New TB Vaccines update for TIM meeting

- Pipeline
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    - Key research gaps & filling
- Much much more…

TB Vaccine Pipeline

TB vaccine candidates in active clinical trials

There are 12 candidates in active clinical trials as of September 2024.

Platform

- Mycobacterial - Live attenuated
- Mycobacterial - Inactivated
- Viral vector
- Protein/Adjuvant
- RNA

Trial target population

- Elderly
- Adults
- Adolescents
- Children
- Infants
- +HIV — People living with HIV
- -HIV — People without HIV infection
- -Mtb — People without Mtb infection
- +Mtb — People with Mtb infection
- aTBd — People with active TB disease
- MDR — People with MDR-TB
- cTB — People cured of active TB

Primary endpoint

- *Sf* — Safety
- *Im* — Immunogenicity
- *POI* — Prevention of Infection
- *POD* — Prevention of Disease
- *POR* — Prevention of Recurrence
- *Thp* — Therapeutic

Information reported by trial sponsors or found in clinical trial registries or other public sources

Institutions listed are the trial sponsors

Additional information about each candidate can be accessed via the QR code or at newtbvaccines.org/tb-vaccine-pipeline/

Stop TB Partnership
WORKING GROUP ON NEW TB VACCINES

Last update: 2 September 2024

~Timeline of adolescent/adult TB vaccine trial results
Ordered by ~time to potential licensure/policy change (Known/ Guessed)

Name	Phase/ outcome	Location	IGRA	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034
VPM 1002/ Im'vac*	Ph3 HHC POD	India	IGRA+	x	x										
GAM TBVAC*	Ph3 POD	Russia	IGRA -	x	x	x	x								
BCG Revax	Ph2b POSI	South Africa	IGRA -	x											
"	Ph4 POD	India	IGRA +/-		x	x	x	x	x?						
M72	Ph3 POD	Multi	IGRA +		x	x	x	x	Primary	x	Final				
MTB VAC	Ph2b POD	Multi Africa	IGRA +		x	x	x	x	x						
"	Ph3 POD										x	x	x	x	x?

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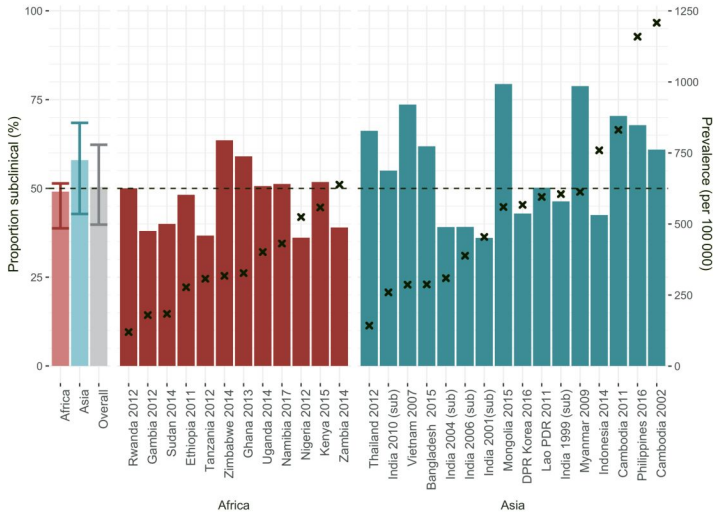
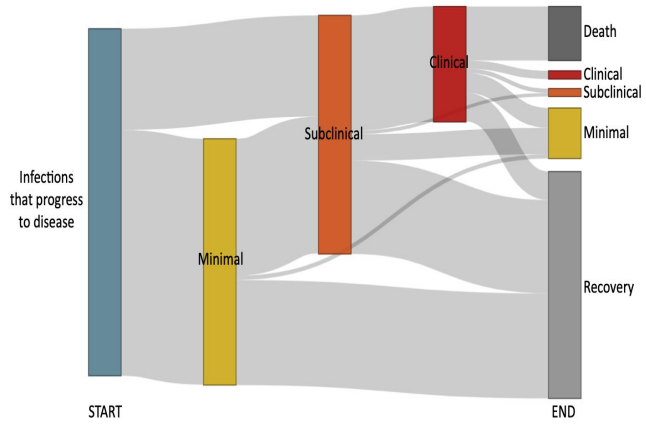
Subclinical TB - Why does it matter for TB vaccines?

- ~Half of prevalent TB
- ~50% may go onto clinical
- May be responsible for alot of global Mtb transmission
- May occur more frequently than clinical TB
- May directly cause morbidity

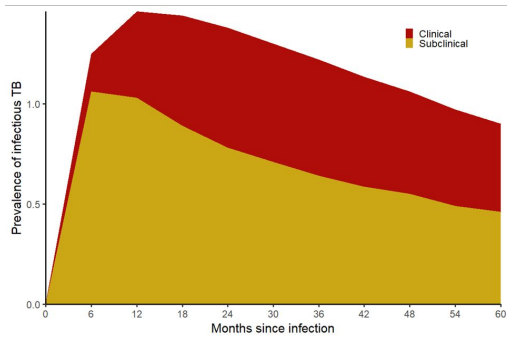




=> Could be important to know if vaccines prevent subclinical TB

=> Could be useful as trial endpoint, by enabling smaller/cheaper TB vaccine licensure trials

Trial endpoints?



Frascella, CID, 2020; Horton PNAS 2023, Emery, eLife 2023, Houben LRM 2022

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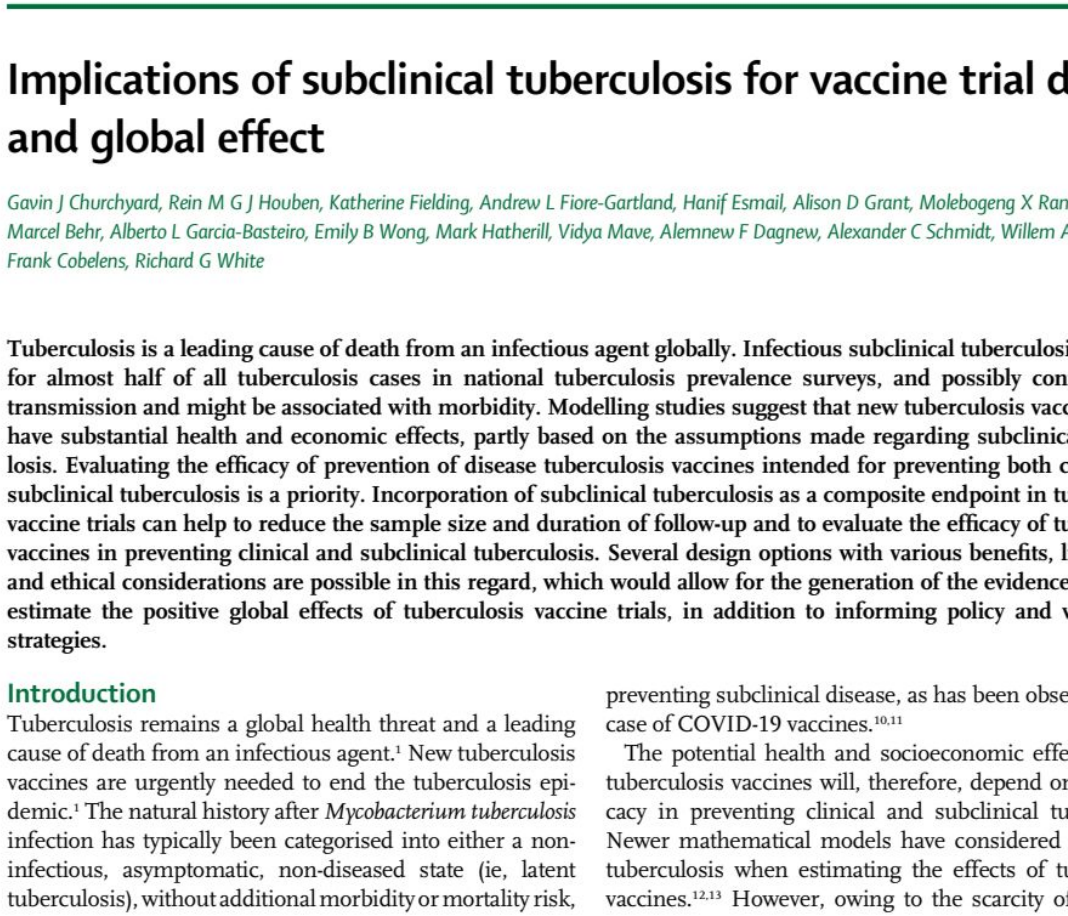


Implications of subclinical tuberculosis for vaccine trial d and global effect

Gavin J Churchyard, Rein M G J Houben, Katherine Fielding, Andrew L Fiore-Gartland, Hanif Esmail, Alison D Grant, Molebogeng X Ran Marcel Behr, Alberto L Garcia-Basteiro, Emily B Wong, Mark Hatherill, Vidya Mave, Alemnew F Dagnew, Alexander C Schmidt, Willem A Frank Cobelens, Richard G White

Tuberculosis is a leading cause of death from an infectious agent globally. Infectious subclinical tuberculosi for almost half of all tuberculosis cases in national tuberculosis prevalence surveys, and possibly con transmission and might be associated with morbidity. Modelling studies suggest that new tuberculosis vacc have substantial health and economic effects, partly based on the assumptions made regarding subclinica losis. Evaluating the efficacy of prevention of disease tuberculosis vaccines intended for preventing both c subclinical tuberculosis is a priority. Incorporation of subclinical tuberculosis as a composite endpoint in tu vaccine trials can help to reduce the sample size and duration of follow-up and to evaluate the efficacy of tu vaccines in preventing clinical and subclinical tuberculosis. Several design options with various benefits, l and ethical considerations are possible in this regard, which would allow for the generation of the evidence estimate the positive global effects of tuberculosis vaccine trials, in addition to informing policy and v strategies.

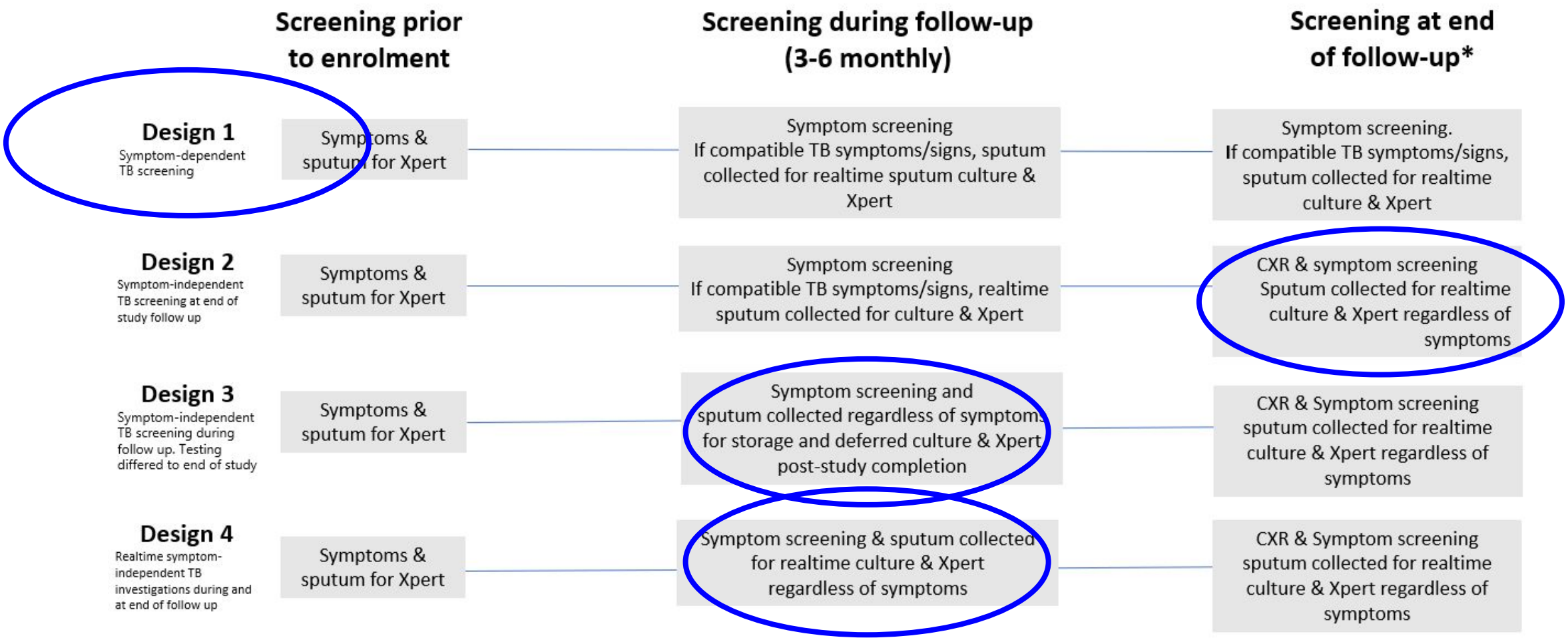
Introduction

Tuberculosis remains a global health threat and a leading cause of death from an infectious agent.[1] New tuberculosis vaccines are urgently needed to end the tuberculosis epidemic.[1] The natural history after *Mycobacterium tuberculosis* infection has typically been categorised into either a non-infectious, asymptomatic, non-diseased state (ie, latent tuberculosis), without additional morbidity or mortality risk, preventing subclinical disease, as has been obse case of COVID-19 vaccines.[10,11]

The potential health and socioeconomic effe tuberculosis vaccines will, therefore, depend or cacy in preventing clinical and subclinical tu Newer mathematical models have considered tuberculosis when estimating the effects of tu vaccines.[12,13] However, owing to the scarcity of

How to measure TB vaccine impact on subclinical TB

- Design options 1/3



* Last study visit likely to occur 2-4 years after study entry depending on how long it takes to complete study enrolment and assuming that the last participant enrolled has at least 2 years of follow up. CXR: chest X-ray, Xpert: GeneXpert Ultra

How to measure TB vaccine impact on subclinical TB

- Design options 2/3

Characteristic	1: Symptom Dependent TB screening	2: Symptom Independent TB screening at end of study	3: Symptom ind. TB screening during study. Test all samples at end	4: Symptom ind. TB screening and testing during study
Analogy	M72/ASO1E IIb (19)	CORTIS (14), Thibela TB (15), WHIP3TB (13)	XACT (16), TB Fast Track (17)	S341/A5349 (18)
Phase/design	IIb/III RCT	IIb/III RCT	IIb/III RCT	IIb/III RCT
Primary objective	Efficacy preventing cTB	Efficacy preventing cTB	Efficacy preventing cTB	Efficacy preventing composite of cTB & scTB
Secondary objective		Efficacy preventing scTB	Efficacy preventing scTB	
Design implications	Does not ascertain subclinical TB	Ascertains subclinical TB at the end of follow up	Ascertains subclinical TB that emerges during study follow up, at the end of study.	Ascertains subclinical TB real-time during study follow up
Sample size	+++	+++	+++	++
Study duration	+++	+++	+++	++

How to measure TB vaccine impact on subclinical TB

- Design options 3/3

Characteristic	1: Symptom Dependent TB screening	2: Symptom Independent TB screening at end of study	3: Symptom ind. TB screening during study. Test all samples at end	4: Symptom ind. TB screening and testing during study
Regulatory considerations	Accepted by regulators	May be acceptable to regulators as powered to show efficacy in preventing clinical TB	May be acceptable to regulators as powered to show efficacy in preventing clinical TB	Composite endpoint of subclinical and clinical TB not currently accepted by regulators May fail to show efficacy for a vaccine that prevents clinical TB but not subclinical TB
Ethical considerations	scTB not detected & treated. Most will regress & those that progress to clinical TB during FU will be detected & treated. Delayed diagnosis of scTB may increase risk of potential transmission to contacts	scTB detected & treated at the end of FU. scTB not detected during follow up that progresses to clinical TB will be detected and treated Delayed diagnosis of scTB may increase risk of transmission to contacts	scTB only diagnosed at end of FU. Only participants that develop clinical TB during follow up would be treated, which avoids over treatment of sc TB. Delayed diagnosis of scTB may increase risk of potential transmission to contacts	scTB detected & treated throughout FU, which may improve reduce transmission May over treat scTB that would have regressed

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- Much much more…

Implications for global impact

- Modelling suggests that 50% efficacy, 10-year duration Vx, targeted at adolescents and adults, could
  - prevent 44 million cases before 2050
  - be cost-effective or even cost-saving
  - improve health equity
  - increase GDP by US$1·6 trillion
- But, great uncertainty in
  - chars of subclinical tuberculosis
  - efficacy of new vaccines in treating subclinical tuberculosis,
- Some bound to be wrong
- Thoughts >>>

- Quant analysis available soon

	The most likely effect of the assumption being wrong on the model-estimated health and economic impact of the vaccine
Vaccine not effective in individuals with subclinical tuberculosis	Higher global impact
Vaccine efficacy lost upon progression from *Mycobacterium tuberculosis* infection to subclinical tuberculosis	Higher global impact
No morbidity from subclinical tuberculosis	Higher global impact
Subclinical tuberculosis slightly less infectious than clinical tuberculosis	Higher or lower global impact
Vaccine efficacy reduces upon progression from *M tuberculosis* infection to subclinical tuberculosis	Lower global impact
No self-resolution of subclinical tuberculosis to *M tuberculosis* infection	Lower global impact

Table 2: **Implications of wrong key assumptions about subclinical tuberculosis in the current model on the model-estimated impact**

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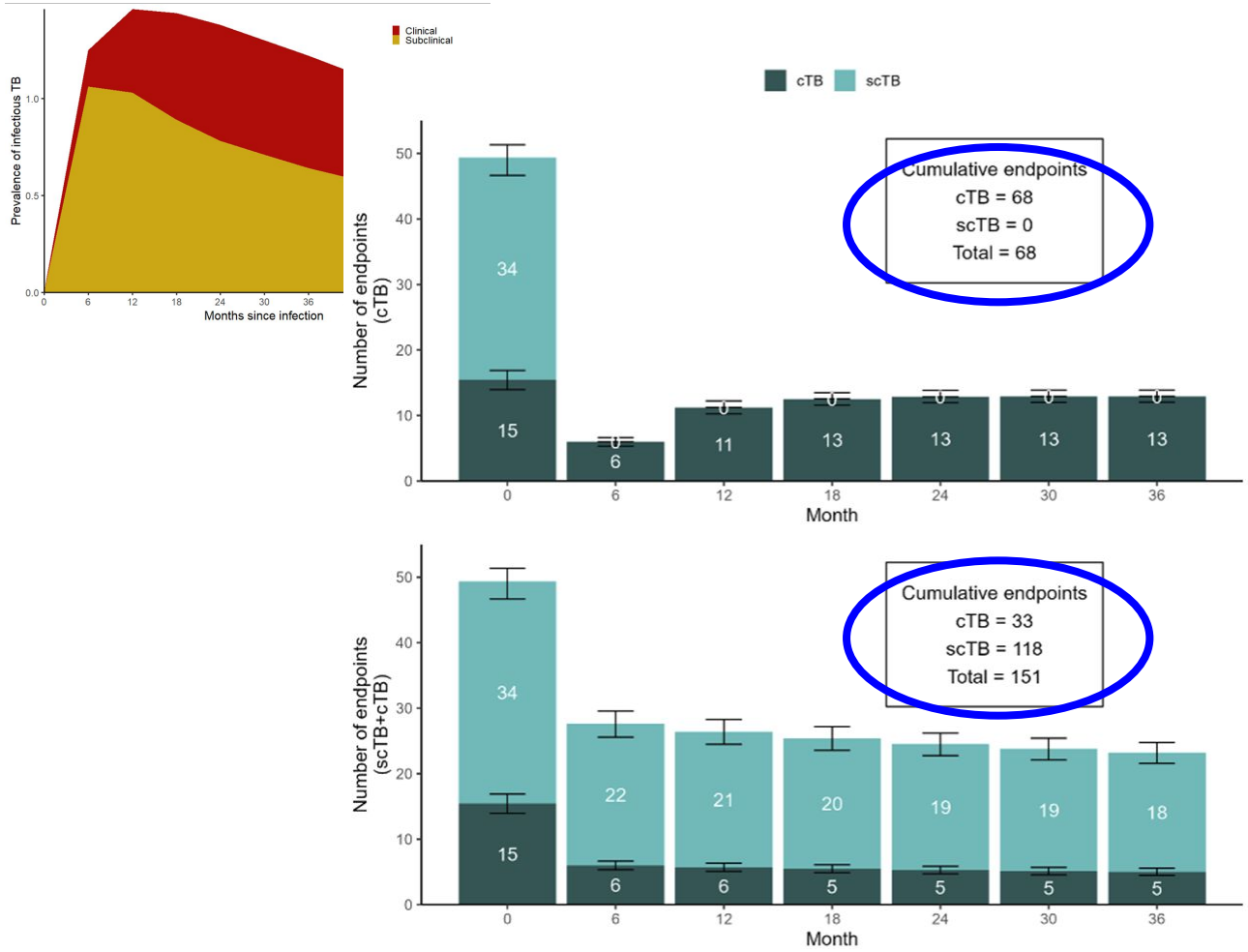
What do we need to know to consider using infectious subclinical TB as a trial endpoint for vaccine licensure?

- Given subclinical TB may occur more frequently than clinical TB
- If we could use for vaccine licensure, might make licensure trials smaller or quicker?
  - Preliminary modelling >>
  - May get ~2x endpoints
- But, would regulators accept infectious scTB for vaccine licensure?

Trial endpoints?



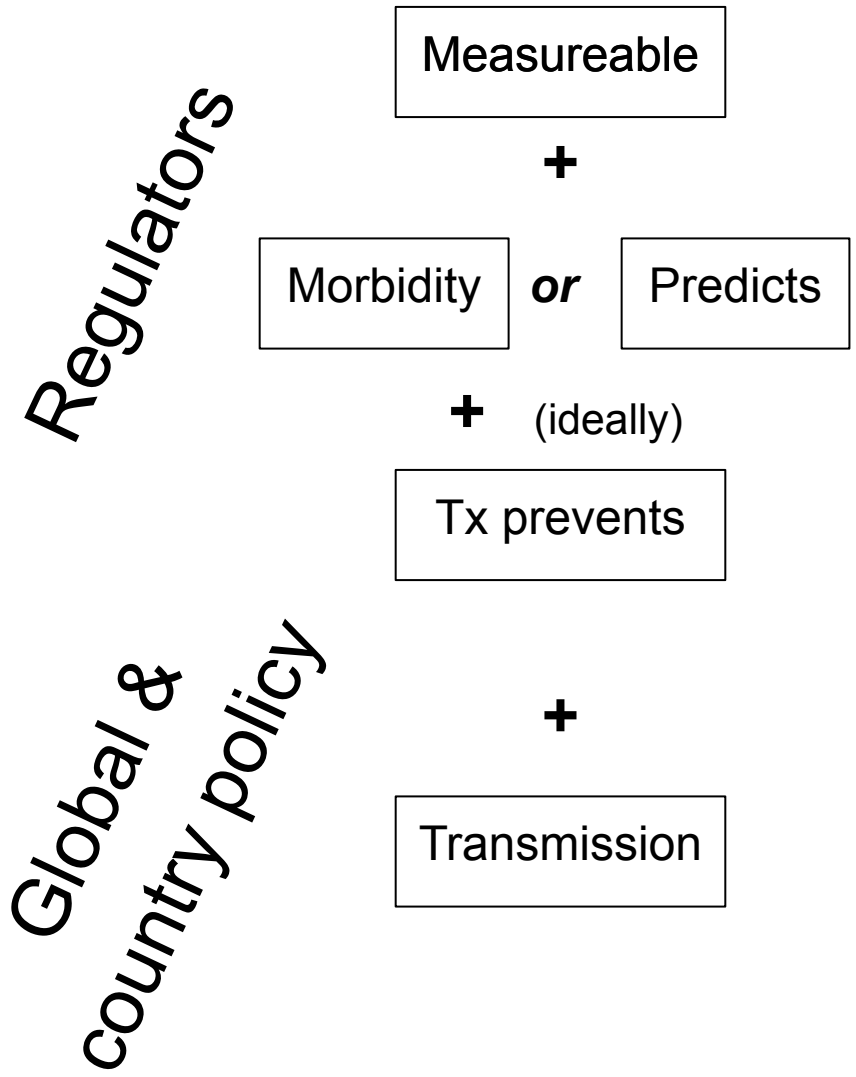
Horton PNAS 2023 ***Endpoint courtesy Dr Katherine Horton, LSHTM, unpublished,.Please do not cite*** *

Start with the end in mind…

We need to know

- Regulators perspective
- Global & country policy makers perspective

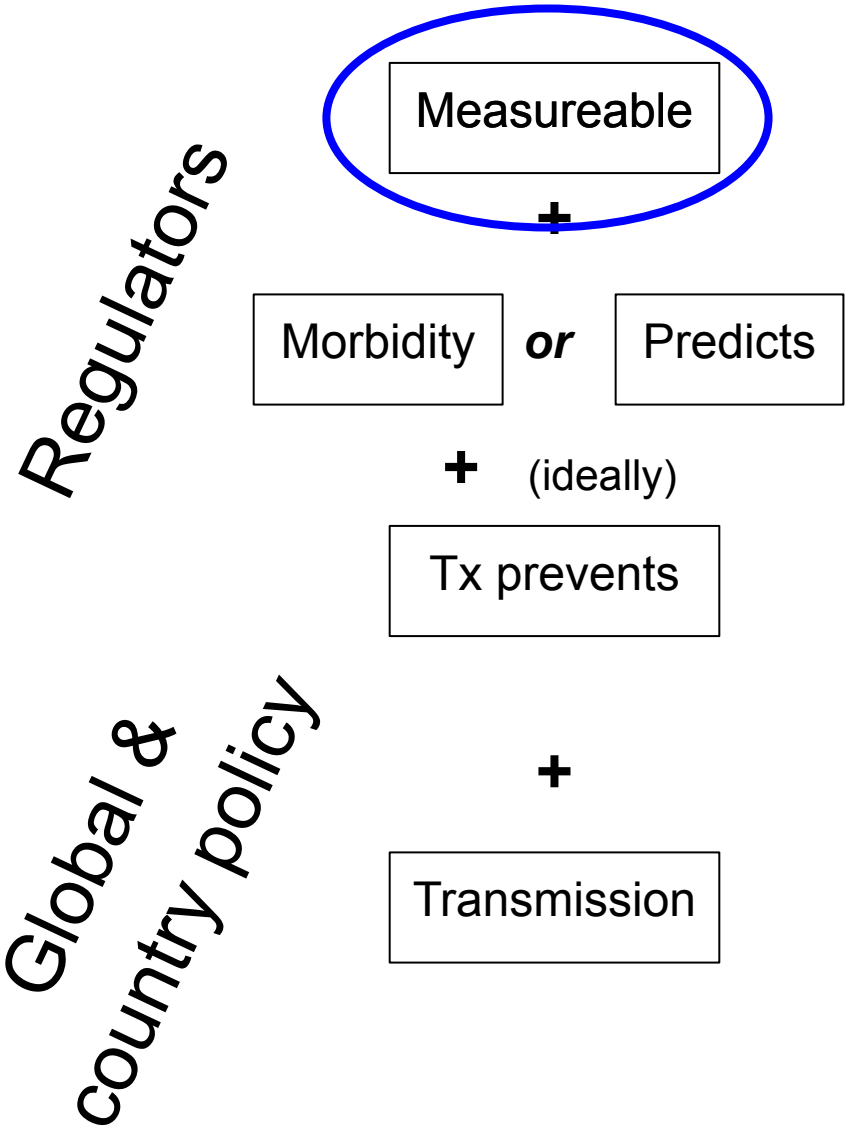
Start with the end in mind…



2 key perspectives

- Regulators
- Global & country policy makers

Regulator need: Subclinical TB is well defined and measurable



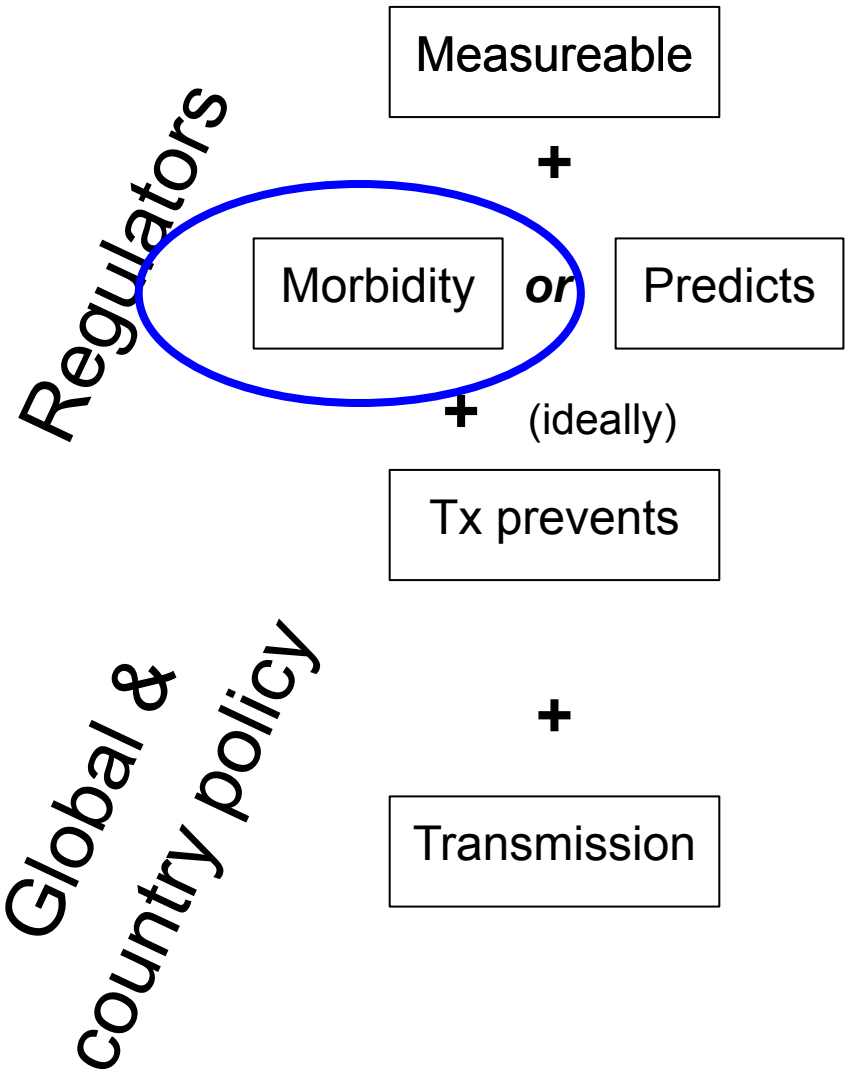
For regulators - **Individual** benefit/risk

- **Needs to be well defined and measurable**

Current Knowledge:

- Infectious scTB already widely recognised and in terms of diagnostics, similar to cTB - just absence of positive symptom screen

Regulator need: Subclinical TB causes sig. heath burden



AND,

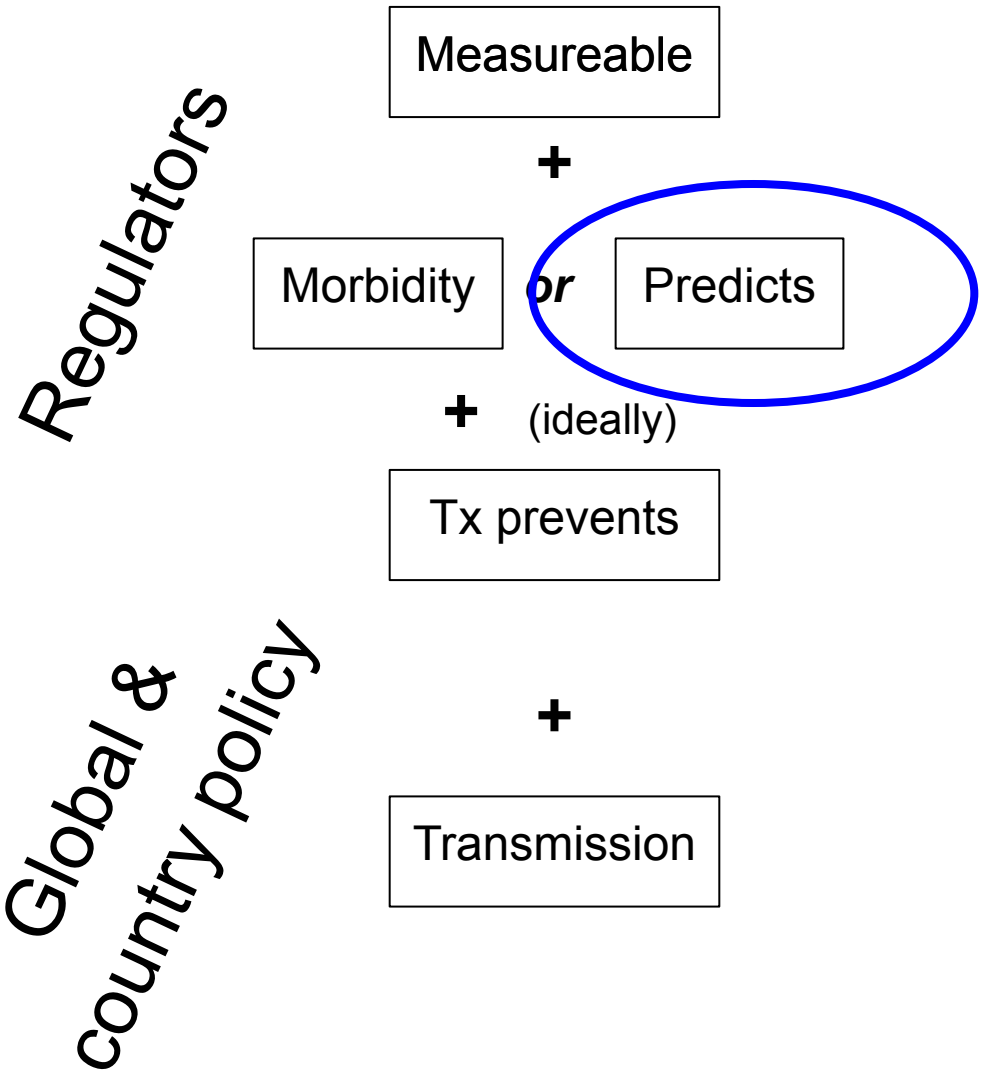
Would need to be *recognised condition for which medical action would be taken* =>

EITHER…

- **Has significant health burden for individual**
  - (rationale for cTB currently)

OR…

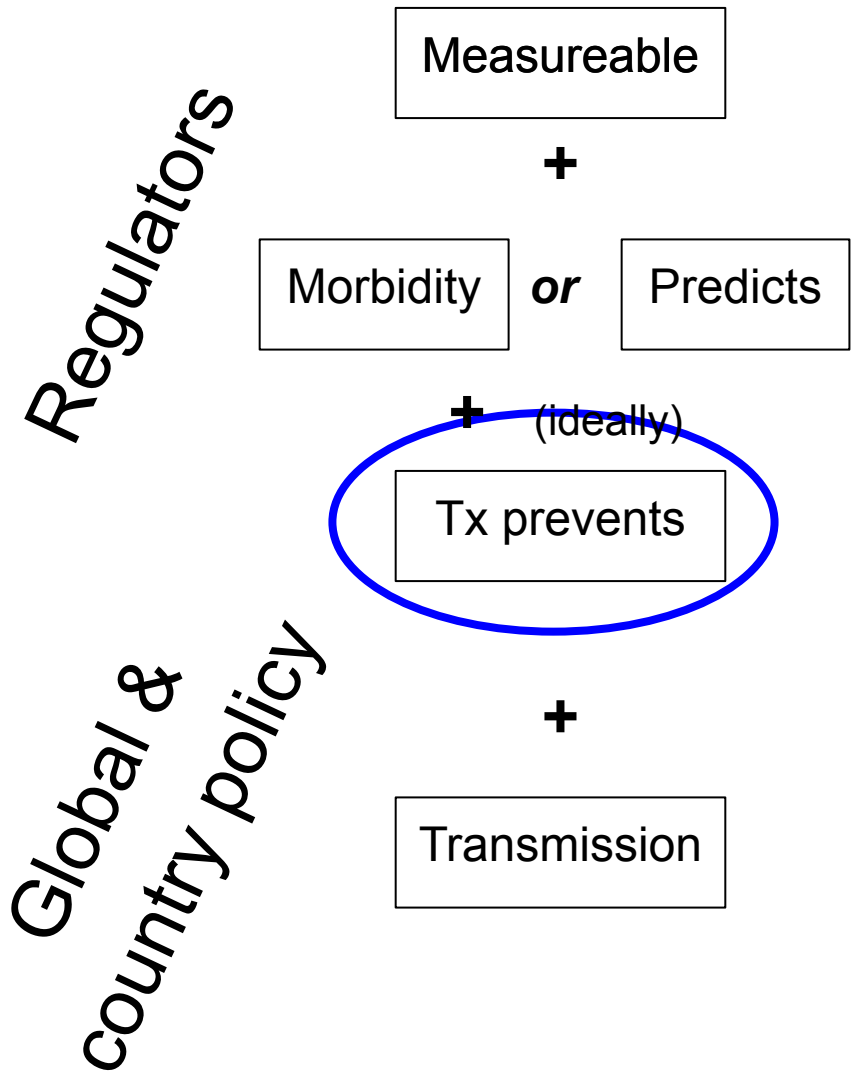
Regulator need: Or, subclinical TB predicts clinical TB



OR…

- **Reliably predicts cTB**
  - (rationale for CIN2/3 to license HPV vaccines at ~30%)

Regulator need: Subclinical TB treatment prevents clinical TB



AND (ideally)...

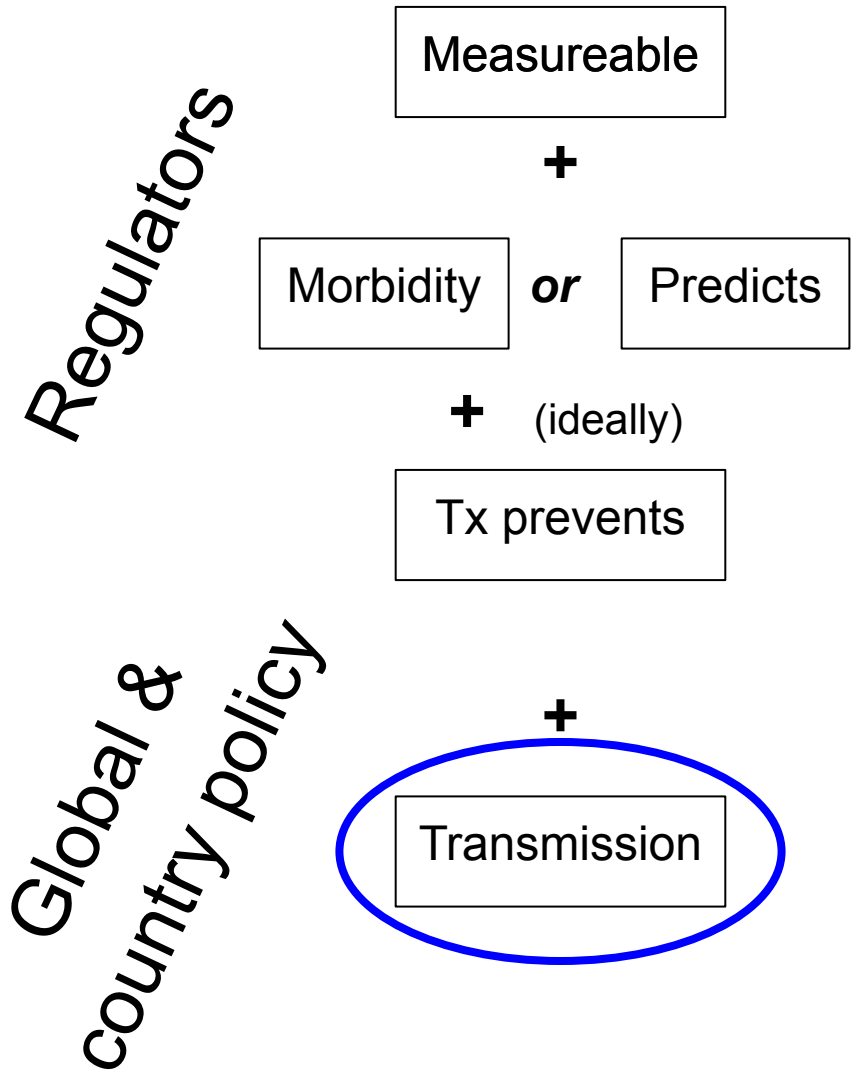
Would help if we can show **treatment of scTB prevents cTB**

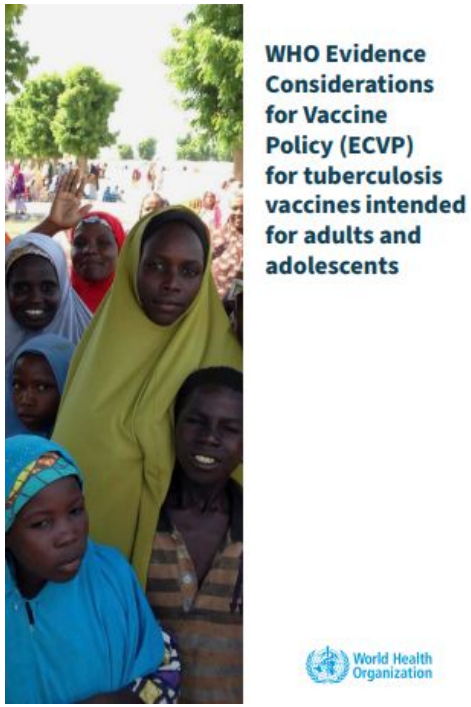
- (known for HPV)

But - current knowledge:

- **No** strong empirical data on scTB morbidity, prediction or prevention
- Modelling estimates

Policy folks need: See EVCP eg transmission





Have good idea what global & country policy perspective is:

- **WHO evidence considerations for Vaccine Policy for TB**
- **GAVI guidlines**
- **Chatting to NITAG reps**

- Consistent with their wider perspective of **overall population benefit**, includes evidence on
- Transmission from scTB

But - current knowledge:

- **No** empirical data
- Modelling estimates

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These research gaps are fillable….

Design	Morbidity	Prediction of cTB	Clinical benefit of preventing subclinical TB	Transmission potential of scTB
Systematic reviews and meta-analyses	X	X	X	X
Retrospective secondary analysis of existing data	X	X	X	
Cross-sectionally in a symptom-agnostic community based screening study (including prevalence surveys)	X			
Prospective cohort (nested or RCT)	X	X	X	
Natural history studies	X			
Cluster randomised trial of treatment or no treatment of scTB		X	X	
Prospective follow-up of HHCs without TB-compatible symptoms randomised to continued follow-up or TB investigations 3-6 monthly	X	X		
Symptom-based vs. symptom-agnostic ACF randomised trial	X			X

- **Very time limited** opportunity to collect progression and regression data on scTB <> cTB, from control arm of M72 trial
  - Every month of delay loses endpoints and power
  - May become unethical soon
- Also important for global TB care and prevention guidelines - when does individual benefits of treating scTB outweigh side effects, costs, inconvenience…?

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- **Much much more…**

Much, much more…

- TB Vx trials in an era of changing TPT usage
- Pros and cons of inviting prisoners to participate in TB vaccine trials

- Pros and cons of including children in TB Vx trial

- Should we primarily be recruiting IGRA+s for TB vaccine trials?
- Organisation going on in introduction/implementation preparedness space

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