KNCV TUBERCULOSIS FOUNDATION

To eliminate TB

Guidance document:

How to evaluate TB prediction tests to inform WHO endorsement?

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‘Wish list’ for a TB prediction test

Intended use:

- Test that can be used to predict risk of progression to active TB from TB infection (within next 2 years)

- Low probability of being positive (high **N**umber **N**eeded to **S**creen)
- But if positive, high probability of disease (low **N**umber **N**eeded to **T**reat)
- Largely independent of population tested
- Predicts only that disease can be expected within a short time period

Our expectations of a TB prediction test

Test	Population					
	Unexposed	LTBI	LTBI treated	Progressors to active TB	Active TB	TB treated
LTBI test (TST or IGRA)	-	+	+/-	+	(+)	+/-
TB prediction test	-	-	-	+	+/-	-
Active TB test	-	-	-	-	+	-

Phases of test evaluation

Analytical phase

- 'Laboratory' phase done by test developers/manufacturers before evaluating the test in the field.
- Test done on sample repositories/easy to get samples

- Variability
- Repeatability
- Robustness
- ….

- OUTSIDE SCOPE OF DOCUMENT

Field evaluation

- 'Clinical' studies done in the field (outside laboratory) together with partners other than test developers/manufacturers
- Test done in intended target population

- Accuracy (sens & spec)
- Predictive ability (PPV, NPV, NNS, NNT, RR, IRR)
- Patient & public health impact (effectiveness, cost-effectiveness)

- WITHIN SCOPE OF DOCUMENT

WHO endorsement – GRADE process

- GRADE approach adopted by WHO for guideline development
- Summary of evidence is generated
  - From SR around pre-defined PICO questions
- Quality of the evidence assessed
  - Using QUADAS tool –risk of bias, directness, consistency, precision, publication bias
- Consensus reached by panel about recommendations & strength based on
  - Quality of supporting evidence
  - Balance between desirable & undesirable consequences
  - Costs
  - Patient important outcomes

Study questions for WHO endorsement

I Questions related to the predictive ability of the test

1. What is the test accuracy (sensitivity & specificity)?
2. What is the PPV and NPV and corresponding NNS and NNT?
3. What is the risk ratio (RR)?
4. What is the IR and IRR?

! *Predictive ability for **incident TB** in a **prespecified period***

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! *Predictive ability for **incident TB** in a **prespecified period***

II Questions related to the public health impact of the test

1. What is the effectiveness of the test for reducing incident TB when combined with preventive treatment?
2. Is the test combined with preventive treatment a cost-effective strategy to reduce incident TB?
3. Is the test combined with preventive treatment more cost effective than alternative LTBI test and treat strategies (using TST and/or IGRA)?
4. What is the effect of the test combined with preventive treatment on the occurrence of side effects, compared to alternative?
5. What is effect of the test combined with treatment on uptake and acceptance of preventive treatment?
6. Which treatment regimen (mono- or multidrug) is most effective when used for individuals with a positive test?

Study questions for WHO endorsement

I Questions related to the predictive ability of the test

1. What is the test accuracy (sensitivity & specificity)?
2. What is the PPV and NPV and corresponding NNS and NNT?
3. What is the relative risk (RR)?
4. What is the IR and IRR?

! *Predictive ability for **incident TB** in a **prespecified period***

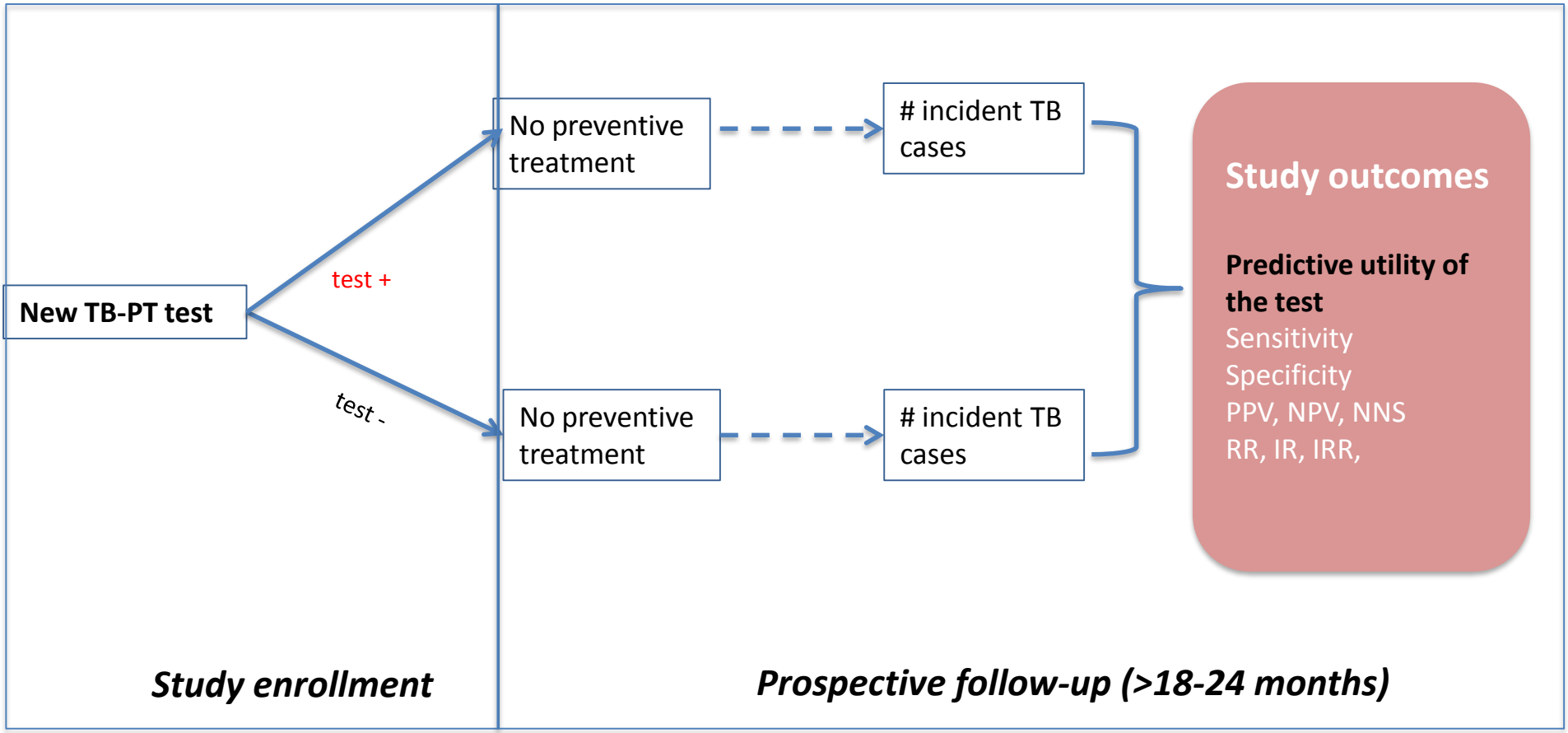
Study designs for measuring predictive ability

OBSERVATION STUDY

- Longitudinal prospective cohort study
- Nested-case control study

→ follow-up needed to find incident TB cases

Example study design for evaluating predictive ability of test



Study populations

- Conduct study in population of intended use
  - People at risk of being infected & at risk of disease progression
  - → Unbiased estimate
  - → Study efficiency: sufficient number of incident TB cases

- ***Studies aiming to assess predictive ability of the test, need to evaluate individuals that do not receive preventive treatment to obtain unbiased estimates***

- Possible study populations:
  - MDR-contacts in countries that currently not recommend PT
  - Individuals in placebo arm of preventive treatment trials / post-exposure vaccine trials
  - Previously treated TB patients
  - HIV-negative adult contacts (in high incidence countries that do not routinely test & treat this group)

Study methods

Baseline

- Exclude presence of TB in accordance with current guidelines (not more rigorous!)
- Conduct the test (at least once at baseline, but may be repeated at additional time points)

Follow-up

- Active ascertainment of incident TB
  - Alternative: passive follow-up through robust registries and close-out visit at end of study
- Similar ascertainment in test positives and test negatives
- Blinded TB ascertainment (with regard to initial test result)
- Limit cohort attrition as much as possible (i.e. though limiting length of follow-up)
- Primary endpoint: Bacteriological confirmed diagnosis of incident TB vs symptom-free, negative bacteriological tests at study close-out.

Design challenge	LIC	HIC	Potential effect	Possible mitigation strategy
Ongoing transmission	NA	X	Bias of accuracy estimates	• Use shorter follow-up time (e.g. 6 months) • Focus on populations with a lower risk of exposure to ongoing transmission in community (e.g. young children)
Use of preventive therapy	X for majority of suitable study populations	X for some study populations (not all)	Bias of accuracy estimates (if included) or limiting enrolment (if excluded)	• Choose study population where IPT is not given (MDR-contacts, ineligible per country guidelines, declining IPT, non-adherent to IPT) • Include individuals assigned to non-intervention arm in RCT of e.g. TB preventive therapy or post-exposure vaccines trials • RCT, comparing LTBI test and treat strategy with new TB-PT test and treat strategy

Design challenge	LIC	HIC	Potential effect	Possible mitigation strategy
Progression rare	X	X	Large sample size needed	• Focus on highest risk groups
Follow-up time long	X	X	Long study duration, loss to follow-up (potential for new infection as discussed above)	• Use shorter follow-up time (e.g. 12 months) or analyze results for different lengths of follow-up (6, 12, 18 months) • Compare RR and IRR to determine how differential loss to follow-up may have affected study outcomes

Additional analysis

Special populations of interest

- Children
- People living with HIV
- Individuals with other forms of immunodeficiency
- Diabetic patients
- Individuals with malnutrition
- Patients with incident extra-pulmonary TB
- Patients with a history of prior TB treatment
- Patients with a history of prior LTBI treatment

Additional variables of interest

- Demographic (age, sex, country)
- BCG status
- TST/IGRA status

Exploratory analysis for

- Assess predictive ability for different thresholds
- Assess predictive ability in combination with other variables
- Assess predictive ability for different time point till disease progression (3 mo, 6 mo, 12mo, 18 mo)

Study questions related to public health impact

II Questions related to the public health impact of the test

1. What is the **effectiveness** of the test for reducing incident TB when combined with preventive treatment?
2. Is the test combined with preventive treatment a **cost-effective** strategy to reduce incident TB?
3. Is the test combined with preventive treatment **more cost effective than alternative** LTBI test and treat strategies (using TST and/or IGRA)?
4. What is the effect of the test combined with preventive treatment on the **occurrence of side effects**, compared to alternative?
5. What is effect of the test combined with treatment on **uptake and acceptance** of preventive treatment?
6. Which **treatment regimen (mono- or multidrug)** is most effective when used for individuals with a positive test?

Study design for evaluating public health impact

INTERVENTION STUDY

- Preferably comparative studies with randomized designs (individual/cluster)
  - Limit bias caused by confounders (e.g age, BCG status, level of exposure, HIV-status, immune status, risk of re-exposure, …)
  - RCTs judged as "highest" level of evidence (in GRADE process)

- Alternative: before-after studies (e.g. stepped-wedge, pre-post cohort studies)
  - More prone to bias

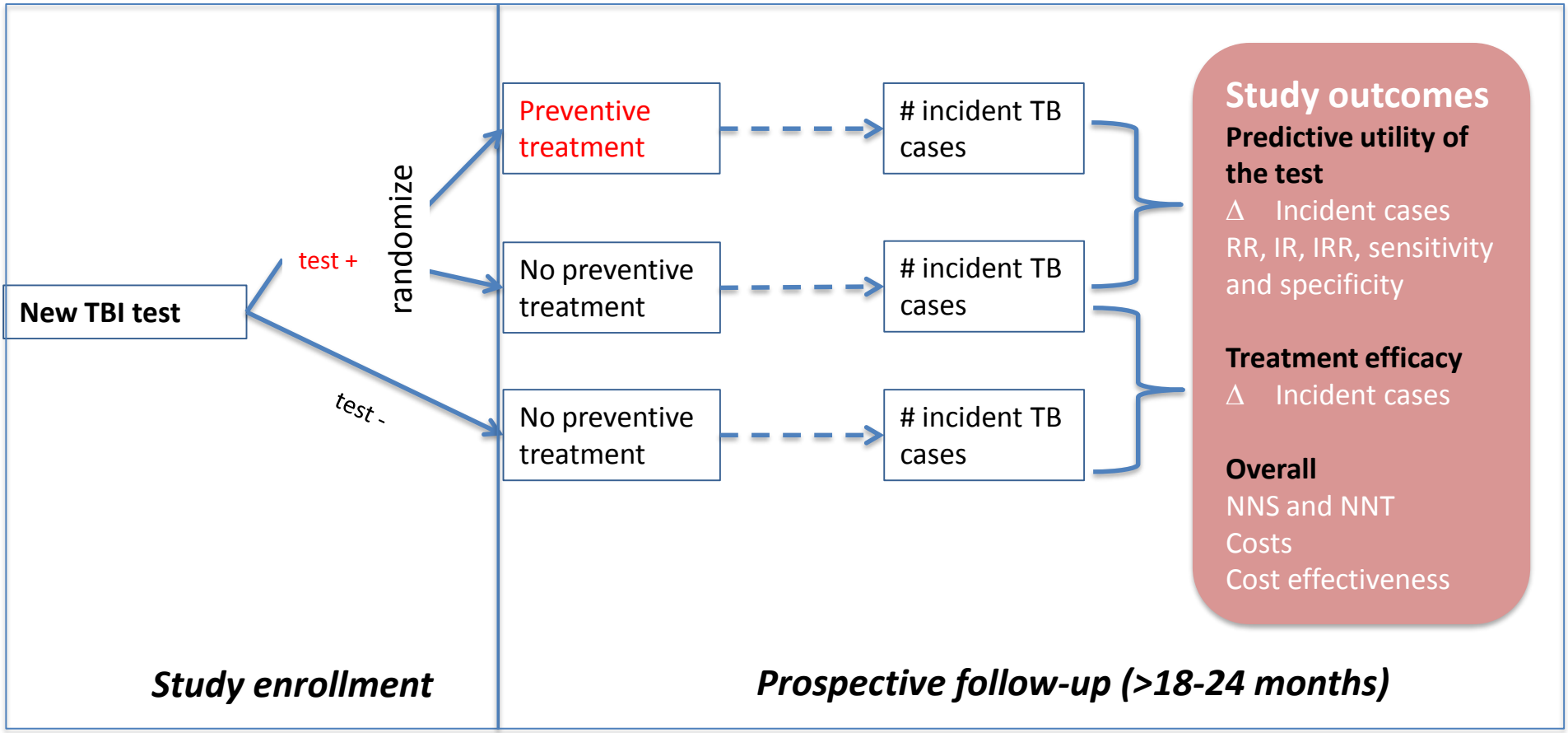
Study populations

- Conduct study in population of intended use
  - People at risk of being infected & at risk of disease progression
  - Could be those currently screened and treated for LTBI

- Conduct studies in sites of intended use
  - 'Real world' evaluation
  - Both in high- and low- incidence settings

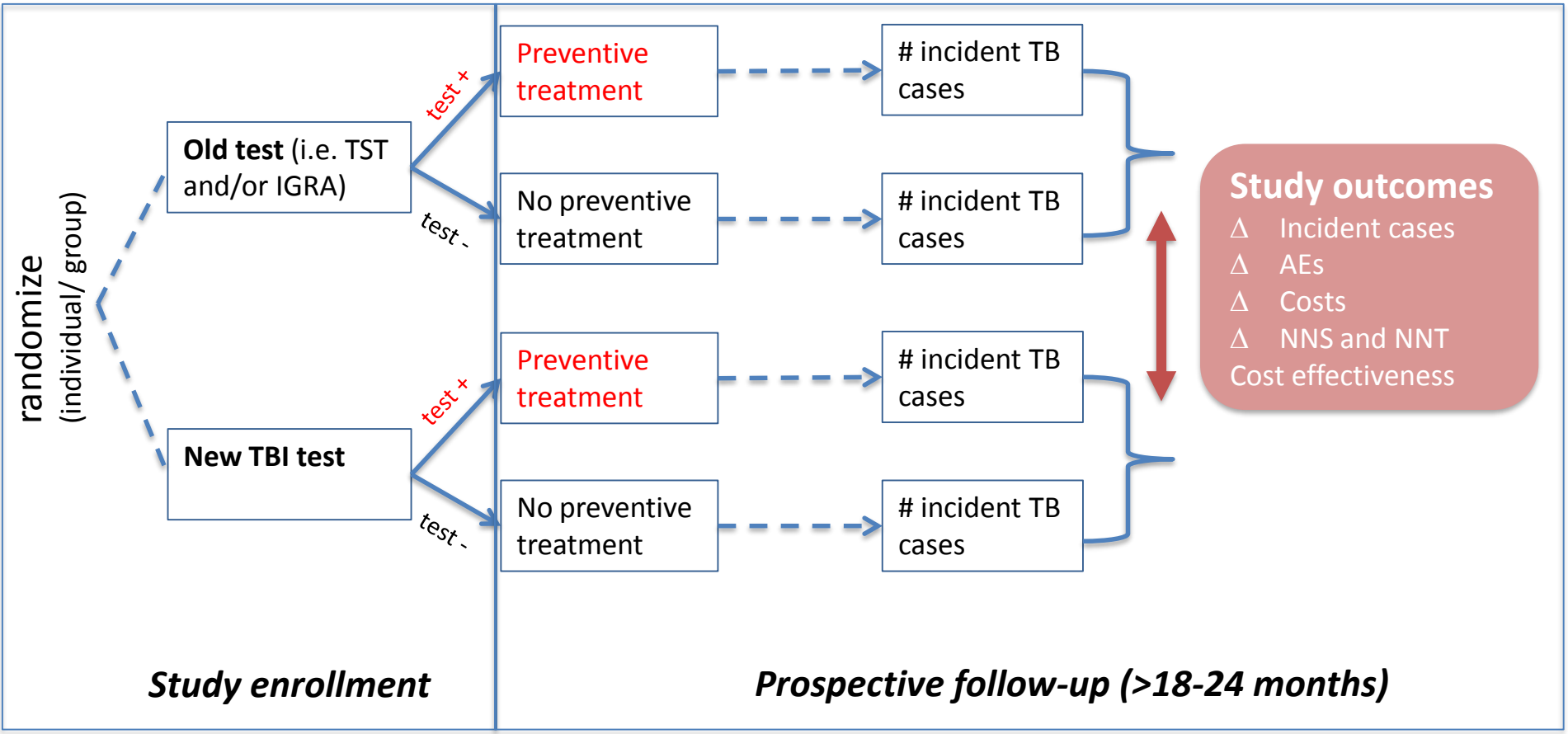
- ***Studies aiming to assess public health impact of the test, may compare the new test & treat strategy with current practice (e.g. LTBI testing & treating or no alternative test)***

Example study design in populations that are currently <u>not</u> tested for LTBI



Source:
Adjusted from M. Hatherill, Union Conference 2015, NDWG symposium
Design of CORTIS trial

Example study design: evaluating public health impact in populations that are currently tested for LTBI tests



Study methods

Baseline

- Exclude presence of TB in accordance with current guidelines (not more rigorous!)
- Randomize individuals
- Conduct the test (dependent on arm)
- Make treatment decision based on test result

Follow-up

- Similar follow-up for test positive, test negatives, those offered treatment and those not on treatment → avoid cohort attrition
- Preferably active follow-up continuing after completion of treatment
- Ascertainment of incident TB according to current guidelines & practice

Outcomes:

- Difference in number of incident TB cases (effectiveness), NNS, NNT
- Difference in cost of strategy (→ Cost-effectiveness)
- Occurrence of AEs, adherence to treatment

Additional analysis

Special populations of interest

- Children
- People living with HIV
- Individuals with other forms of immunodeficiency
- Diabetic patients
- Individuals with malnutrition
- Patients with incident extra-pulmonary TB
- Patients with a history of prior TB treatment
- Patients with a history of prior LTBI treatment

Exploratory analysis

- Budget implications for scaling up intervention
- Modelling of most effective strategy

Additional variables of interest

- Demographic (age, sex, country)
- BCG status
- TST/IGRA status

Main discussion points on predictive ability studies

- Can we find sufficient study populations and setting to conduct studies to assess predictive ability of novel prediction test?

- How long should study duration be in low- and in high- incidence settings?

- Repeated measurements of the test during follow-up?

Hopefully solved already this morning:

- Which groups belong to the target population of the test?
  - If same as current risk groups recommended for LTBI screening, the first set of research questions might be hard to assess in countries that follow current LTBI screening guideline (e.g. high- and middle-upper income countries)

- How far ahead should test predict future development of TB?

  → Current TPP states 2 years. Should this be shorter?

Main discussion points for public health evaluation studies

- Which target populations?
  - In low incidence settings, will novel prediction test be an alternative for current LTBI tests? Or do we foresee a different testing strategy?
- How long should follow-up last after treatment completion to evaluate public health impact?
- Should we do additional test after LTBI treatment?

Thank
You
Merci
Gracias
Danke
Spacibo
Hvala
Arigatô
KamSahHamnida
Xièxie
Mèsi
Grazie
Chokrane
Kiitos
Dziakuju
Mauruuru
GratiasAgimus
GratiasAgo
Ačiū
Dankie
Tak
TänanVäga
Motashakkeram
KopKhunKha
Gracie
CámOn
Multumesc
Saha
Salamat
Obrigado
Bayarlalaa
Nirringrazzjak
Efharisto
Faleminderit
Gràcies
NajisTuke
TerimaKasih
Rahmat
Blagodaram
ThintKo
Buznyg
WaadMahadsantahay
TapadhLeat
Köszönöm
Murakoze
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Grazzi
Tanemirt
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Taiku
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Matondo
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Grandmercé
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KhobChaiDeu
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KeYaLeboha
Vinaka
TesekkurEdirem
Shukriya
Buznyg
TapadhLeibh
AsanteSana
Waita
FaafetaiLava
Ngiyabonga
Enkosi
M-Sapo
Bedankt
Zikomo
Dhanyavaad
Trugarez
Aabhar
TeşekkurEderim
Sobodi
AabhariAahe
Nouari
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KopKhunKrap
Tau
Nanni
Trugere
Misaotra
Akpe
Tanmirt
MaloTeOfa
Graçie
Dankie
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