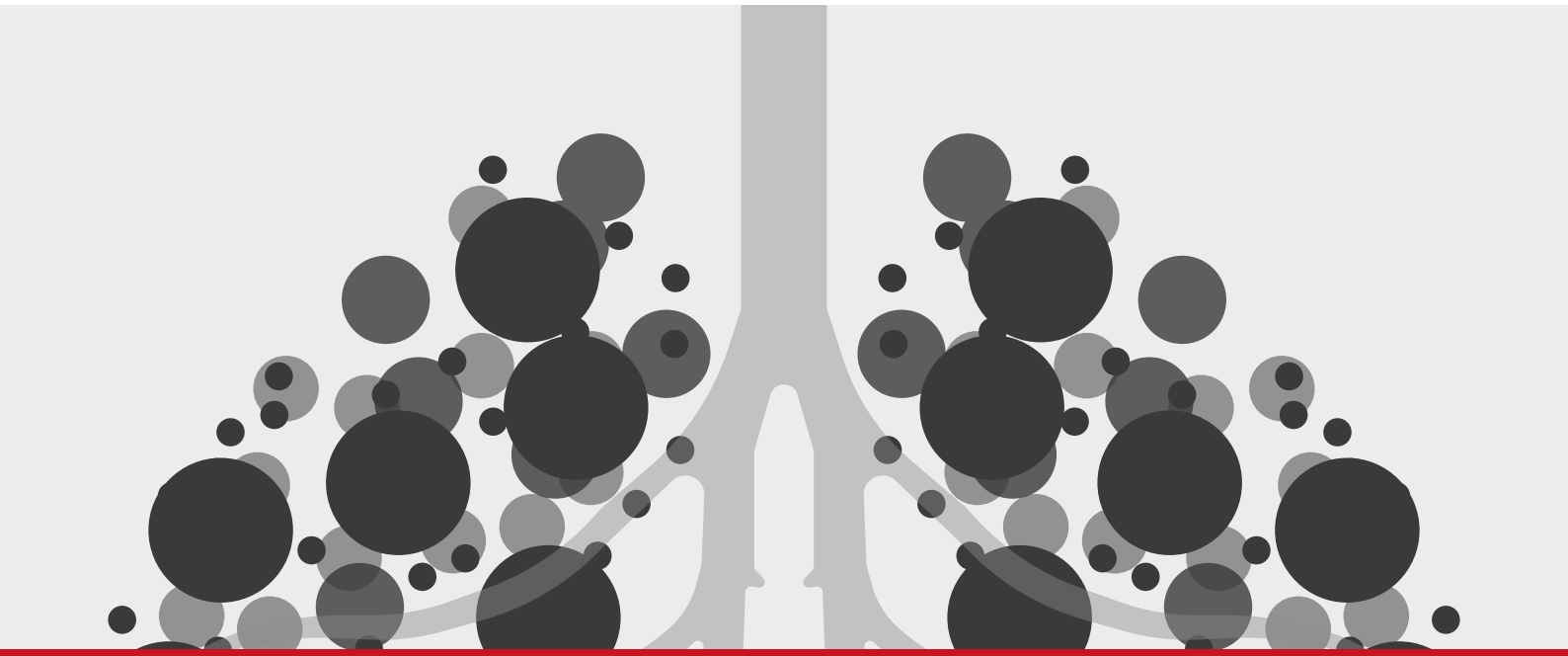
Stop TB Partnership

New Diagnostics Working Group

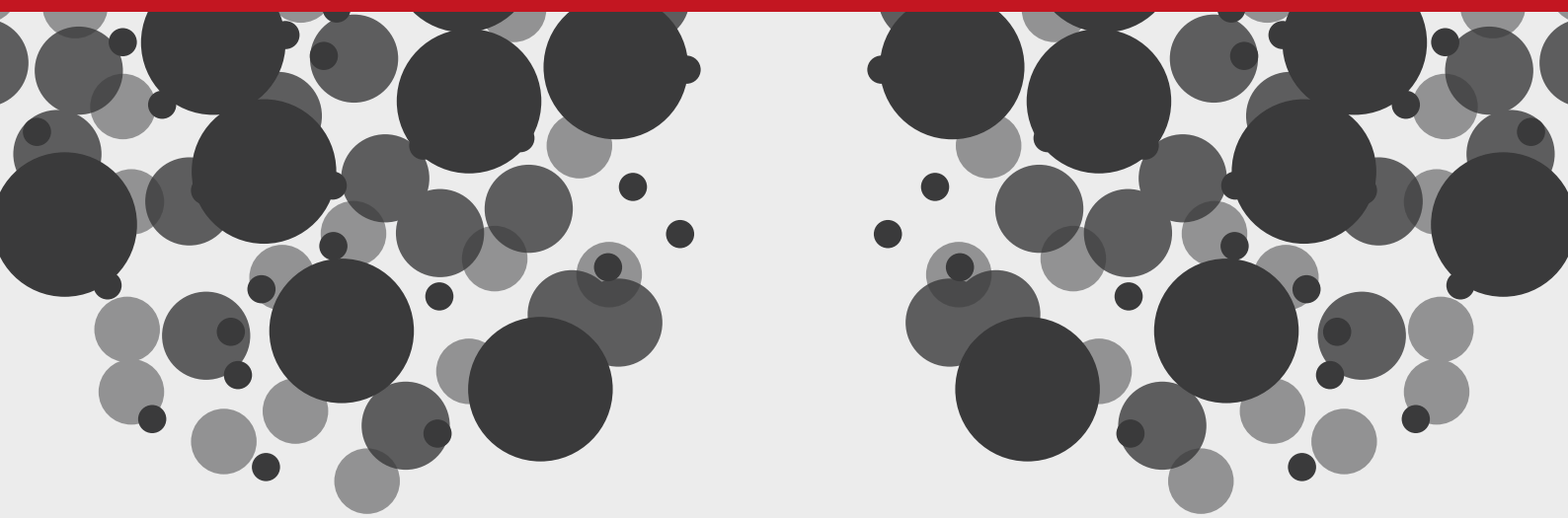


Meeting Report

EXECUTIVE SUMMARY

Second Expert Workshop

on the development of tests for progression of latent tuberculosis infection (LTBI) to active disease.



1st July 2016

Organized by the New Diagnostics Working Group
Hosted by San Raffaele Hospital, Milan, Italy

Introduction

Among the key components of the first pillar of the WHO END TB strategy (1) is preventive treatment of persons at high risk of developing active disease. A direct measurement tool for *M. tuberculosis* (Mtb) infection in humans is currently unavailable. Research into cost-effective diagnostic tests with improved performance and predictive value for reactivation TB is needed (2).

The Task Force on latent TB infection (LTBI) of the New Diagnostics Working Group (NDWG) and its partners met in Milan, Italy on 1st July 2016 to gather expert advice.

Objectives of the NDWG LTBI Task Force

Conception

new evidence on the nature and significance of LTBI and its relevant implications on the conceptualization of diagnostics

TPP

development of the Target Product Profile (TPP) for a test of progression of LTBI

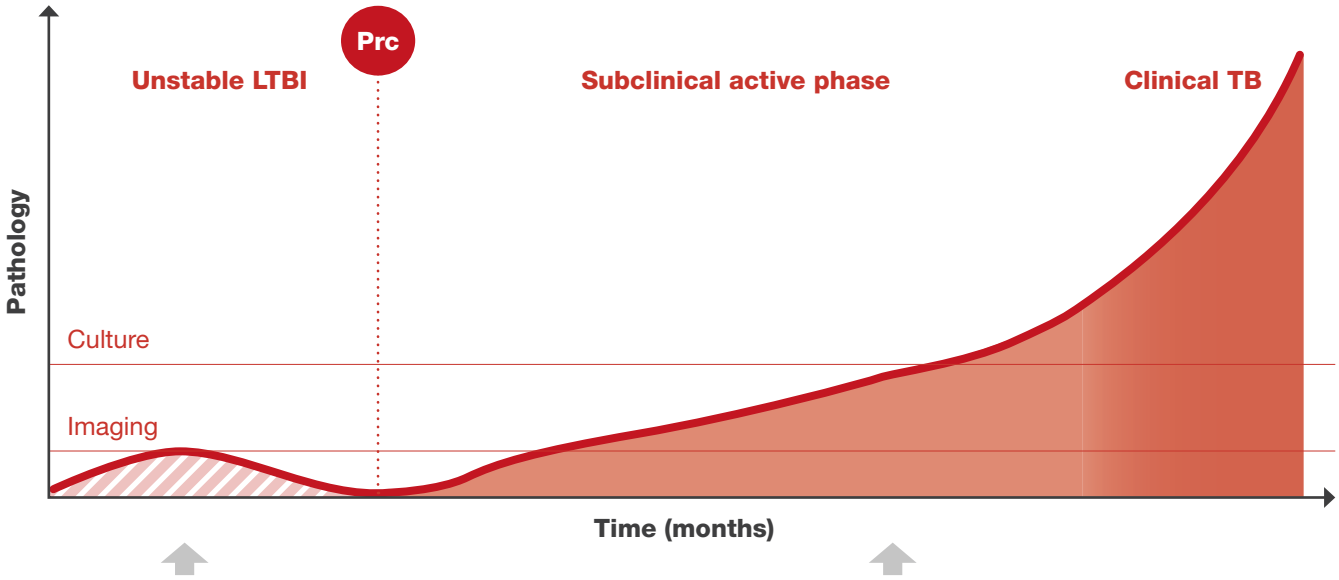
Guide for evaluation

development of guidance to optimized study design that will produce data for policy development

Nature and significance of LTBI and limitations of diagnostic tests

Current diagnostic tests – interferon gamma release assays (IGRAs) and the tuberculin skin test (TST) – identify historical exposure and immune sensitization to Mtb. Results often remain positive post-infection, either spontaneously or with preventive treatment. They have a poor positive predictive value (PPV) for predicting active TB, resulting in a very high 'number need to treat' (NNT) to prevent one TB case through preventive therapy.

What tests are needed – Two novel options



Predicts that disease cannot happen because there is no persistent infection

"Persistent infection test"

Predicts that disease occurs because it has already started...

"Incipient TB test"

Tests for persistent infection

The first type should identify those with persistent infection (i.e. results are negative after infection has cleared). Such a test will likely not identify those at greatest risk of progressing to TB due to a low PPV, but could be used to single out those at high risk of progression to severe disease, such as patients with HIV infection, those awaiting anti-TNF-alpha treatment, and infants. These are tests for persistent infection.

Tests for incipient disease

The second type should detect that the disease is active while the patient is still asymptomatic. It would be highly predictive for clinical disease, in particular for those recently exposed. These are defined as tests for incipient disease. The recent 16-transcript disease risk signature recently described by Zak et al (3) is an example of a biomarker that may fulfil this role. The incipient TB test should have a semi-quantitative read-out and might potentially revert to negative after treatment.

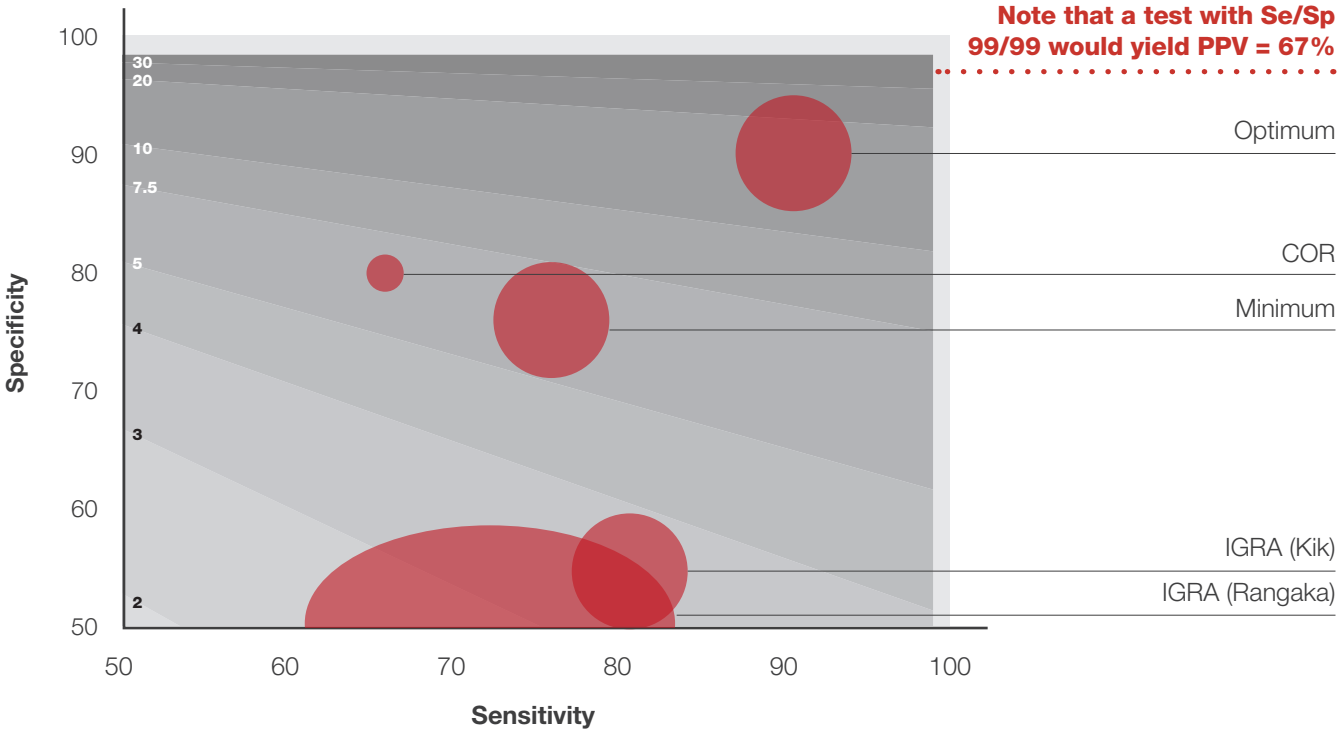
Target product profile for a test of progression

The reasonable time horizon for a test of incipient TB should be prediction of future progression to active TB within two years, taking into account that ~60% of progression occurs in this timeframe (~45% in year one). Acceptable PPV and NNT values – as identified by patients, clinicians, and policy makers – were proposed. Minimal performance is represented by an increase of the PPV by a factor of ~2 compared to IGRAs. Optimal performance is represented by an increase of the PPV by ~5 compared to IGRAs.

The test should be developed with combinations of sensitivity/specificity that are compatible with these values. Expectations for accuracy should not be the same for a predictive test as they are for a diagnostic test: even with a very high sensibility and specificity (99%), a low PPV would be reached (67%). The specificity threshold for candidate tests for incipient TB should be 50%.

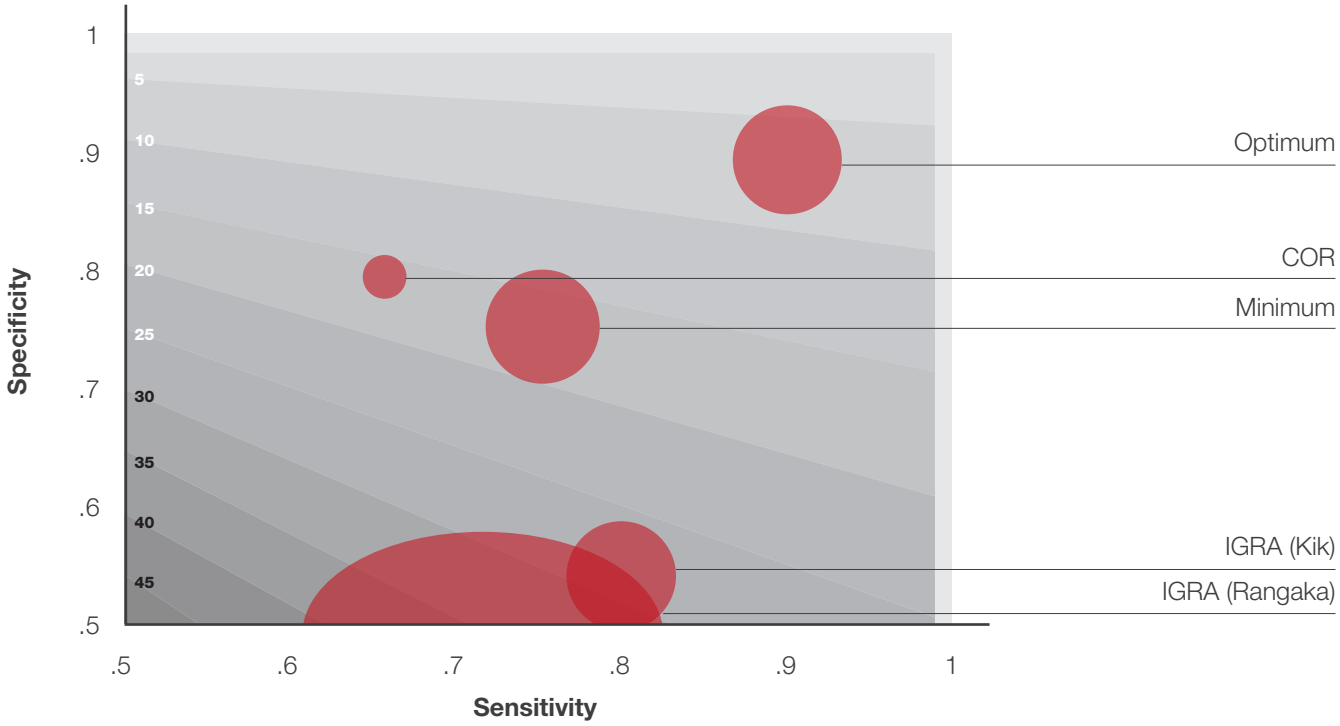
PPV in a given setting should be considered as an important parameter to guide decisions on implementation. Different country programmes will have differing preferences in the trade-off between sensitivity and specificity – e.g. re-testing of individuals with an initial negative result could be an attractive option in programmes that aim to maximize sensitivity.

‘Positive Predictive Value’ according to Sens/Spec for risk of progression



2% Cumulative incidence

‘Number Needed to Test & Treat’ according to Sens/Spec for risk of progression



2% Cumulative incidence

Guidance to optimized study design

To be consistent with the WHO GRADE process for endorsement of a diagnostic test, the test evaluation programme should mainly establish its ability to predict active TB and its health impact from both patient and community perspectives.

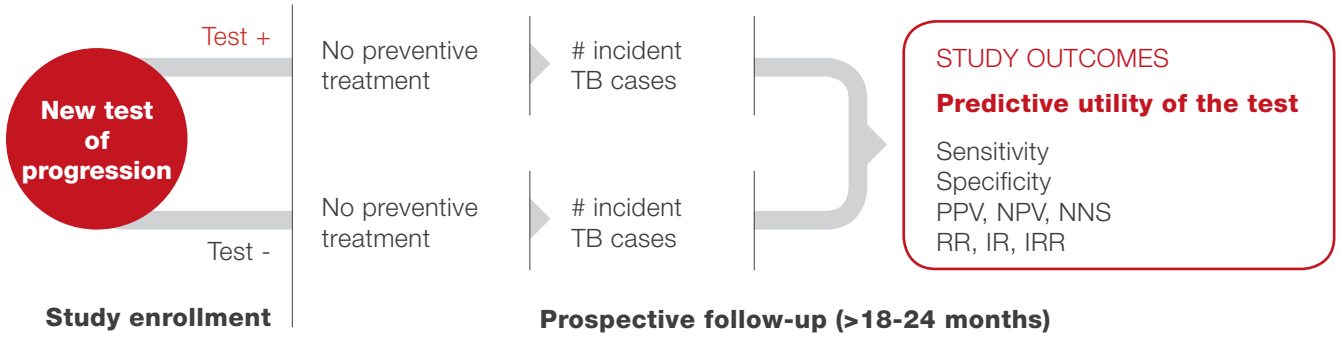
A) Assessing predictive ability

The study population should be represented by individuals at risk of being infected and at risk of disease progression and who are observed over time. Ideally, individuals who do not receive preventive treatment would be included in order to avoid biased results (i.e. contacts of MDR-TB patients and other contacts that do not accept the offer of preventive treatment).

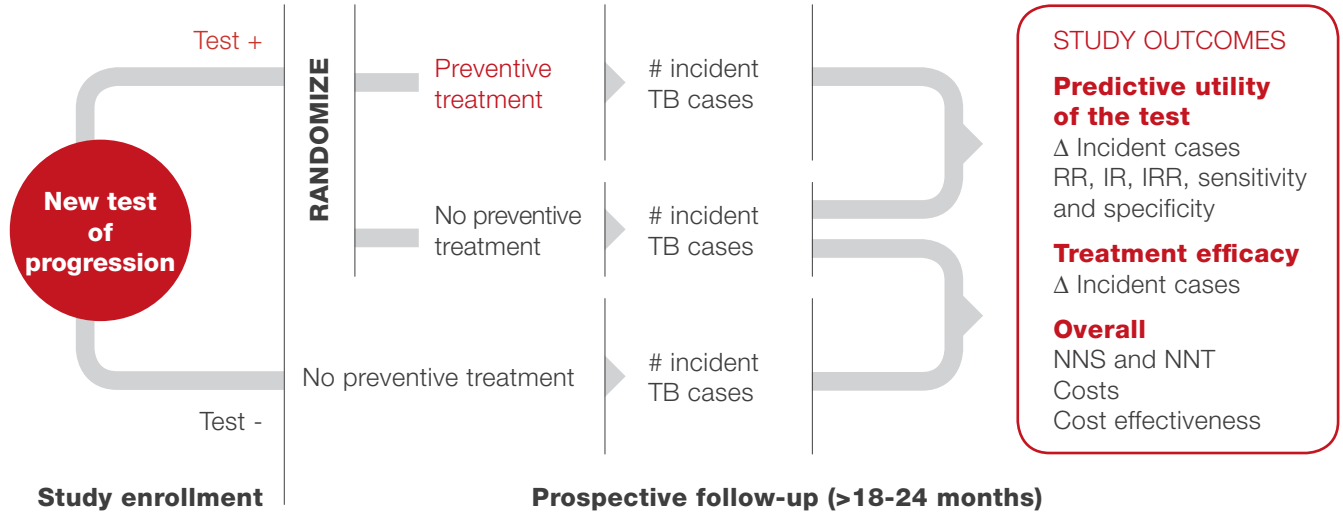
B) Assessing public health impact

Comparative, randomized intervention studies around the public health impact should assess efficacy, cost-effectiveness, treatment adherence, and side effects. The comparator is represented by standard practice (i.e. test and treat strategy based on TST and/or IGRA or no LTBI testing and treating at all).

Example of study design for evaluating predictive ability of the test

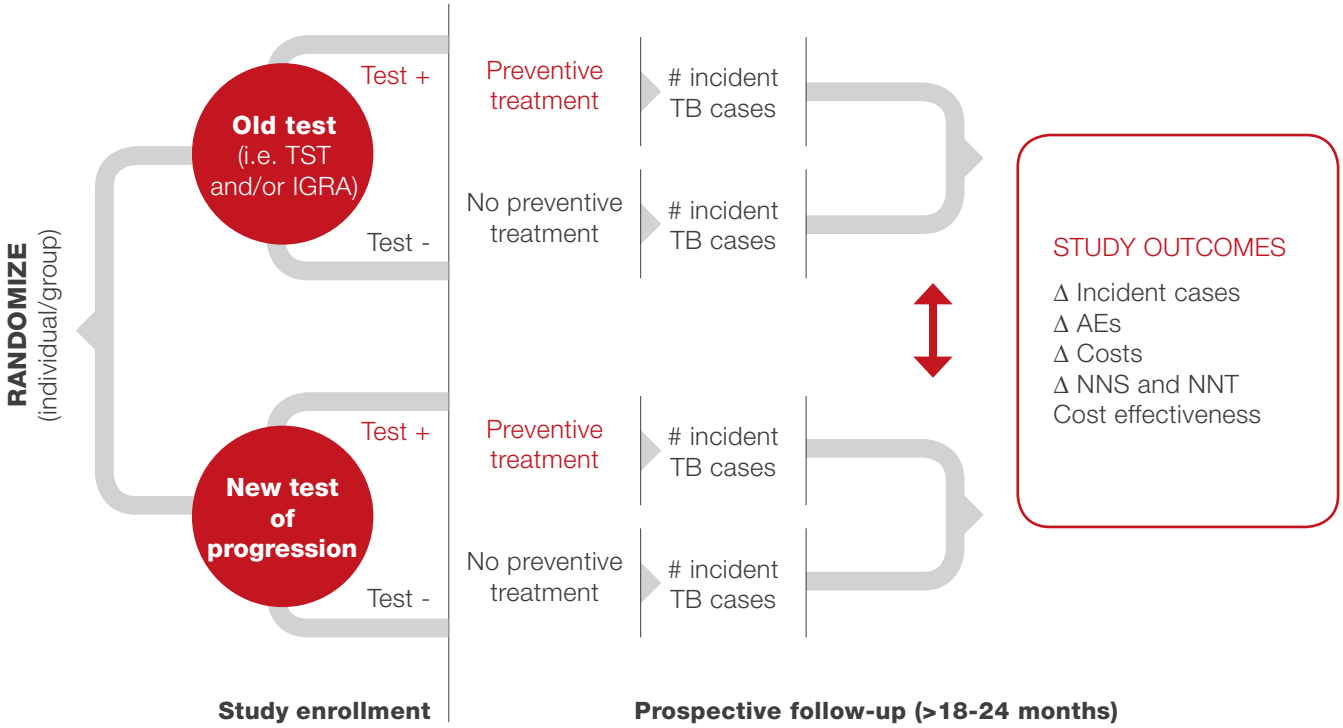


Example of study design in populations that are currently <u>not</u> tested for LTBI



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

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



References

1. World Health Organization. Implementing the END TB strategy: the essential. WHO/HTM/TB/2015.31
2. World Health Organization. Guidelines on the management of latent tuberculosis infection. WHO/HTM/TB/2015.01
3. Zak DE, et al. Blood RNS signature for tuberculosis diseases risk: a prospective cohort study. Lancet 2016; 387:2312-2322

List of participants

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