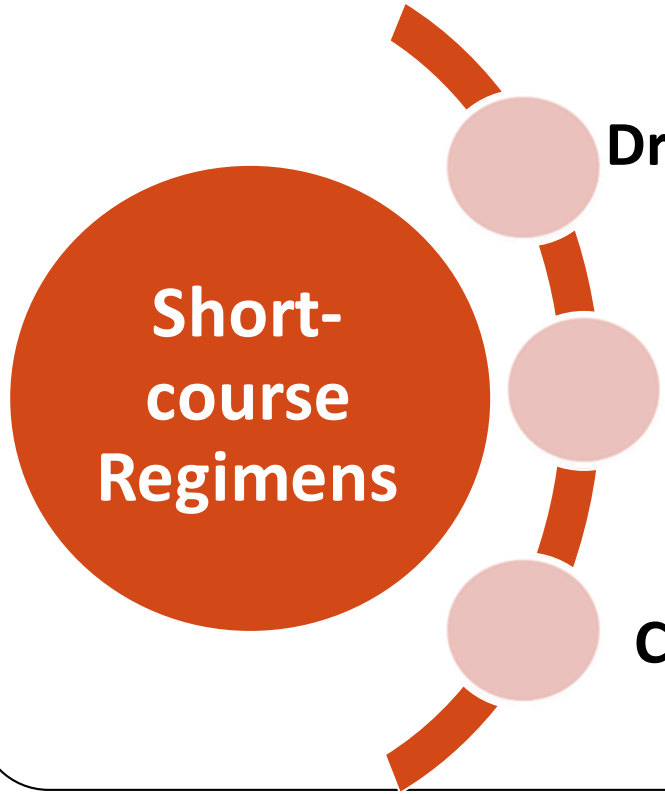
Household contacts <5 years

Household contacts ≥5 years

Other people at risk

(Oxlade et al. Int J Tuberc Lung Dis. 2021)

People living with HIV



- Drug-drug interactions
- Cost effectiveness
- Children and pregnant women

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DOLPHIN

- 3HP with DTG was well-tolerated & safe in PLHIV
- Trough DTG concentrations were reduced by ~ 50%
  - Median values > 300 ng/mL at all time points
  - No dose adjustment of DTG required
- Virologic suppression maintained throughout

DOLPHIN TOO

- DOLPHIN protocol amended to describe the rate of decline of plasma HIV-1 Viral load among ART naïve participants starting either IPT (n=25) or 3HP (n=50) with a DTG based ART regimen
- **Timeline:** Ready to open

IMPAACT4TB

PREVENTING TB TO END TB

(Dooley. Lancet HIV. 2020)

Pediatric TPT for Different Populations

Household Child TB Contact <5 years

Asymptomatic

4-9.9kg (<2 years)			>10kg (2 years and up)		
HIV negative or HIV exposed not on NVP	HIV Positive on LPV/r (or NVP)	HIV-exposed on NVP ppx	HIV Positive		HIV Negative
			LPV/r	EFV	
3RH	6H	6H	6H	3HP	

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PREVENTING TB TO END TB

TBTC Study 35

- Is a dose finding and safety study of 3HP in at least 60 HIV-infected and HIV-uninfected children (0-≤12years) with LTBI
- Formulations:
  - A child-friendly Fixed Dose Combination tablet of 3HP that dissolves in water
  - A rifapentine single tablet, to optimize doses for the youngest children

DOLPHIN KIDS

- **Objective:** to assess the safety, tolerability and pharmacokinetics of three months of 3HP among infants, children and adolescents living with HIV taking DTG based ART
- **Timeline:** Start Q3 2022 with Sanofi crushed singles

IMPAACT4TB

One month of daily isoniazid and rifapentine (1HP) *(Ultra short)*

1HP vs 9H

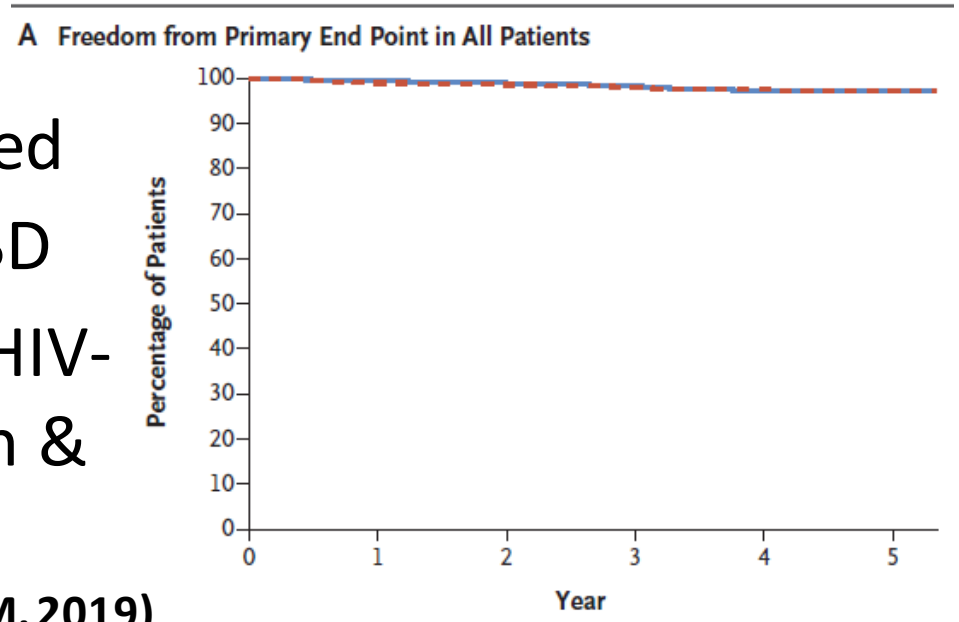
- 1HP non-inferior to 9H
- Better
  - Safety & tolerability
  - treatment completion
- Unknown whether dose adjustment of DTG is required
  - A5372: DTG given QD or BD
- No evidence yet for use in HIV-uninfected persons, children & pregnant women

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 14, 2019 VOL. 380 NO. 11

One Month of Rifapentine plus Isoniazid to Prevent HIV-Related Tuberculosis

S. Swindells, R. Ramchandani, A. Gupta, C.A. Benson, J. Leon-Cruz, N. Mwelase, M.A. Jean Juste, J.R. Lama, J. Valencia, A. Omoz-Oarhe, K. Supparatpinyo, G. Masheto, L. Mohapi, R.O. da Silva Escada, S. Mawlana, P. Banda, P. Severe, J. Hakim, C. Kanyama, D. Langat, L. Moran, J. Andersen, C.V. Fletcher, E. Nuermberger, and R.E. Chaisson, for the BRIEF TB/A5279 Study Team*



(Swindells. NEJM. 2019)

1HP vs. 3HP (One-to-Three) trial

Primary objective

- Among adult & adolescent HIV-positive persons & household contacts to compare one-month of 1HP to 3HP with respect to:
  - Treatment completion
  - Treatment limiting adverse events

Secondary objectives:

- To compare the 1HP arm to the 3HP arm with respect to:
  - Study defined grade 3 or 4 adverse events (safety)
  - Cost-effectiveness
- **Sites:** South Africa, Indonesia, India, Mozambique
- **Timeline:** Start August 2022

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Cost-Effectiveness of 1HP vs 3HP
A Comparison of TB Short-Course Preventive Regimens

- Assuming 1HP is noninferior to 3HP, it would cost an additional $16 per patient to achieve the same outcomes at current prices
  - Falls to $0.70 if the price of rifapentine per 600mg can be reduced by 66% (corresponding to $15 per course of 3HP)
- Cost effectiveness of 1HP is driven by 1HP completion rates & efficacy relative to 3HP, cost of rifapentine, and LTBI prevalence

Ferguson et al, Union 2019

IMPAACT4TB
PREVENTING TB TO END TB

Rifapentine based TPT in pregnant HIV-positive women

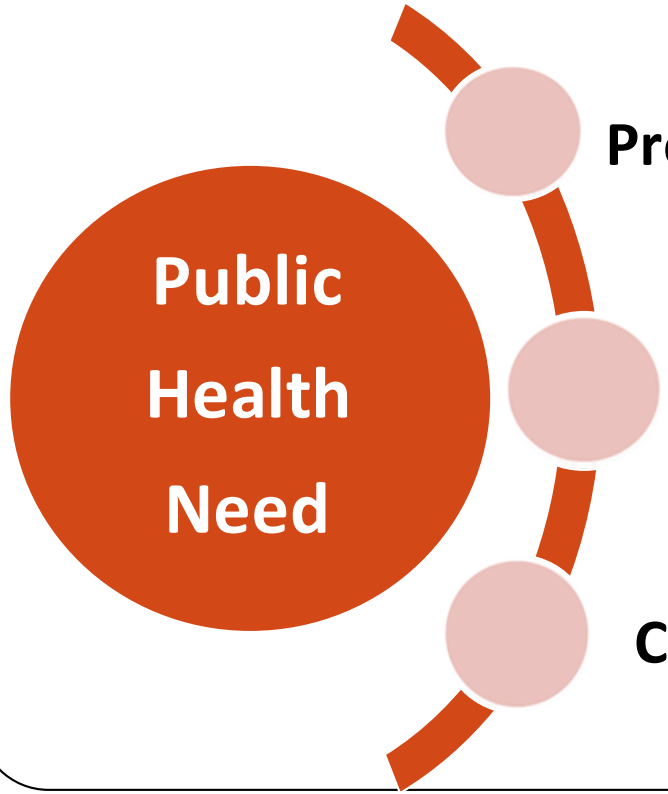
- **IMPAACT 2001**
  - N=50 (20 had HIV)
  - Tolerable and safe
  - No dose adjustment of rifapentine required in pregnant & postpartum women with and without HIV

(Mathad, CROI, 2020)

- **WHIP3TB**
  - Pregnancy outcomes on 3HP will be reported at Union 2021 conference
- **IMPAACT4TB**
  - DOLPHIN MOMS, will evaluate the safety, tolerability, and pharmacokinetics of 1HP vs. 3HP initiated antepartum vs. postpartum
  - Timeline: start in Q3 2022

IMPAACT4TB
PREVENTING TB TO END TB

Household contacts



- Prevalent & incident TB
- High risk household contacts
- Combined value of contact investigation & TPT

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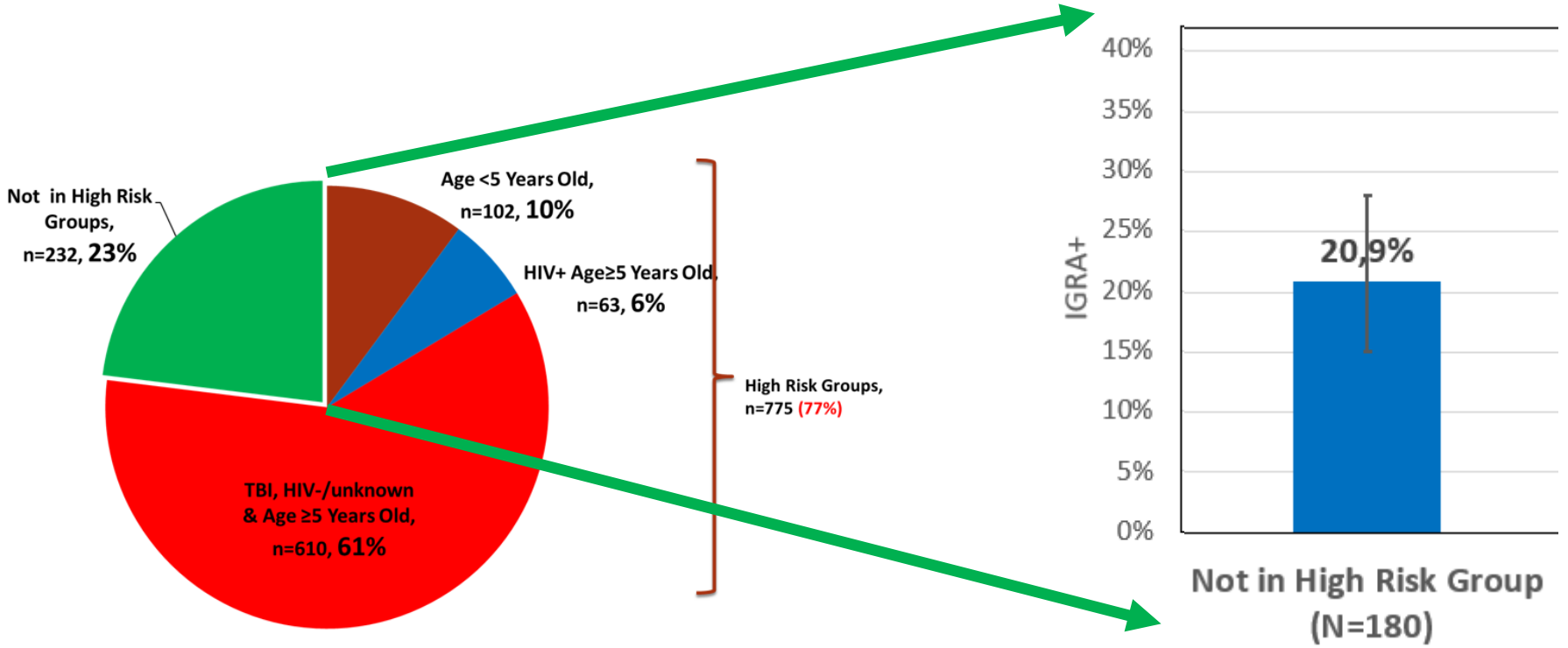
Incidence of TB infection among persons not in a risk group

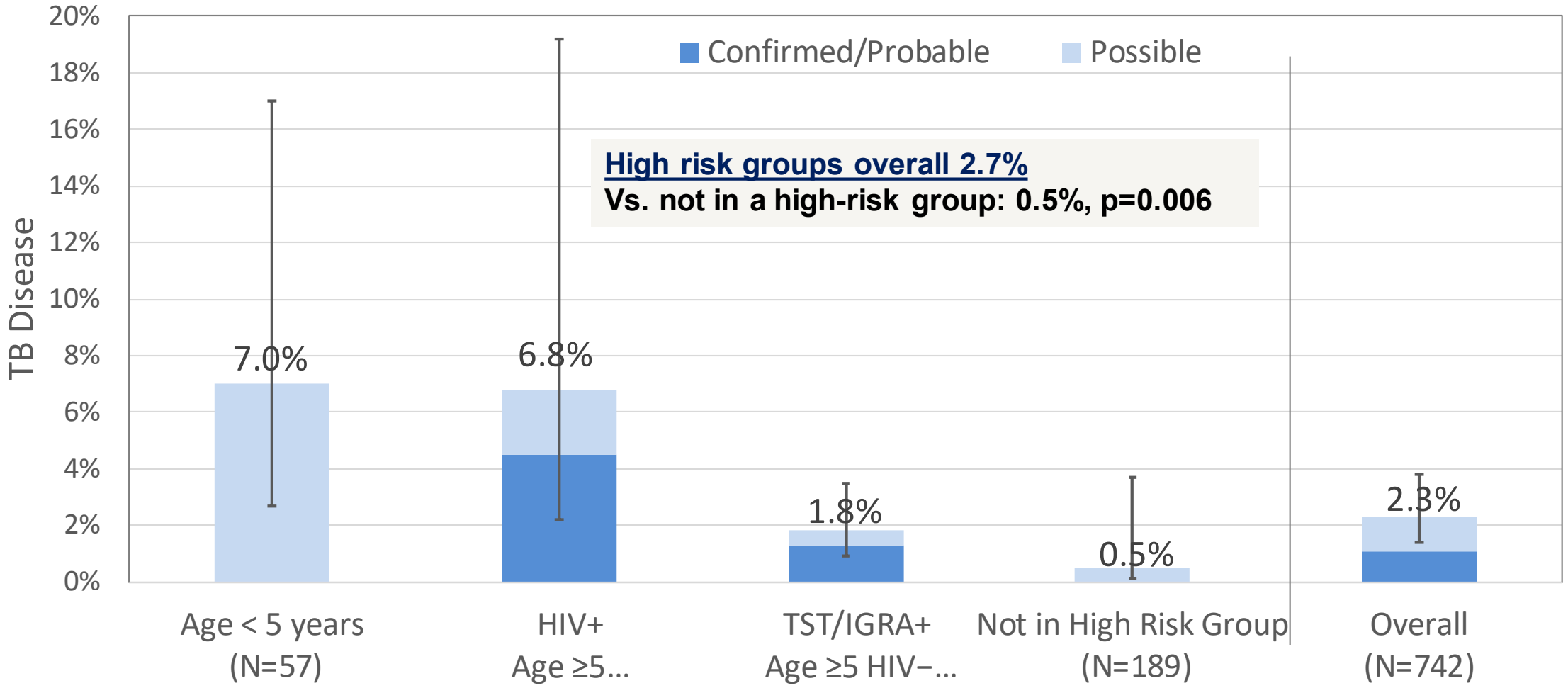


At enrolment

Proportion of HHCs≥5 years, HIV- that converted from IGRA negative at baseline to positive after one year

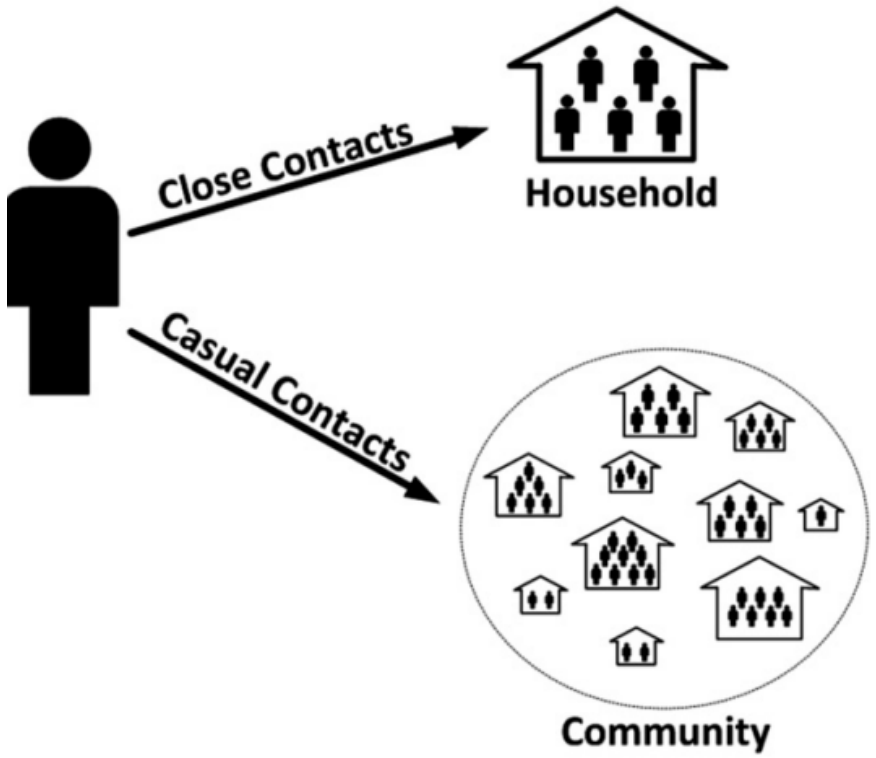
(Gupta. CID. 2019, Kim. CROI. 2020)

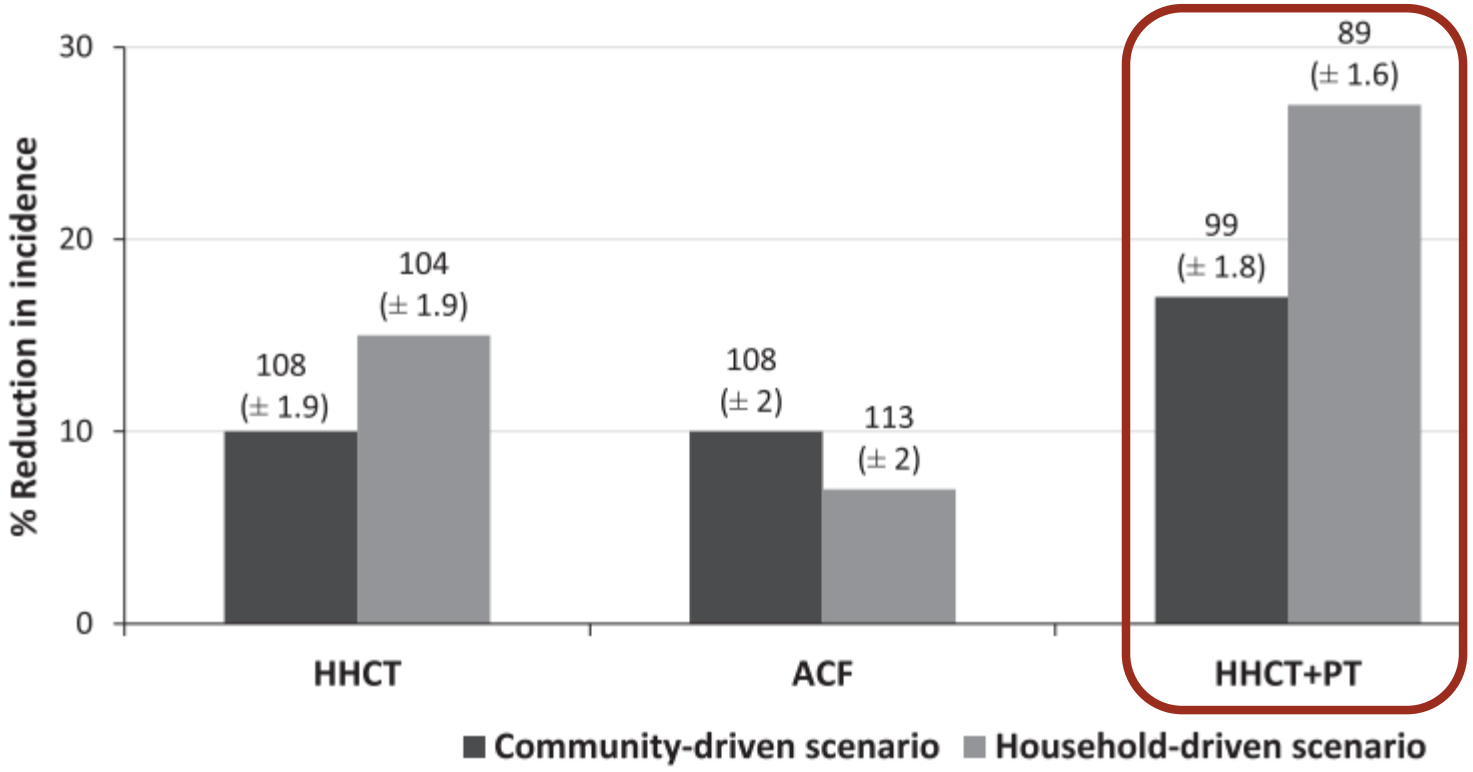
Incidence of TB Disease differed by risk group



(Gupta. AIDS. 2020)

Combined impact of household case-finding & TPT





(Kasaie, et al. Am J Respir Crit Care Med. 2014)

Trials of treatment for MDR TB infection

	TB-CHAMP	V-QUIN	PHOENIX
Intervention	LVF (paediatric dispersible tablet formulation) vs. placebo daily for 6 months	LVF vs placebo daily for 6 months	DLM vs INH daily for 26 weeks
Design	Cluster randomized; superiority Community-based	Cluster randomized; superiority Community-based	Cluster randomized; superiority
Target Population	0-5 years of age regardless of TST or HIV status	All ages (including infants < 6 mo), TST +	1. Children 0-5 yrs, HIV +, TST/IGRA + over 5 year olds
Assumptions	LVF decreases incidence from 7 to 3.5%; 80% power	LVF decreases incidence by 70% from 3% untreated; 80% power	DLM decreases incidence by 50% from 5% to 2.5%; 90% power
Sample size	788 HH 1565 contacts	1326 HH 2785 contacts	1726 HH 3452 contacts
Sites	South Africa	Viet Nam	ACTG & IMPAACT sites

Future TPT regimens

Priorities

- Modelled impact of optimal TPT regimens
- Shortening treatment for DS & MDR TB infection
- Develop long-acting formulations

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2R2: Higher Dose Rifampicin for 2 Months vs Standard Dose Rifampicin for Latent TB

Aim

- To determine if rifampin at double or triple the standard dose for 2 months is as safe and effective as 4R

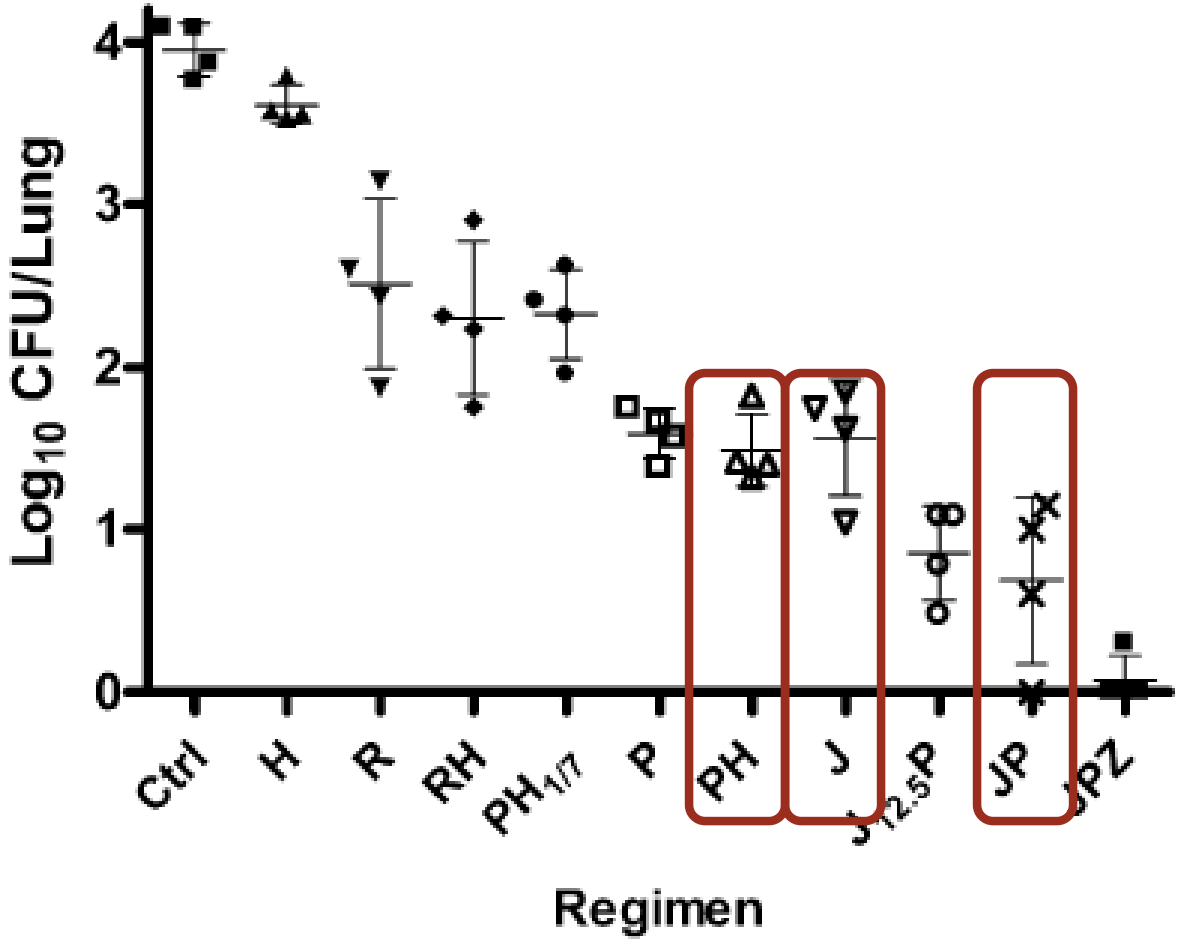
Assessment of the Safety, Tolerability, and Effectiveness of Rifapentine Given Daily for LTBI (ASTERoiD)

Aim

- To compare the safety and effectiveness of 6-weeks of daily rifapentine (6wP) with 12-16 weeks of rifamycin-based treatment

Can we shorten TPT regimens further?

Potentially shorter LTBI regimens in the murine model Lung CFUs after 4 weeks of treatment



Zhang et al., Am J Respir Crit Care Med,184:732–737, 2011

Conclusion

- Managing the global burden of TB infection is essential to meeting the End TB targets
- Further research is required to address barriers to implementation, gaps in the TB prevention cascade and gaps specific to certain high-risk populations
- Further innovation is required to improve potency and further reduce the duration of treatment of DS & DR TB infection & maximise public health impact

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