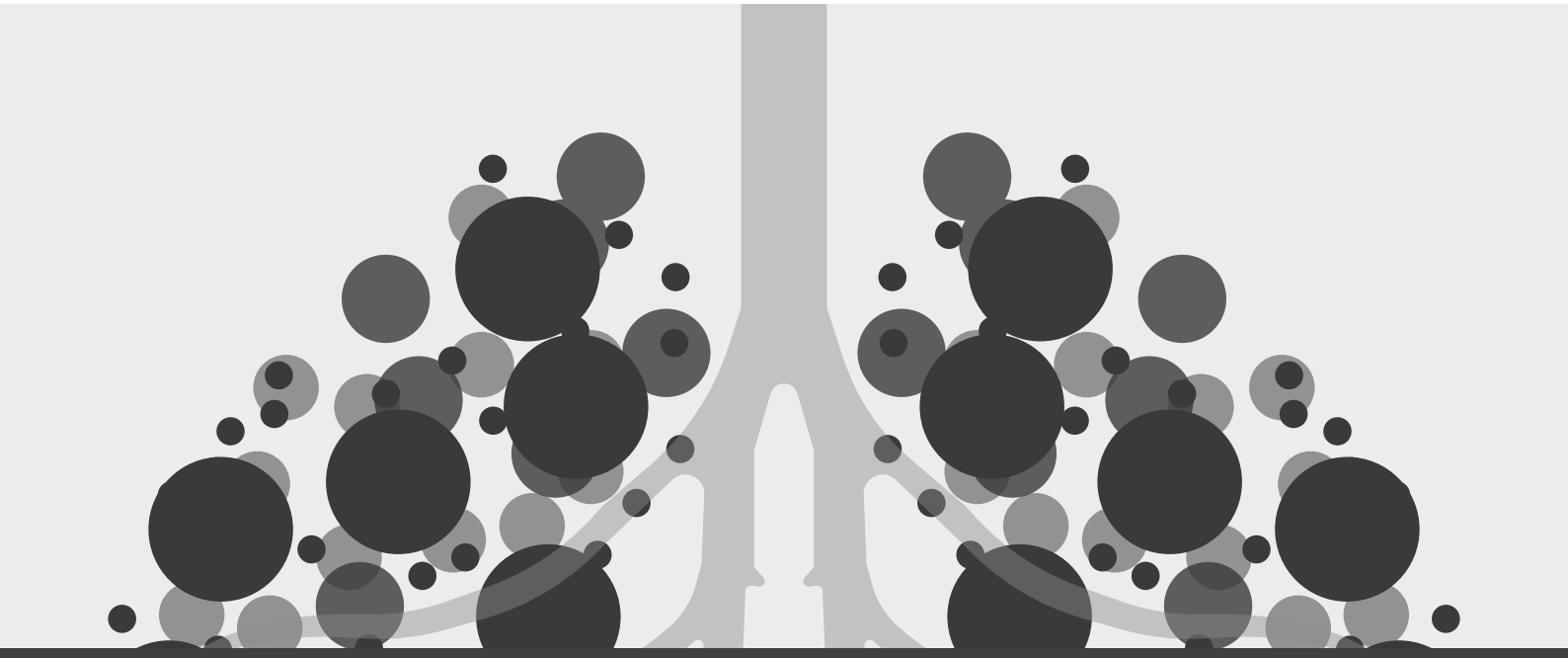
Stop TB Partnership

New Diagnostics Working Group



Modelling the impact of incipient tuberculosis testing

REPORT

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1. SUMMARY

Background

Incipient TB (ITB) is defined as the asymptomatic phase of early disease during which pathology evolves, prior to clinical presentation as active TB disease. Targeting ITB may be a better strategy than targeting latent TB infection (LTBI). Our objective was to estimate the public health impact and cost-effectiveness of screening for and treating ITB for 4 countries with different endemicity levels, assuming an ITB test meeting the WHO Target Product Profile performance targets.

Methods

We adapted a published deterministic dynamic cohort model, initially developed for ECDC, to include (1) an ITB stage, (2) both pulmonary and extra-pulmonary TB, and (3) no specific asymptomatic stage. Also, we distinguished 4 age groups (0-4, 5-14, 15-44 and 45+ years) and the model assumed stable transmission situations. Country and age-specific model variants were applied for screening close contacts of TB patients, HIV infected and other immunocompromised persons (persons using anti-TNF alfa blockers, candidates for transplantation, patients on dialysis and patients with silicosis). The model was quantified to represent the following 4 countries in order of increasing endemicity: Netherlands (NL), Portugal (PT), Viet Nam (VN) and South Africa (SA). Patients with a positive ITB test were assumed to be treated with preventive TB therapy (6 months of isoniazid). The test is applied according to different strategies: for contacts at 0, and at 3, 6 and/or 12 months after exposure; and for HIV infected persons and other immunocompromised once, annual or every 3 years.

Data on TB, demography and costing were collected for the four countries by literature review and expert interviews. An exception is PT where unit costs were calculated based on NL applying the purchasing power parity method. VN was visited to collect data. Cost-effectiveness was analysed from the health care perspective. Quality adjusted life years (QALYs), including averted disease and life years lost, were used as effectiveness measure. In the baseline scenario we compared ITB screening to doing nothing and we assumed 0.5 secondary cases prevented per index case prevented. Also, each ITB strategy was compared to the current WHO recommended strategy, usually based on testing with interferon gamma release assay (IGRA), chest x-ray(CXR), both, or immediate preventive therapy for children under 5 in VN and SA.

For cost-effectiveness, a willingness-to-pay threshold of 2x average income was applied. Calculations were based on assuming ITB test costs of 0, 25 and/or 50 US$, in addition to the cost of two consults. Through sensitivity analyses we explored the impact of alternative therapies, different performance (coverage and treatment success), as well as different numbers of averted secondary cases per averted primary case.

Results

The model fitted reasonably well to age specific TB incidence and LTBI prevalence data in all 4 countries. Testing and treating for ITB among close contacts is never cost-saving but is cost-effective in all 4 countries. In contacts in NL and PT, the health impact of the WHO recommended strategy of one-time testing with IGRA is comparable to two to three times ITB testing, and overall costs are similar if an ITB test can be done for US$ 25. In VN and SA, ITB testing strongly outperforms the use of CXR for contacts, by resulting in a much higher health impact.

Testing and treating for ITB of HIV patients and other immunocompromised persons in very low incidence settings such as the Netherlands is never cost-effective, but it can be cost-effective in medium and high incidence countries and for migrants from high-incidence countries. For HIV patients, screening every 3 years for ITB results in roughly the same health impact as the WHO recommended strategy of one time using IGRA and CXR combined for NL, PT, VN; the costs are comparable if an ITB test costs in the order of magnitude of US$ 10.

Cost-effectiveness outcomes were rather dependent on assumptions of TB-associated life years lost and whether or not prevention of secondary cases was considered, and to a lesser extent on the timing of ITB testing (6 month time-interval performed a bit better than 3 and 12 for close contacts) and LTBI therapy used (with 3HR slightly profitable relative to 6H). The maximum test-costs that can be charged by manufacturers can be one hundred to several hundred US$ for screening contacts in all countries, as well as HIV patients in SA, but much less so for HIV infected migrants in NL, and all HIV infected persons in PT and VN.

Conclusions

Testing and treating for ITB among contacts is always cost-effective. For high incidence countries substantial QALYs are gained, at the expense of relatively minor investments. Testing immunocompromised is not cost-effective for people born in very low incidence countries, but for all other groups it can be borderline cost-effective (migrants from high-incidence countries and inhabitants of moderately endemic countries) to very cost-effective (high-incidence countries). Recommended costing of testing for ITB differs widely between countries, depending on the costing approach and control strategy considered.

2. BACKGROUND

The LTBI task force of the New Diagnostics Working Group of the Stop TB Partnership (STBP) requested a mathematical model to estimate the public health impact of LTBI screening and treatment given a new diagnostic test for incipient tuberculosis (ITBT). The 'Development of a Target Product Profile (TPP) and framework for evaluation of a test for predicting progression from tuberculosis infection to active disease'(1) serves as a guideline for the model. The team of the Department of Public Health of Erasmus MC (Jan Hendrik Richardus, Sake de Vlas and Suzanne Verver) submitted a proposal to develop such model. The specifications of the model and results have been discussed between members of the NDWG (Alberto Matteelli, Daniela Cirillo, Samuel Schumacher, Alessandra Varga) and Erasmus MC. FIND hosts the secretariat of the NDWG and facilitated the country collaboration. The Stop TB Partnership funded the work through the NDWG.

3. INTRODUCTION: INCIPIENT TB

Elimination of TB requires detection and treatment of persons latently infected with *Mycobacterium tuberculosis* (LTBI), estimated to be 23% of the world population (Houben 2016). Treatment of LTBI should particularly focus on groups at high risk of disease due to clinical, epidemiological or socio-economic reasons/causes. Ideally only latently infected persons with a very high risk of progression to disease, so called incipient TB(2), will be treated.

Incipient TB (ITB) is defined as the prolonged asymptomatic phase of early disease during which pathology evolves, prior to clinical presentation as active disease, according to the Target Product profile (TPP)(1). It is likely that a subset of patients with incipient TB will eventually not progress to active disease. As such ITB is a phase within latent TB infection (2-4).

The target groups for an ITB test are:

- asymptomatic individuals who have increased exposure to a person with active TB, and
- individuals with increased risk of progression of LTBI to active disease.

Although such test is still in development and not on the market yet, several manufacturers and research groups are developing such test (5) (presentation Claudia Denkinger, FIND symposium, UNION conference 2017). The health impact and associated costs of screening with an incipient TB test and treating those with a positive test, together called ITB control, is unknown up to now.

4. OBJECTIVES

The objective of this project is to develop and use a mathematical model to estimate the public health and economic impacts of screening and treatment of high risk groups for latent tuberculosis infection with the incipient tuberculosis test, compared to doing nothing and the currently WHO recommended strategy.

This objective includes the question: What cost for the new incipient TB test would make the use of this test cost-effective or possibly even resulting in cost-savings?

The model has been applied to 4 example countries: Netherlands (low TB incidence), Portugal (medium TB incidence), Viet Nam (high TB incidence and low HIV prevalence) and South Africa (high TB incidence with high HIV prevalence).

5. METHODS

5.1. Scenarios

5.1.1. Target groups

The WHO operational guidance on systematic screening for TB (6) include the following high risk groups for screening for LTBI: HIV infected persons, other immunocompromised persons, health care workers, contacts, prisoners, migrants, drug users, children under 5. However it was agreed to focus modelling scenarios only on the following risk groups with *strong evidence*.

- Household contacts.
- HIV infected persons plus other immunocompromised persons, such as persons using anti-TNF alfa blockers, candidates for transplantation, patients on dialysis and patients with silicosis. (For the Netherlands we split these into natives and migrants, and for Portugal we only consider natives and for VN and SA the general population)

5.1.2. Algorithm for use of incipient TB test and treatment

We assumed the incipient TB test will be applied in above mentioned risk groups and replace the existing screening method: interferon gamma release assay (IGRA) and/or chest x-ray (CXR) followed by culture for confirmation and/or Xpert test. In the main analysis screening for ITB will be compared to doing nothing; in a sub-analysis we will also compare to WHO recommended practice (maximum scenario). It should be noted that current screening practices are in between doing nothing and WHO recommendation.

After a positive incipient TB test it is necessary to exclude active disease by assessing symptoms, CXR, culture and/or Xpert test. We assumed a standard algorithm (see Figure 1). If there is no active disease, the person will be treated with 6 months of isoniazid. Since the TPP did not specify what treatment would be suitable, we agreed to model as a sensitivity analysis also alternative LTBI treatment (3HR), and treatment for active TB (2HRZE/4HR, assuming drug-sensitive TB). We choose 3HR rather than 3HP due to non-availability of costs of 3HP for some countries.

We used treatment assumptions as specified in Table 1.

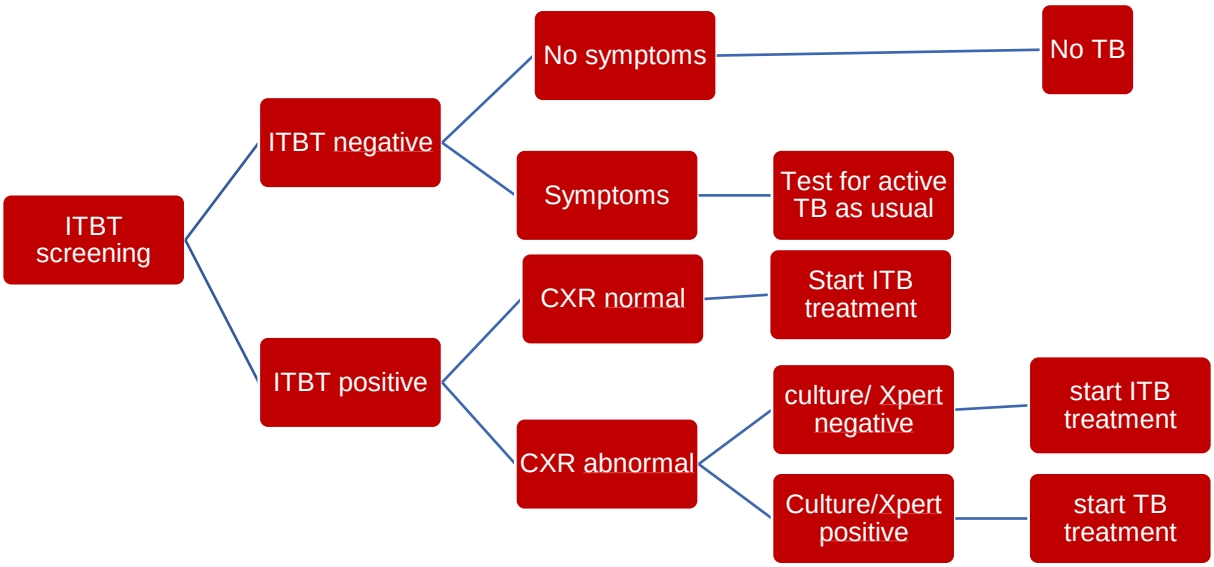
Table 1. Screening and treatment assumptions

Range indicates higher and lower alternative value in sensitivity analysis

	6H	3HR	2HRZE/4R	Source
Coverage of screening	90%(50-95%)	90%	90%	Assumption
Proportion starting and completing treatment				
LTBI/ITB	70%(50-95%)	75%	70%	(7-9)
Active TB			90%	Assumption
Efficacy of treatment: Proportion of those completing treatment who are cured**				
LTBI	90%	90%	95%#	For 90%:(7, 10, 11). For 95%: assumption
ITB	80%	80%	95%	Assumption
Active TB	10%*	10%*	90%	For 10%: assumption; for 90%: (12)

#in case of false positive active TB test; *in case of false negative active TB test. ** in the model we assume that all cured patients become susceptibles again. Thus, ‘cure’ is used differently from the definition in WHO TB treatment outcomes.

Figure 1. Algorithm for use of an incipient TB test in the model



With the model, we assume the following ITB testing strategies:

- For close contacts: at 0, and at 3, 6 and/or 12 months after exposure
- For HIV infected persons and other immunocompromised:
  - For low incidence settings (PT and NL): once
  - For high incidence settings (VN and SA): annual or every 3 years

Everyone is tested for ITB; not excluding persons who have been tested positive before.

It should be noted that the incipient TB test is meant for persons without TB symptoms. However, before performing the test **AND** when discussing the results of the test, the health worker should always ask for symptoms. As shown in Figure 1, in the model those testing positive for ITB as well as those reporting symptoms will always be tested for TB (i.e. through CXR, followed by culture or Xpert).

5.1.3. Current practices and comparison algorithms

Current screening practices recommended by WHO (6, 13-16)are described in Table 2.Only *strong* recommendations are being used; not conditional ones. Furthermore, symptom screening will always take place at the same time as LTBI screening, as recommended by WHO (17). In this way those with PTB can still be detected when their LTBI test is false-negative.

Table 2. WHO recommended screening for LTBI and/or TB for asymptomatic persons by country*

	NL & PT		VN & SA	
	WHO	**Model**	**WHO**	**Model**
Contacts under 5 yrs	LTBI[$]	IGRA at diagnosis index	Provide preventive therapy without LTBI screening[#]	immediate preventive therapy
Adult contacts (>=5 yrs)	LTBI [$]	IGRA at diagnosis index	TB[&]	CXR
HIV infected persons	LTBI [$] and TB[&**] at diagnosis	IGRA&CXR once at diagnosis	TB[&] (at HIV diagnosis), followed by PT for at least 3 years if negative(18)	Same as NL & PT
Other immunocompromised	LTBI [$] and TB[&**] at diagnosis	IGRA & CXR once at diagnosis	Same as NL&PT	Same as NL&PT

* We only used *strong recommendations.* These screening practices have been simplified since in the model we cannot differentiate all risk groups. In those with symptoms we assume a CXR will be done; followed by culture or Xpert if abnormalities on CXR. Preventive therapy for LTBI and ITB is usually modelled as 6H, but in sensitivity analysis we apply for ITB also 3HR and 2HRZE/4HR.

$WHO recommends TST or IGRA (13). For simplicity we have assumed IGRA is available. When IGRA is positive, this will be followed by CXR. IGRA detects LTBI and TB, and it leads to preventive treatment when CXR is normal. When CXR shows abnormalities, this leads to TB treatment after confirmation tests (culture). When confirmatory test negative, this will lead to LTBI treatment. When IGRA is negative, symptoms are always checked.

** in immunocompromised persons at diagnosis test for LTBI and TB since LTBI test can be false negative (for simplicity we have modelled these TB patients as 90% symptomatic, as for immunocompetent TB patients)

& For simplicity we assumed screening for active TB consists of CXR, if positive followed by culture (and in VN and SA replaced by GeneXpert)

WHO recommendation for high incidence countries not to test for LTBI since these are often not available.

5.2. Model

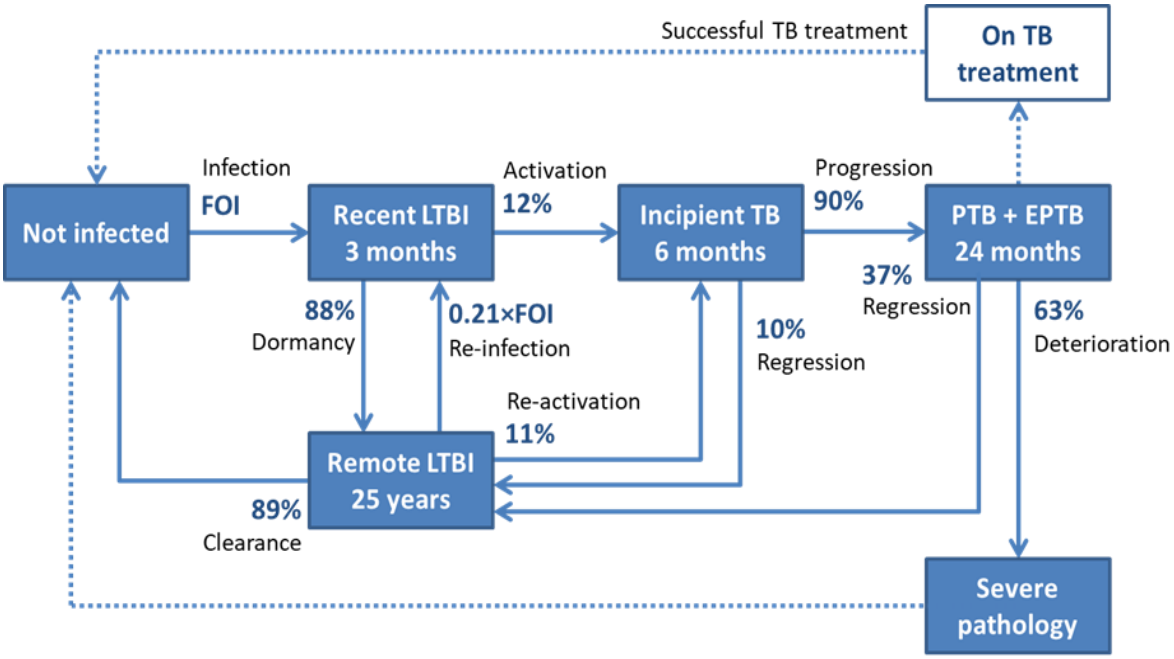
5.2.1. Natural history

Erasmus MC has recently developed a TB transmission model for and supported by the European Centre for Disease Control (ECDC). The objective of this model was to evaluate the contribution of certain LTBI control strategies (screening and preventive therapy) on TB transmission and towards elimination of TB. The previous modelling exercise was published as 2 reports on the ECDC website March 2018(19, 20).

Individuals in the current model can move forward and backward through a series of compartments or health stages that mimic the natural history of TB infection as follows: not infected (i.e. susceptible), recent LTBI, remote LTBI, incipient TB, active TB (PTB and EPTB), and severe pathology (i.e. usually hospitalized, sometimes leading to death due to

TB[1]) (Figure 2). Individuals in the stage 'not infected' have never been in contact with *M. tuberculosis* before or have completely cleared a previous infection, spontaneously or after receiving LTBI or TB treatment. The term LTBI re-activation was used to indicate activation after remote infection, to distinguish it from activation after recent infection. Rates of activation and re-activation were assumed to be age-dependent, and can be increased for those with HIV or otherwise immunocompromised (see paragraph 5.2.8).

Figure 2. Schematic representation of model for natural history of TB infection and disease



LTBI: latent TB infection, PTB: pulmonary TB, EPTB: extrapulmonary TB, FOI: force of infection. The time in each compartment indicates the assumed average duration that an individual spends in a certain health state. The % indicates the proportion that moves to another health state, when leaving a compartment. Individuals with remote LTBI can get re-infected, but at 21% of the rate for not infected susceptible individuals, due to some degree of immunity. Durations and proportions given for active TB (PTB + EPTB) are in the situation of no treatment taking place. Severe pathology is included as a flow through which individuals immediately return to not infected. Similarly, patients with TB return to not infected after self-reporting and successful TB treatment. Hospitalization and death due to TB are proportionally related to the flows through severe pathology (hospitalization and death) and self-reporting (only hospitalization).

The original ECDC model also included a 6 month stage for individuals with asymptomatic TB. In the current model this stage was basically divided over active TB (i.e. for the last 2 months that patients can be detected by culture or CXR) and ITB (for the first 4 months). Therefore, in the current model we assume the duration of active TB (until treatment or development of severe pathology) 2 months longer than used for the ECDC calculations. Furthermore, in the TB stage we now also include EPTB, based on country and age-group specific proportions of EPTB among all active TB derived from data.

Infected individuals can progress and regress between the different states according to transition rates (or corresponding durations and probabilities, as shown in Figure 2), that are a result of assumptions and/or fitting, further explained in the following sections. The duration (sojourn time) in a compartment is the reciprocal of the sum of the rates of progression or regression from that same compartment.

[1]Hospitalization and death are independently linked to severe pathology

5.2.2. Force of infection

In the model, individuals are infected by a fixed force of infection (FOI; i.e. the annual rate of TB infection), depending on the TB situation in the country where they reside. Individuals with remote LTBI are assumed to be able to get re-infected, but at a substantially lower rate than for not infected susceptible individuals, due to some degree of immunity. Note that re-infection is here included as a movement from remote LTBI to recent LTBI, where the rate to develop active TB is higher. This reduced rate of re-infection due to immunity was based on the findings of several studies (21-23). Following this observation, the rate to move from remote LTBI to recent LTBI was assumed to be 21% of that by fully susceptible individuals to move from not infected to recent LTBI, as a result of the same FOI.

As was done for part of the calculations for ECDC(19, 20), we assumed all situations to be in equilibrium, so that population groups could be modelled as cohorts with a fixed FOI. Cohorts of close contacts are assumed to have experienced a short period (3 to 6 months depending on the country) of an extremely increased FOI due to the nearby presence of a case with active pulmonary TB. Thereafter, the FOI immediately returns to the original level. People living with HIV and other immunocompromised individuals experience the same FOI as any individual in the same country and age group. They only have an increased rate to activate from LTBI to active TB via ITB (see below).

The model does not have a separate MDR epidemic. MDR is included mainly as additional costs for treatment in a fixed proportion of the patients, based on actual proportion MDR in the country.

5.2.3 Assumptions on diagnostic tests

The model includes a differentiation of the compartments to reflect history of previous TB as follows: (0) naive, (1) having had LTBI, or (2) having had PTB. The different stages of the model, correspond to different chances of testing positive with incipient TB test, chest X-ray (CXR), interferon gamma release assays (IGRA), GeneXpert and culture. Here, only for CXR we use history of previous TB, as people who have experienced PTB in the past sometimes have CXR abnormalities.

The structure of the natural history model is partly inspired by allowing adequate links to the outcome of different diagnostic tests. For example, the process of clearance of remote LTBI is assumed to be linked with the test outcome of IGRA versus TST as follows: after clearance TST still tests positive, but IGRA not anymore, the latter reflecting the observed process of waning.

The sensitivity and specificity of each of the mentioned tests is summarized in Table 3, and shown in relation to the different health stages in Annex 2. Cross reactivity of Bacille Calmette-Guérin (BCG) vaccination with TST is not included since in all 4 countries BCG is only given at birth and will thus have limited effect on the TST(24). Note that all tests also have false positive test results, due to imperfect specificity. Culture is used in this model as gold standard, and therefore assumed to have 100% specificity. The probability to report symptoms of active TB has also been included. Most LTBI control strategies ask for symptoms in order to avoid missing patients of active TB, as both TST and IGRA do not have 100% sensitivity for this stage.

Sensitivity and specificity of an ITB test (ITBT)

The TPP specifies: the specificity and PPV of an ITBT will be high, population-independent, and determined primarily by the probability that asymptomatic progression is halted spontaneously. However, its sensitivity will be variable and depends on whether the test is done before or after a precipitating event has taken effect. Therefore, both sensitivity and specificity (and thus PPV) of an ITBT will improve if performed closer to the point of clinical presentation of tuberculosis.

The model cannot take this into account and will assume a constant sensitivity and specificity.

We agreed to use the following specifications for the ITBT:

- Predict high risk of progression to active TB from TB infection (LTBI)
- Test result to revert to negative with treatment
- Sensitivity: ideal 90%, minimum 75%
- Specificity: ideal 90%, minimum 75%

The sensitivity component has been included in the natural history of the model, where only 90% of those with incipient TB progress to active TB. Therefore we assume that 100% of those in the incipient TB box will test positive on an incipient TB test. The specificity component is included in the model by assuming that 10% of those who are in LTBI stages also test positive with the incipient TB test (see Annex 2). Further we assumed 0.5% of those who are not infected also tests positive on the ITB test, which is similar to that for culture after CXR (Table 3).

Specifications for other diagnostic tests

Specifications for other diagnostic tests have been obtained from the literature (see Table 3 and Annex 2).

Table 3. Diagnostic parameters of different tests for active pulmonary and extrapulmonary tuberculosis and latent tuberculosis infection

Diagnostic parameter	Value / range in literature	Chosen value	Source(s)
TST sensitivity in those with LTBI or past LTBI [a,b]	89%	89%	(25, 26)
TST sensitivity in those with active TB	70 – 82%	75%	(26-28)
TST specificity [c]	92 – 98%	95%	(26, 28)
IGRA sensitivity in those with LTBI[bh]	83 – 84%	83%	(29, 30)
IGRA sensitivity in those with active TB[h]	81 – 82%	81%	(26-28)
IGRA specificity[h]	98 – 99.4%	98%	(25-27, 29)
CXR positivity in those with a history of PTB	10.5–40%	25%	(31, 32)
CXR sensitivity in those with active PTB [f]	97.5%	97.5%	(28, 33, 34)
As above – EPTB	Unknown	50%	Assumption[g]
CXR specificity [f]	75.4 – 97.7%	96%	(33, 35, 36)
Culture sensitivity after CXR for PTB	90%	100%[d]	(33, 34)
As above – EPTB	Unknown	50%	assumption
Culture specificity after CXR	96-100%	99.5%[d]	(37-39)
GeneXpert sensitivity for PTB	89%	89%	(40)
As above – EPTB	47%	47%	(40)
GeneXpert specificity	99%	99%	(40)
Symptom screening sensitivity for active TB [e]	77%	90%	(33)
Symptom screening specificity for active TB [e]	68%	90%	(33)

CXR= chest X-ray; LTBI= latent TB infection; IGRA= interferon gamma release assay; TB= tuberculosis; TST= tuberculin skin test.

These values should be interpreted as follows for the model (see Annex 2): sensitivity is proportion positive in the group with disease; specificity is 100% minus the proportion positive in those without the disease.

[a] TST is included here since we fitted the model to data of TST and IGRA at entry of migrants to the Netherlands, but we do not use TST scenarios in this study.

[b] PPV ranged from 1-7% for TST and 0-13% for IGRA. NPV ranged from 92-100% for TST and 88-100% for IGRA(41). A recently published review in children, immunocompromised people and migrants, found that cumulative TB incidence rate after positive TST or IGRA are similar but studies had many limitations (42). Both do not give sensitivity and specificity.

[c] Middle value were chosen to take into account positive TST due to non-tuberculous mycobacteria.

[d] For at least 2 cultures; assuming use of confirmatory tests and no-cross contamination, since lab procedures continue to be improved.

[e] LTBI screening strategies were assumed to always include questions on symptoms.

[f] Values for 'any abnormalities' on CXR were chosen to have high sensitivity. In nationwide prevalence surveys in high risk countries a CXR specificity of 75.4% was found in a review (33), while in migrants in the Netherlands 97.7% was found in an older study (35) and 95.0% in a more recent report (36).

[g] Some forms of extrapulmonary TB can be detected using CXR, such as lymphadenopathy and pleural TB.

[h] Values chosen are those for Quantiferon Gold and T-Spot TB. In reviews, sensitivity and specificity of IGRA for active TB in HIV infected persons was 61-69% and 72-76%, respectively; lower than for HIV uninfected TB patients (43, 44). Also the sensitivity for LTBI among HIV infected persons seemed lower as for HIV uninfected persons (45). Recently a new Quantiferon-Plus assay was found to have a sensitivity for active TB of 88% in European hospitals(46, 47). Also this new QFN-Gold-Plus assay had a sensitivity of 81% for HIV infected TB patients, and no significant difference between HIV infected and uninfected TB patients in Zambia(48). Values are better for HIV infected persons who are detected early with higher CD4 counts; we expect this to be more common in future. For both reasons we assume that for future IGRAs sensitivity and specificity are similar for HIV infected and uninfected. Persons with a positive IGRA can become negative again after clearance, to allow for waning (30) (see Annex 2).

5.2.4. Fitting procedures

The deterministic cohort model was developed in Microsoft Excel version 2010. A one-month time-step was deemed adequate to reproduce all dynamic processes, given the shortest average durations considered in the modelling: i.e. three months for the average durations of recent LTBI.

The model was fitted in the following successive steps.

1. First, the natural history of TB (proportions given the chosen durations in Figure 2) was fitted to
    a. Literature on survival of smear-positive patients to fit transition rates concerning progression and regression of TB (**paragraph 5.2.5.**)
    b. Literature on activation to PTB after recent infection and re-activation of remote LTBI (**paragraph 5.2.6**)
    c. Actual data on LTBI (TST, IGRA) and PTB (CXR + culture) of migrants in the Netherlands at entry (**paragraph 5.2.7**)

2. Then we adapted the model to country specific values (**paragraph 5.2.8**).
    a. The duration of disease till diagnosis and treatment was assumed to be different between countries, see Table 6.
    b. TB (PTB & EPTB) estimated incidence was used to tune country-specific force of infection (FOI) values
    c. Hospitalization rates were used to tune ratios of hospitalization of self-reporting and/or severe pathology patients (see Table 6).
    d. WHO estimated TB mortality was used to tune death of severe pathology patients, see Table 6.

5.2.5. Fitting transition rates of progression and regression of TB disease

The probabilities of deteriorating from TB to severe pathology (or reversely: regressing to remote LTBI) in the natural history model (Figure 2) were fitted to historic data of the survival of smear-positive PTB patients in the absence of treatment, as reviewed by Tiemersma *et al*. (49), as well as studies mentioned by Berg *et al*. (50). Appendix 2 of the ECDC report of the previous version of this model shows the observations from each of these studies(19). **Error! Reference source not found.** shows the best fitting trend. This trend was derived by starting a cohort of people with TB and following it over time. The annual background mortality (not due to TB) was set to be 2%, which associates with an average survival of 50 years, crudely corresponding to the risk of dying for the study populations at that time. Any person deteriorating from TB to severe pathology was assumed to have died from TB, as no chemotherapy was available yet. We assumed that the derived rates to severe pathology and remote LTBI for PTB patients apply to EPTB patients as well.

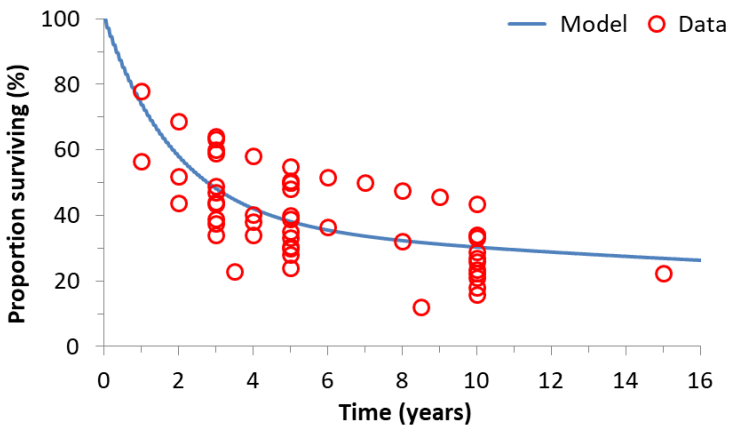


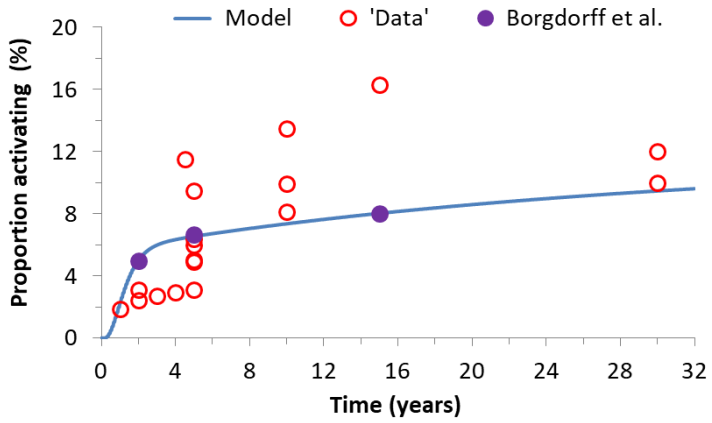
Figure 3. Fitting the model to survival of smear-positive patients

5.2.6. Fitting transition rates of activation of recent and remote LTBI to ITB

A critical component of any modelling study about the impact of LTBI control is to properly reproduce activation of LTBI to TB, here via ITB. Figure 2 shows that in our model, after infection, individuals first move to recent LTBI, a health state with a chosen average duration of 3 months. Those with recent LTBI can progress to incipient TB (12%), but most (88%) eventually move to remote LTBI, a process called dormancy. Remote LTBI is a health state that is chosen to last for on average 25 years, after which 11% re-activate to incipient TB and the remaining 89% clear the infection. Figure 4 explains how these proportions were derived from fitting to data about activation after recent infection. It should be noted that in the literature reference is made to activation from LTBI to active (pulmonary) TB, while in the model we first use activation from LTBI to ITB, followed by a chosen progression rate to

active TB. The later rate reflects 90% of ITB cases moving to active TB after on average 6 months, and this rate is kept constant when fitting the (re-)activation rates from recent and remote LTBI to ITB.

Figure 4. Fitting the model to activation to PTB after recent infection



The curve followed the general findings of Borgdorff et al. (2011)(51), assuming that 8% will activate after 15 years, such that overall a life-time activation rate of about 10% is reached. Data points to compare the trend with are listed in appendix 3 of the ECDC report of the previous version of this model (19). The trend crudely follows the general idea of about 50% of activations occurring rapidly (i.e. within about two years) and another 50% later in life. In the model, the early activations are mainly due to those activating from recent LTBI, the late activations result from re-activation from remote LTBI. The model includes active TB (PTB and EPTB), but a fixed 60% PTB among all active TB was used to relate to the data in the Netherlands (52).

The probabilities of progressing from recent LTBI to incipient TB ("activation" in Figure 2) and progressing from remote LTBI to incipient TB ("re-activation" in Figure 2) were fitted to best reproduce the findings of Borgdorff et al. (2011) based on patients whose *M. tuberculosis* isolates had identical DNA fingerprints and who were interviewed to identify epidemiological links between patients(51). They concluded that of those developing PTB within 15 years, 83% did so within five years, and 62% within two years[2](51). The number of diagnosed PTB patients over time was fitted by starting a cohort of recent LTBI, leaving them to progress through the model with the pre-set durations for the recent LTBI (3 months) and remote LTBI (25 years) compartments. In the model, diagnosed PTB patients were interpreted as either self-reporting or moving to severe pathology, both of which were here absorbing stages. This means that individuals diagnosed with PTB were assumed not to return to earlier health stages of the model and hence could not be counted twice. Here, the rate of natural mortality was set at 0%, as the study by Borgdorff et al. (2011) corrected for mortality by censoring (51). Also, the rate of self-reporting was set such that the average duration in TB was 6 months (as for Portugal in the current calculations). Furthermore, a fixed proportion of 60% PTB among all active TB was used to compare with the data(52).For comparison, Figure 4 also shows the outcomes of several other studies on the risk of activation after recent infection (see Appendix 3 of (19)), but these showed a wide variation and often concerned children (with a lower risk of activation) or migrants (with a high risk of previous infection). Our activation assumptions using two successive LTBI compartments seem to largely agree with empirical evidence, as was recommended by Menzies (53).

The data and the resulting rates of (re-)activation in Figure 4 are assumed to be illustrative of healthy individuals in the age group 15-44 (young adults). For children 0-4 years and 5-14

[2]Borgdorff et al. (2011) also concluded that 45% of those activating after 15 years did so within one year. This observation was not considered in this report, as their retrospective study did not allow making such short term estimates.

years, the rates of activation (both from recent and remote LTBI) were set at 100% and 50% respectively of the values for adults, since very young children have a higher risk of progression while primary school children have a substantially lower risk of progression to TB disease(54-57). The rate of activation in the 45+ group was assumed to be 75% that of the 15-44 group to account for the observation that in the Netherlands persons with LTBI aged 25-44 had a 1.3 times higher chance to develop TB than those aged 45+ (58), although other studies showed both higher and lower estimates (22, 59, 60).For the other 3 countries the same age adjusted rates were used except for South Africa, activation in age group 15-44 was assumed to be 160% of the reference value, to account for high proportion of population that is HIV infected (about 20% have an HIV-associated relative risk of 4 to activate). Among the 45+ age group in South Africa we assumed the activation rate was 100% of the reference value to account for higher activation rates among HIV infected, taking the proportion of HIV infected persons into account (about 10% in latest data in 2012 (61); they are assumed to have activation rate RR = 4). In summary see Table 4. More details in Annex 3.

Table 4. Relative FOI and activation rates from recent and remote LTBI to incipient TB

Age group	FOI	Activation (NL, PT, VN)	Activation (SA)
0-4 years	50%	100%	100%
5-14 years	50%	50%	50%
15-44 years	100%	Reference value = 100%	160%
45+ years	100%	75%	100%

5.2.7. Validating the model to data about screening of migrants at entry

The above quantified natural history model, together with the assumptions regarding diagnostic testing, was then used to compare with Dutch data on TB (CXR) and LTBI (IGRA and TST) among migrants from high-endemic countries (i.e. with total TB-incidence >50 per 100,000) screened at entry. This was done (1) to validate the model and (2) to choose a reasonable the duration of remote LTBI. Key values resulted from two relatively recently conducted studies. First, KNCV Tuberculosis Foundation reported on migrants from countries with WHO estimated incidence >50/100,000, entering the Netherlands from 2005 to 2010 (36), updating the data previously published by Erkens et al (35). These data were used to calculate that 93 individuals out of 84 166 tested positive with CXR and culture for bacteriological confirmation, i.e. 11.05 per 10,000 (36). In the same updated report, 5,937 / 117,389 migrants had an abnormal CXR (506 per 10,000), requiring further testing with culture(36). The second study, by Mulder et al. (2012), reported that 23.4% migrants from high-endemic countries to the Netherlands tested positive with IGRA (raw data obtained from first author to select migrants from countries with WHO estimated incidence > 50/100,000)(62). In addition, Mulder also found 42.9% of migrants at entry were TST positive (excluding migrants from Europe and Americas), and this was also used for fitting (63).

The FOI (average immigrant-country specific)and the tendency of TB patients to travel (relative to all other individuals) were fitted in order to obtain 23.4% migrants testing positive with IGRA, 42.9% testing positive with TST, and 0.11% testing positive for CXR and culture. The same age distributions as in the studies by Erkens and Mulder were applied. Further, the average duration of TB (until treatment) was assumed to be 7 months in the country of origin, which was similar to what we assumed for VN in the current study (Table 6). This duration may very well reflect the average situation in high TB-endemic countries (64,

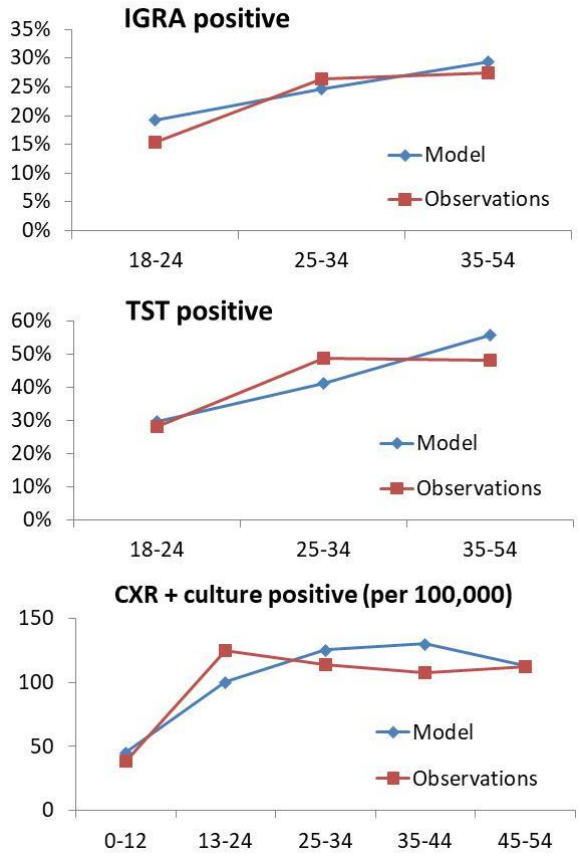
65).The resulting best fitting FOI was 0.00213 per month and 22.3% of TB patients was estimated to not travel.

It should be noted that the chosen duration of remote LTBI (i.e. 25 years) was also based on the comparison with these data, in particular the overall proportions testing positive for IGRA versus TST. This is because after clearance from remote LTBI to susceptible, individuals are assumed to remain positive for TST, but not for IGRA (see Table 3 and Annex 2.4). Furthermore, the chosen duration of remote LTBI determines the distribution of those re-activating to ITB and those clearing LTBI: i.e. with a longer duration the proportion activating will increase to arrive at the same overall proportions as determined by Borgdorff et al.

Figure 5 shows that the observed overall proportions testing positive for IGRA, TST and CXR/culture could very well be reproduced, including the crude trends with age. It is further reassuring that the model resulted in 453 per 10,000 with an abnormal CXR, which is relatively close to the reported value of 506 per 10,000. On the other hand, the model-predicted proportion of all CXR/culture positive patients having symptoms is 74%, which is substantially higher than the observation that only 1/3 of migrant TB patients at entry report symptoms (66).

Figure 5. Fitting the model to migrant screening at entry in the Netherlands

Age-dependent data for all patients; correction is for high-endemic countries (incidence >50/100,000)
Additional assumption: 7 months duration of TB in home country.
Fits (**model** vs. **data**): IGRA (**24.0%** vs. **23.4%**); TST (**41.5%** vs. **42.9%**); CXR/culture (**110** vs. **110** per 100,000). The latter value fits perfectly after assuming that 22.3% of TB cases do not travel.



CXR= chest X ray; IGRA= interferon gamma release assays; TST= tuberculin skin test.

Including EPTB

EPTB was included since the ITB test probably also prevents EPTB, although very little data are available to make EPTB specific model adjustments, e.g. there are little data on diagnostic test specifics of EPTB. The reported proportion EPTB is much lower in VN and

SA as in NL and PT, probably both due to more progression to PTB and due to underdiagnosis in both VN and PT. It was assumed that most EPTB will be detected by symptoms (included in our algorithm) and turn into PTB when undiagnosed by screening. That is, after screening and treatment of active TB we assume that among untreated active TB cases the proportion EPTB will remain the same at subsequent screening rounds.

5.2.8. Applying the model to countries

The model was applied to the Netherlands (low incidence example), Portugal (medium incidence example), Viet Nam (Asia high incidence example) and South Africa (Africa high incidence with HIV example). Data for Netherlands and Portugal had already been collected for the previous ECDC version of the model(19, 20). Country data were collected by literature review, consulting local experts and by using available data from local databases. A staff member of Erasmus MC (AK) visited Viet Nam for 1 week to collect relevant data. For South Africa a visit was not necessary since there is extensive literature on TB and costs of TB control in South Africa.

Demography

The model takes into account age by distinguishing four age groups: 0-5, 5-14, 15-44 and 45+ year olds. Those starting in the 45+ year group are pre-set to stay there for on average of another 12 to 37 years, depending on the life expectancy in the country considered. Death (due to other causes than TB) is assumed to only play a role for the 45+ groups. Information about the size of the overall population in the 4 countries, and the distribution over age groups, was obtained from UNDP (67).

Population groups

Table 5 gives an overview of demography and TB data used for the model, by country. We used WHO estimated TB incidence, and incidence by age and proportions EPTB were converted from notified incidence to estimated numbers. Table 6 gives country specific assumptions on duration of disease and mortality. For the Netherlands and Portugal, TB incidences for the cohorts (not for the model fitting!) were split between natives (persons born in same country plus migrants from low incidence countries) and migrants (from countries with TB incidences > 50/100,000). Since migrants entering low incidence countries can differ a lot between years, these were calculated for the average of years 2005-2014, as explained in detail in the ECDC report of the previous version of the model (19).

Table 5. Overview of demographic and TB data from 2015*used for model, by country

	NL	PT	VN	SA	source
Population 2015					
0-4	890,687	442,407	7,752,861	5,663,766	(67)
5-14	1,947,460	1,024,186	13,856,295	10,561,595	
15-44	6,304,769	3,922,054	46,238,350	27,353,615	
45+	7,795,576	5,029,816	25,724,063	11,712,250	
Total	**16,938,492**	**10,418,463**	**93,571,569**	**55,291,226**	
Years of life lost when dying from TB					(67-69)
age 0-4 (mean 2)	80.33	78.87	75.30	62.80	
age 5-14 (mean 10)	72.40	70.94	70.18	58.10	
age 15-44 (mean 30 for NL PT)	52.65	51.25	48.70	37.45	
age 45+	22.31	20.40	24.20	17.45	
age 45+: correction for other mortality**	6.33	8.76	14.26	15.95	
Total TB pts WHO estimated	980	2400	128,000	454,000	(70)
WHO estimated total TB incidence per 100,000 population	5.79	23.04	136.79	821.11	(67, 70)
Total TB pts notified	867	2124	102,676	294,603	(70)
% notified versus estimated	88%	89%	80%	65%	
Estimated TB incidence/100,000 in subgroups					(19)
Natives	3.20	28.93			
Migrants	87.15	120.03			
% EPTB among notified TB patients by age					A
0-4	61%	28%	19%	10%	
5-14	61%	40%	19%	10%	
15-44	44%	20%	19%	10%	
45+	41%	27%	19%	10%	
Hospitalization[##]					B
Proportion (DS&MDR TB)	30%	30%	12%	10%-90%	
TB death rate per 100,000	0.26	2.5	18	179	(70)
Notified TB incidence by age/100,000			New PTB only		A
0-4	1.0	2.7	0.4	323	
5-14	1.7	2.1	0.7	94	
15-44	7.6	21.4	47.7	672	
45+	4.2	24.1	108.6	674	
% MDR[##]	1.6%	0.98%	4.1%	3.5%	(70)

*All data for 2015, unless mentioned otherwise

** For the Netherlands, we assumed 75% of those dying due to TB in the age group 45+ had a remaining life-expectancy of 1 year, and 25% had a remaining life-expectancy similar to the

average person in the age group; loosely based on data from the Netherlands (52). For Portugal these proportions were 60% and 40%, for VN 42.9% and 57.1%, and for South Africa 9.1% and 90.9%.

Included in 5-14; so 0-4 and 5-14 are combined

Only used for costing. The WHO estimates are for new cases; while in the model we use these percentages for all cases.

$ Minor differences with total above due to different sources (WHO versus country informants).

A. Source NL&PT: ECDC TESSy database; VN: NTP; SA: NTP/WHO. NB for VN this is only known for new PTB; proportions extrapolated

B. Source NL: (71); PT: Raquel Duarte unpublished data, VN: Binh Hoa (NTP), South Africa: 21 days hospitalization for DS TB from (72) and 54 days for MDR TB from(73).

Table 6. Overview of rather arbitrary country specific assumptions

	NL	PT	VN	SA
Duration of TB disease till diagnosis (months)**	5	6	7	8
As above, for contacts and immunocompromised	3	4	4	4
45+ year-old patients with severe pathology have x times higher risk to die*	4x	2.5x	1.75x	1.1x

*Explanation see **Table 5**. The 4x in NL was based on data from the Netherlands (52) and multiplier from other countries has been adapted from this. For PT, VN and SA it was chosen such that the death rate for severe pathology cases of 45+ was close to 90% (PT and VN) and not above 100% (SA).

** Seems long, but crudely 2 months the asymptomatic TB is included here.

Risk groups with cohort model

Different cohort models were used to calculate the cost-effectiveness of incipient TB screening in high risk populations. Each cohort model is an adaptation of cohort model for an entire country, and works as follows. First a country-specific cohort model was tuned to arrive at the WHO estimated TB incidence, accounting for demography. This resulted in an overall FOI for the country, thereby assuming that the FOI is half for children compared to adults. The corresponding outflow to severe pathology was then used to assess the proportions hospitalized and dying to arrive at the country specific rates. For NL and PT it was necessary to assume that 100% of severe pathology cases were hospitalized, as well as part of the self-reported cases. Furthermore, only for NL and PT, alternative cohorts were made for native and migrant populations, using the TB incidence for these population groups, resulting in different FOI values, but the proportions hospitalized and dying were assumed to be same as for the whole country.

Based on the country cohort models, the average distribution over the different compartments of TB, LTBI and ITB was calculated for each age group. Subsequently, this distribution was used as the starting situation for specific high-risk cohort models, using the same country-specific FOI, which were followed for a period of 20 years. This 20 years

follow-up implies that persons spend part of the time in their age group where they started, and part of the time in the next age group, for example, a child of 5-14 years is on average 10 years old and spends on average 5 years in age group 5-14 and another 15 years in age group 15-44. Below the simulation of each cohort is described.

Contacts were simulated to experience a temporary higher FOI because of exposure to an infectious index case. The higher FOI is only experienced for a short period of time of three to six months, equal to the average duration of TB, minus the about 2 months of being asymptomatic and not/less infectious. Thus, the exposure to the TB case was assumed to last on average 3, 4, 5 and 6 months in NL, PT, VN and SA, respectively. Immediately after this period of higher exposure the FOI returns to the original country-specific value. With these cohorts, we explored the effects of ITB control strategies under different screening intervals. The FOI during increased exposure was based on data for NL, and validated against data from the other three countries (see Chapter 6.1 and Figure 7b).

Immunocompromised patients: Cohorts of immunocompromised patients were simulated for all groups together (i.e. HIV infected persons, diabetes patients, silicosis patients, transplant candidates, anti-TNF alfa users). Again, the cohort originated from the cohort of the general population, but with an increased rate of activation due to the underlying immune-compromising morbidity. Different rates of increased activation were explored (from both recent and remote LTBI) and different screening intervals (one time, yearly and every 3 years). HIV infected persons starting early ART are assumed to have a 4x higher risk of activation(74-78), while children have a 2x higher risk of activation (79). For other immunocompromised patients these range from 2-10 times higher risk of activation than the general population (13).

Only for the Netherlands, a cohort of immunocompromised migrants was modelled, based on the migrant incidence that was used in the previous ECDC version of the model (19), and corrected for under notification.

5.2.9. Overview of parameters and sources

The **box** below lists where all parameters can be found.

Where to find all parameters of the model?	
Natural history:	**Figure 2** and **Table 4** and **table 6** for general values, and **Annex 3** for details
Diagnostics:	**Table 3** and **Annex 2**
FOI:	**Annex 3**

5.2.10. Sensitivity analysis

A sensitivity analysis was done for the following aspects:

1. Using alternative therapies for persons with a positive ITB test.
2. Comparing screening with ITB test not only to baseline doing nothing but also to WHO recommended policies
3. Alternative assumptions on prevention of secondary cases (baseline 0.5 secondary cases prevented)

4. Alternative ranges for coverage of screening and start and completion of treatment

5.3. Cost-effectiveness analysis

5.3.1. Cost data for 4 countries

The costs were mainly analysed from the healthcare perspective. Healthcare costs included all testing, screening, and treatment costs (including costs for treatment monitoring), as well as costs associated with hospitalization, directly observed treatment and contact tracing for TB patients. The additional costs for MDR treatment were taken into account using the proportion MDR patients as reported by WHO.

Unit cost data for all components of TB and LTBI control were collected **for 2015** following the WHO-CHOICE approach (80), which consists of the following:

(i) we have used an ingredient approach to costing analysis which separates the reporting of prices and quantities (p x q) of TB interventions. This allows a rough generalisation of cost estimates across countries;

(ii) our analysis followed the principles of 'generalized cost-effectiveness analysis' as proposed by WHO-CHOICE, which implies the comparison of current and new/hypothetical program against a scenario representing the absence of any TB control – this allows insights in the cost-effectiveness of current program. In addition to this baseline scenario we also compared to scenarios as if WHO recommendations are applied in the countries (see **Table 2**), and assume the actual practice is in between these extremes;

(iii) following WHO-CHOICE we discount costs and effect both at a discount rate of 3% in our base-case analysis.

For calculating the healthcare costs, programmatic TB control was categorised into the following activities: screening, LTBI treatment, TB treatment, contact tracing, directly observed treatment, and hospitalisation. For the treatment activities, a distinction was made between traded goods (medicines) and non-traded goods (all other items). It is assumed that the medicines can be purchased throughout the whole EU at the lowest price level available. Next, prices were attached to each item under the different activities. In-depth information on costs was derived from studies in the Netherlands and was partly based on the year 2015 and partly on 2016.The third step was to attach a quantity to each item under the different activities, e.g. number of consultations, number of PCR tests performed, average size of contact investigations, how often contact tracing is performed, etc. The costs of severe side-effects were ignored, because they are negligibly small. An estimated 0.01% of those that start treatment will have severe side-effects requiring hospitalization (81, 82). Assuming the average duration of hospitalization would be one month (equals about EUR 10, 000) for these severe side-effects, the additional costs of treatment of side-effects would be about EUR 1.

All cost were adapted to 2015 US$ using exchange rates from www.xe.com and inflation rates from www.usinflationcalculator.com.

For the 4 countries slightly different costs could be included, since we had to base costing on published documents and locally available knowledge. The advantage of this approach is that local researchers and policy makers can compare our results to previously published methodologies. The disadvantage is that comparing costs between countries should be done

with caution. First we describe the costing method and sources per country, and then give an overview of differences between countries (Table 7).

For the **Netherlands**, KNCV Tuberculosis Foundation provided an overview of costs in the Netherlands, and this could be supplied with published (Dutch) references (see Annex 4.1).

For **Portugal**, we applied purchasing power parities (PPPs) to extrapolate costs from the Netherlands to Portugal since for Portugal very limited data on costs were available. This approach is also recommended by WHO-CHOICE. The purchasing power parity (PPP) of Portugal was applied to the prices, with the Netherlands being the reference value 1.00 (83). PPP takes into account the relative costs of local goods, services and inflation rates of the country, rather than using international market exchange rates which may distort the real differences in per capita income (84). Costs of traded goods were derived by calculating the price (p) times the quantity (q). For contact tracing of PTB patients the average number of contacts screened per country was taken into account, and for hospitalisation the average duration of being hospitalised per country was taken into account. Local numbers were provided by the ECDC contact person. Costs for non-traded goods were derived by calculating the price times the quantity times the PPP ($p \times q \times PPP$). Some validations of costs were possible, see Annex 4.2.

For **Viet Nam**, costing was based on a recently published paper with countrywide costing details (85). This paper elegantly split costs for different type of patients (smear-positive, smear-negative, EPTB, MDR in new and retreatment patients, all split by age (<15 and >=15), and also split by national, provincial and district level. Since this paper included costs of 2014 and missed some costs, we used quantities and proportions from this paper but updated costs by using a locally issued pricelist for hospitals‘ Prices of medical examination services, Ministry of Health and Ministry of Finance; Joint Circular No. 37/2015 / TTLT-BYT-BTC dated 29 October 2015)’**(**Annex4.3**)**. Only for costs of 3HR we used MSH drug price indicator as was also done for South Africa by (72). Since no published reference was available for LTBI treatment, we added a monthly visit to the costs of the medication, so 6 visits for 6H and 3 visits for 3HR, using visit costs from Minh(85).

For **South Africa**, we based costing of diagnostics and treatment (Annex 4.4) on a recently published paper on a trial of GeneXpert versus microscopy in 20 clusters in 4 provinces in South Africa (86), supplied with cost for preventive therapy from the MSH drug price indicator(87), as was done in a paper on HIV/TB interventions (72). As in Viet Nam, we added a monthly visit to the cost of the medication, so 6 visits for 6H and 3 visits for 3HR, using consultation costs from Vassall (86). Costs for 2nd line DST were used from a paper on rifampicin resistance (88). We assumed 10% of DS patients and 90% of MDR patients are being hospitalized, although other another costing study (89) assumed these proportions to be 0 and 100%, and there is a trend towards less hospitalizations. Costs for DS TB hospitalization were obtained from a paper on cost-effectiveness of 3 I’s (72) (based on 21 days WHO-CHOICE approach) and costs for MDR hospitalization (average 54 days) from the mean of scenarios A and B in a paper on decentralized MDR care (73).

Table 7. Main differences in costing approach between countries

	NL & PT (see Annex 4.1 and 4.2)	VN (see Annex 4.3)	SA (see main text and Annex 4.4)
Type of patients used for cost calculations	C+/C-, DS/MDR TB	SS+, SS_, EPTB, MDR new, MDR retreatment	SS+, SS-, new, retreatment, MDR
Age groups for costing	Not applied	<15, >=15	Not applied
Costs at different levels of health system included	No, assumed all decentral	District/national	PHC
Type of cost included besides direct cost			
- Staff cost	Y	Y (except for IGRA)	Y (except for IGRA)
- Other overhead	Some#	N	N
Contact tracing costing available and included in treatment cost**	Y*	N	N
Additional drugs for side effects included	Y	N	Y

C+/- = culture positive/negative, SS+/- = sputum smear positive/negative
*contact tracing in PT adapted based on number of contacts (see main text)
since hourly tariffs for staff applied and not only salaries
** This is mainly used when a person is treated for active TB, with one exception: when a positive ITB test is followed by full treatment, a CXR will be done. When this CXR shows TB related abnormalities, it will be followed by contact tracing (for costing); but not in case the CXR is normal.

5.3.2. Cost for ITB test

We assumed that those with a positive ITB test treated as LTBI or as active TB, but in both cases without contact tracing cost. In order to estimate the maximum costs of an ITB test to make it cost-saving or cost-effective, we assumed the costs of implementation of the screening would be 2 consultation visits, one for offering and doing the test, and one for explaining the result. This is similar as assumed for an IGRA. We used standard cost of US$ 1, 25 and 50 to show results of the model.

5.3.3. Burden

The effectiveness of the screening included averted TB disease (both PTB AND extra-pulmonary TB) and life years lost.

The TB burden calculated in the mathematical models was expressed in quality adjusted life years (QALYs). For TB disease (PTB or EPTB), a QALY loss of 0.331 was used, based on global burden of diseases estimates (90). In order to calculate the burden of TB morbidity, the number of person-years lived with TB was multiplied by 0.331. For individuals self-reporting and receiving treatment we assumed 0.5 month of additional burden, whereas this was 1 month for severe pathology cases. A year of life lost due to death corresponds with one QALY loss. In the baseline cohort models, the transmission effects were also included: we assumed 0.5 prevented secondary case per index case prevented, since we considered 0.19 based on own calculations from a review on contact tracing (91) too low, since the review only includes known secondary cases. As alternative scenarios we used 0 secondary cases, 0.19 prevented secondary cases (minimum based on the review on contact

tracing(91)), and 1 prevented case. In the model, alternative assumptions on secondary cases were included both in the cost and in the QALYs, assuming all secondary cases are part of the same age group as the index case.

In order to calculate the number of years of life lost (YLL) due to mortality, country specific life tables were obtained (Sources: Netherlands (92); Portugal (69); Viet Nam(67); South Africa(67)), and the average age was determined in each of the four age groups using population composition data from the United Nations World Population Prospects(67). The average remaining life-expectancy corresponding to the average age in each age-group was then applied as the number of YLL due to TB mortality for TB deaths in the population aged 0 – 4, 5 - 14 and 15 – 44 years. For NL, mortality rates due to TB were about four times higher in the 45+ age group (52), and the excess mortality compared to the 15 – 44 year age group might be explained by the fact that relatively many people who die due to TB at an older age are in poor health and would have died due to other causes relatively soon after TB activation, as suggested by Tiemersma et al(49). Therefore, applying the same approach to calculating YLL for people aged 45+ years would have resulted in an overestimation of the total number of YLL due to TB. Thus, for the Netherlands it was assumed that 75% of those dying due to TB in the age group 45+ had a remaining life-expectancy of 1 year, and 25% had a remaining life-expectancy similar to the average person in the age group. For Portugal these proportions were 60% and 40%, for VN 42.9% and 57.1%, and for South Africa 9.1% and 90.9%. Annex 3 shows the resulting proportions hospitalized and dying.

5.3.4. ICER

The cost-effectiveness of LTBI control strategies was expressed as an incremental cost-effectiveness ratio (ICER), which was calculated by dividing the cost difference (incremental costs) between the strategies of interest and the baseline (current policy) with the burden difference (incremental QALYs gained). In short ICER= (C1-C0)/(E1-E0). When C1 is smaller than C0, and E1 is larger than E0, the strategy is cost-saving. Arbitrary willingness-to-pay thresholds (2 x per capita GDP) were chosen per country in order to determine whether a strategy was cost-effective. When the total incremental costs indicated cost-savings compared to the baseline, yet the strategy results in QALY gains, the intervention is said to be dominant, and no ICER was calculated. For both costs and effect a 20 year time horizon was applied. Costs and effects are discounted at 3% annually.

In order to more directly compare strategies, the total incremental costs were plotted against the total incremental effects in a traditional cost-effectiveness plot.

5.4. Other model outcomes

We also calculated a number of other outcomes for the cohorts of 10,000 contacts and cohort of 10,000 HIV infected persons, and compared these to baseline scenario of doing nothing, and compared to WHO policy.

- Costs per treated case averted when the costs for a test is US$ 50
- Predicted number of (averted) TB cases receiving TB treatment
- Predicted number of (averted) TB deaths

- Number of persons with a positive ITB test detected by screening, starting LTBI treatment
- Number needed to screen to detect 1 person with ITB

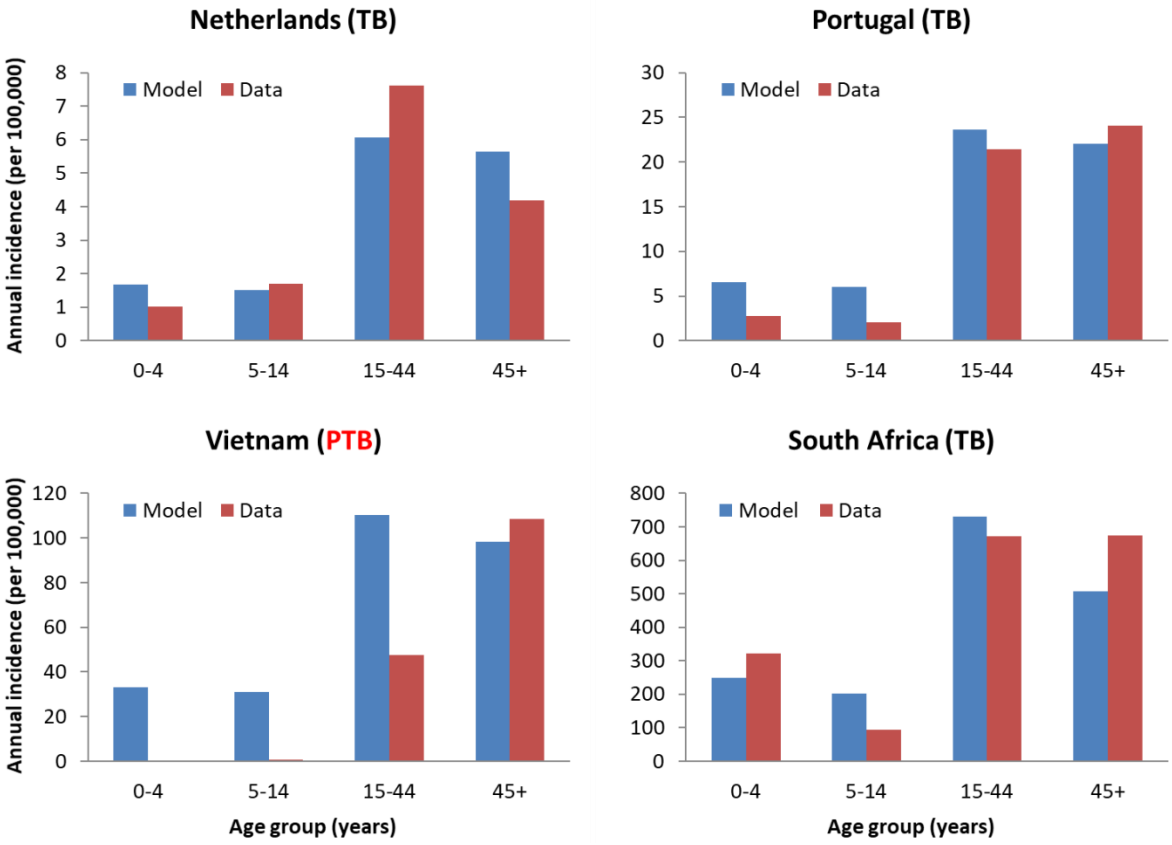
We also extrapolated these cohort model results to countrywide data, using rough estimates of the number of contacts and HIV infected persons in the 4 countries. This was not possible for other immunocompromised persons since very little epidemiological information was available on those.

6. RESULTS

6.1. Comparison of model to country data

The model was fit to WHO estimated total TB incidence in the countries, for all age groups together. Figure 6 shows how these fits resulted in notified total TB incidence by age group for the 4 countries (age estimates based on total incidence, multiplied with notified/estimated correction). We show a reasonable model fit for age groups in the Netherlands and South Africa. In Viet Nam, and to a lesser extent Portugal, the model shows much higher incidences among children than notified data. However it is well known that particularly childhood TB is underdiagnosed and under notified in many countries.

Figure 6. Comparison of model results with data on notified* TB incidence in 4 countries.

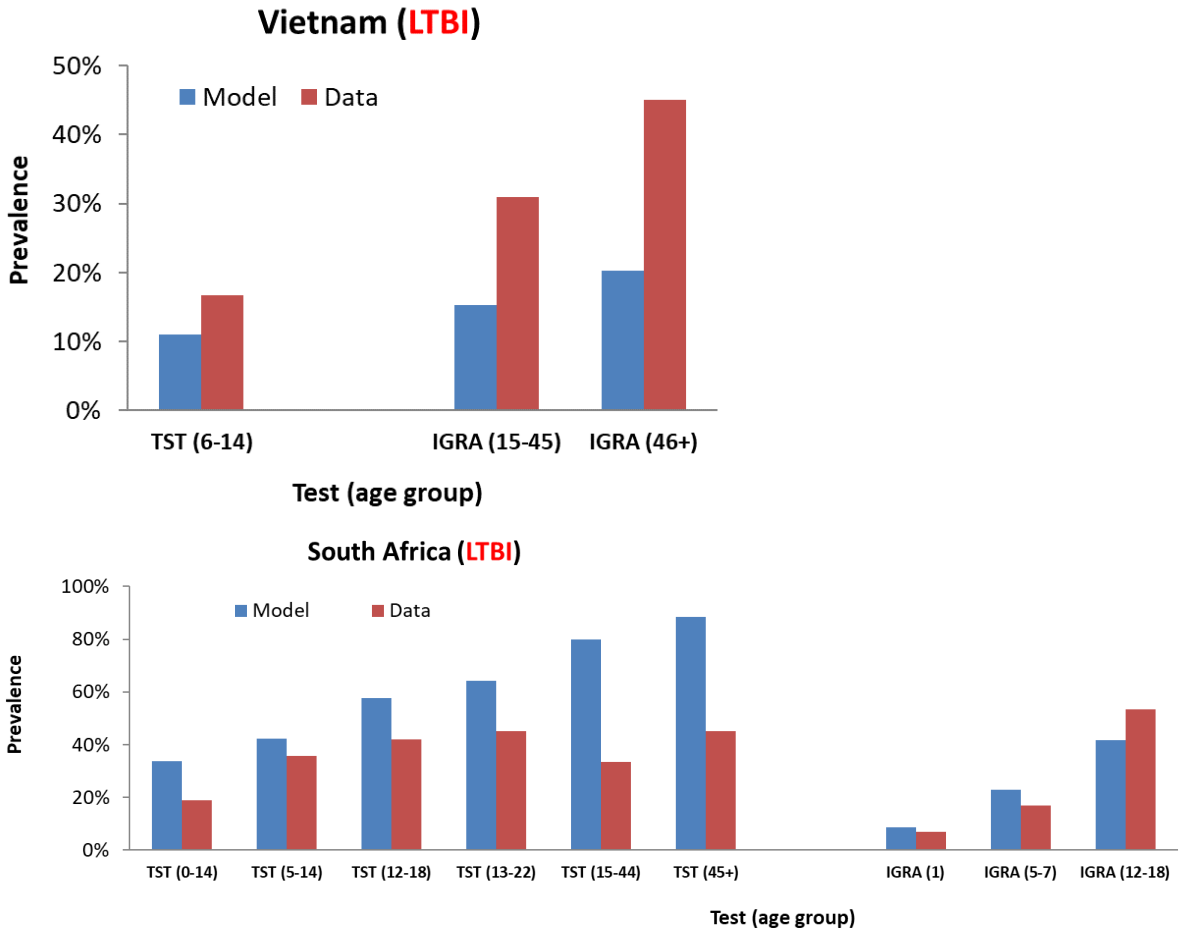


*The model results on WHO estimated TB-incidence were corrected for the proportion notified versus estimated to obtain comparison to data on notified TB incidence.

Figure 7a shows the corresponding model fits to age specific LTBI prevalence data from published studies in Viet Nam (top) and South Africa (bottom). Those studies are often done in only a small area of the country or have a selection bias. Therefore often the model is different from the data. The only nationwide study was a national tuberculin survey in Viet Nam in 2006-2007; 8-9 years before the model data in 2015. The decreasing trend in TB in Viet Nam may explain why the model estimates lower LTBI prevalence than the survey. Another example is the last study in South Africa among adolescents in Worcester, South Africa, an area with one of the highest TB incidences in the country. This may explain why

the model estimates a lower proportion IGRA positive than the data show. In South Africa the model estimates a much higher proportion TST positive than published studies show. This may be due to some degree of waning of the TST, where our model assumes all TST-positive individuals to remain positive. This is not a problem for our model predictions since TST is not used in scenarios of this report. One other modelling study estimated the LTBI prevalence to be 31% in South Africa(93), while our model estimated 56% (not shown). This may be due to population groups that do not mix with infected persons and remain uninfected; while our model assumes homogenous mixing; also, the LTBI concept may differ between the 2 models.

Figure 7a. Comparison of model data with published studies on LTBI prevalence in Viet Nam (top) and South Africa (bottom)



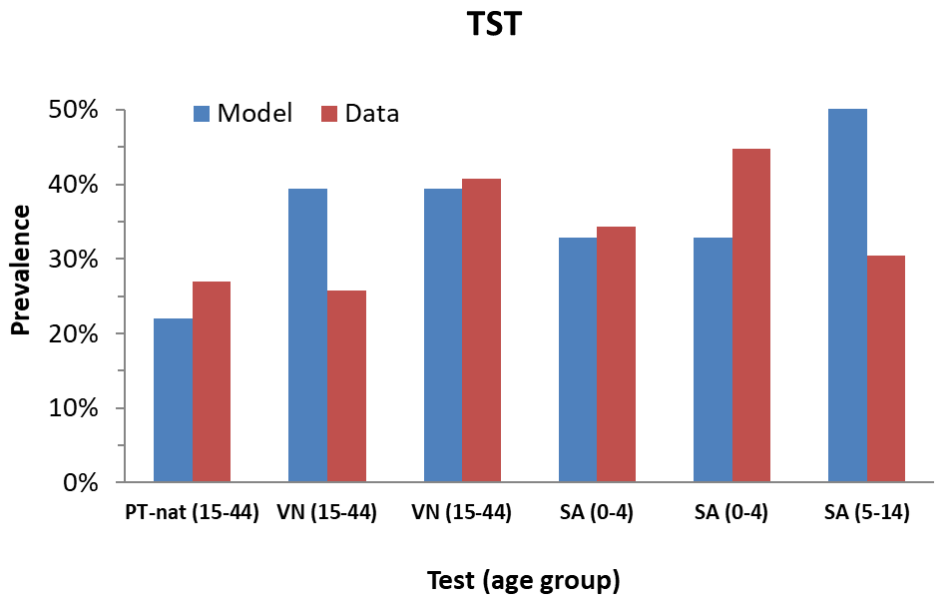
References Vietnam (94, 95); South Africa(96-101).

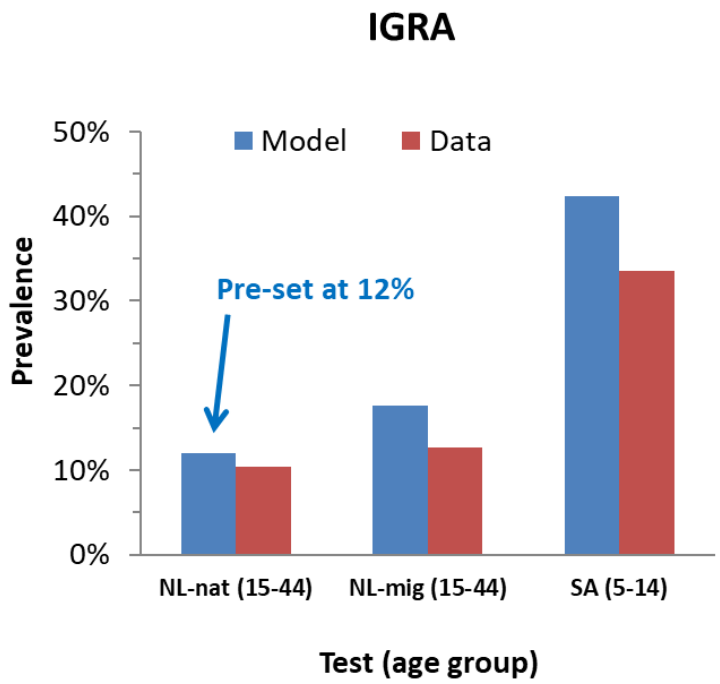
Regarding the modelling of close contacts, our model was tuned such that contacts of 15-44 having had an increased exposure for 3 months resulted in 12% IGRA positive immediately after exposure in the Netherlands. This is based on latest study in the Netherlands on contact tracing, that found 10.4-12.6% of close contacts of PTB patients had LTBI, based on TST or IGRA (102)). Using the same FOI for other countries and age groups, but different lengths of increased exposure, the resulting proportions IGRA positive contacts are presented in Annex 3.

Figure 7b shows comparison of model results with published studies on contact tracing in all 4 countries. The Netherlands contact tracing data have been used to pre-set the model. It is reassuring that the model results for other countries match the data rather well.

Figure 7b. Comparison of model results with published studies on contact tracing in all 4 countries.

Studies are sorted by LTBI test: TST studies (top) and IGRA studies (bottom). nat= natives, mig = migrants. References Netherlands (102), Portugal(103), Vietnam(104), South Africa (105, 106). Age comparisons are limited by lack of data on the distribution of tested individuals over the different age groups. All 15-44 age group comparisons (both TST and IGRA) were actually with all age groups in the data. The SA study on 6 months to 15 years using IGRA was compared to age group 5-14 in the model.





6.2. Costing

Table 8 indicates the costs in 2015 used to calculate ICER by country.

Table 8. Costs in 2015 used to calculate ICER by country*

Costs	NL	PT	VN	SA
Screening tests				
CXR	$ 69.55	$ 51.90	$ 3.12	$ 15.41
GeneXpert/culture*	$ 57.78	$ 43.12	$ 99.32	$ 24.81
IGRA	$ 101.46	$ 75.72	$ 60.95**	$ 64.30
Treatments				
Treatment DS TB	$ 1,569.72	$ 1,089.66	$ 147.62	$ 181.28
Treatment MDR-TB	$ 20,283.15	$ 19,803.10	$ 1,420.60	$ 6,344.22
DOT TB#	$ 366.30	$ 273.36	$ 5.92	included above
DOT MDR-TB#	$ 1,828.17	$ 1,364.31	$ 45.15	included above
LTBI-treatment				
6H	$ 577.61	$ 450.60	$ 13.76	$ 92.98
3HR	$ 512.38	$ 354.27	$ 28.58	$ 61.65
Hospitalizations				
DS TB	$ 7,039.06	$ 8,755.05	$ 117.36	$ 1,320.80
MDR TB	$ 43,836.08	$ 33,552.30	$ 49.51	$ 3,987.74
Contact tracing	$ 4,493.28	$ 2,791.69	N/A	N/A
2 consultation visits for ITB testing##	$ 42.18	$ 31.48	$ 3.43	$ 25.48
Willingness to pay threshold (2x per capita GDP)	$ 91,276	$ 39,676	$ 4,340	$ 10,550

* References and limitations see text in methods/costs paragraph. ** only available at 3 hospitals. N/A = not applicable or not available. # not yet included in treatment cost

These costs were also included in the ICER calculations. Costs of ITB testing= chosen test costs ($ 1, 25 or 50)plus costs of two consultation visits.

6.3.Results of screening contacts

6.3.1 Using basic assumptions

We modelled cohorts of 10,000 contacts for all 4 countries and 4 age groups, and we found substantial QALYs gained by screening and treating contacts with an ITB test (see Figure 8). QALYs gained are higher in countries with higher TB incidence (SA highest, then VN, PT, NL) due to the assumed longer exposure to the source case and longer average duration of TB before treatment, and thereby higher risk to die.

In Figure 8 all outcomes are related to the baseline of doing nothing. However, we can also see the results when using an alternative baseline, by comparing the ITB test with doing the IGRA in NL/PT and CXR in VN/SA (green bullet).

Testing and treating for ITB among close contacts is highly cost-effective in all 4 countries (Figure 9). In contacts in NL and PT, the health impact of the WHO recommended strategy of one-time testing with IGRA is comparable to two to three times ITB testing, and overall costs are similar if ITB test costs US$ 25 (Table 9a). This is because the IGRA is rather expensive and the test leads to many more LTBI treatments required, but on the other hand these extra treatments also avert future (re-)activation, making a single IGRA relatively effective. Also, the timing of the ITB test is not ideal immediately after detecting the index case (t=0), as many with infection are still in the early LTBI stage and have not (yet) developed ITB. Usually waiting a couple of months is better (results not shown). In VN and SA, ITB testing strongly outperforms the use of CXR for contacts, by resulting in a much higher health impact. This can be explained by the average time it takes before infection leads to detectable active TB, which is often longer than the duration of increased exposure, so that CXR at t=0 is relatively inefficient. In children 0-4 in VN and SA, WHO recommends immediate preventive therapy, without testing. In VN this results in the baseline of immediate preventive therapy outperforming the ITB testing, but not in SA.

The difference between countries in cost-effectiveness can be achieved is largely explained by difference in costing approach: in NL and PT all averted future costs (i.e. TB treatment, hospitalization and contact investigations) are relatively high (e.g. by including overhead in the staff costs), which exceed the initial investments in costs for ITB screening and treatment of detected ITB and TB cases. In the test cost to achieve cost-effectiveness are higher for PT than for NL since similar averted high future costs are combined with a substantially lower willing-to-pay threshold. Also, contacts in PT are assumed to experience a one month longer exposure to the index case.

On purpose the terminology used for cost saving and cost-effectiveness is ITB TESTING rather than ITB TEST. The former includes both the costs of the test plus staff costs to perform the test. The testing costs are test cost plus 2 consultation visits (see Table 8). The TEST costs are the maximum test-costs that can be charged by manufacturers.

It should be noted that countries may apply rather different thresholds than the 2xGDP used here. Also, strategies should be considered affordable by decision makers; cost-effective interventions still require the necessary funding.

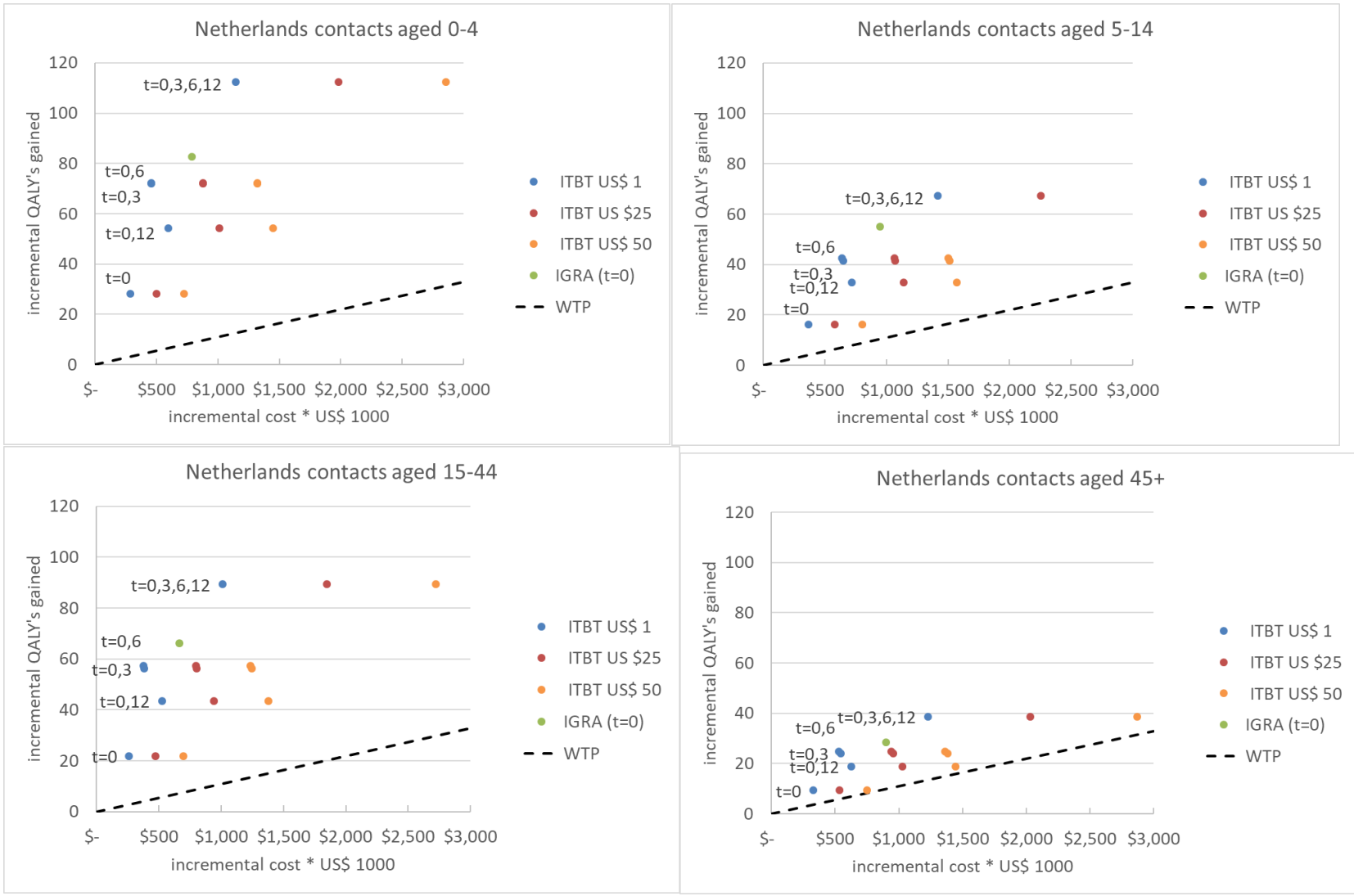
Among the different age groups, the age group 0-4 is the most cost-effective to screen for LTBI, since the risk of activation is relatively high, together with the highest number of years of life lost if a death from TB is averted. The age group 15-44 shows comparable results as it has the same risk of activation, together with a higher TB-death rate for those entering the 45+ group within the 20 year time horizon. The least cost-effective group to screen is 45+, followed by those 5-14 years.

When comparing different frequencies and time points to do the incipient TB test, we found it was best to do duplicate incipient TB testing twice at 0 and 6 months after diagnosis of index case, instead of 0 and 3, or 0 and 12. Postponing the first test 1 month to 4 months after diagnosing the index case is even more cost-effective (data not shown since contact tracing will in practice start immediately after diagnosis of index case for early detection of symptomatic TB patients among contacts). Testing 4 times (at t = 0, 3, 6 and 12 months) is very expensive.

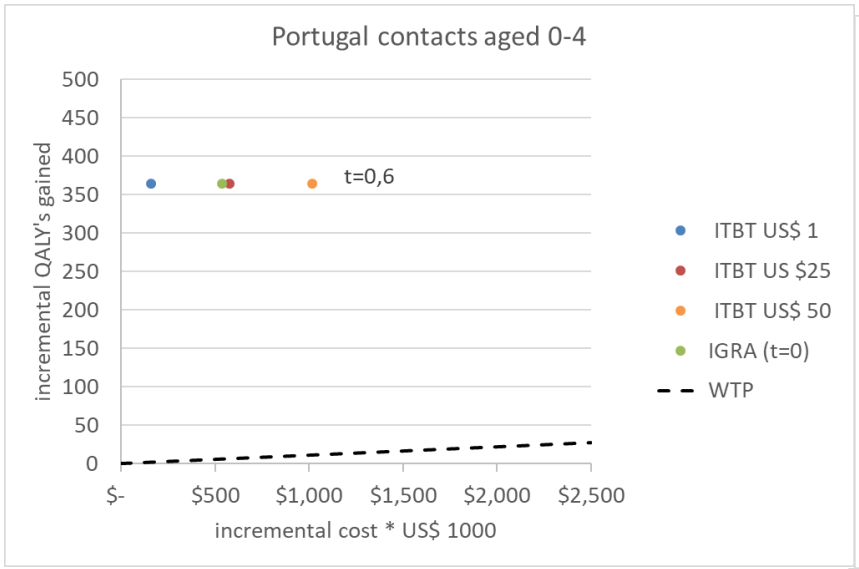
Figure 8. Incremental costs and QALYs gained of a cohort of 10,000 contacts in (a) the Netherlands (b) Portugal, (c) Viet Nam and (D) South Africa

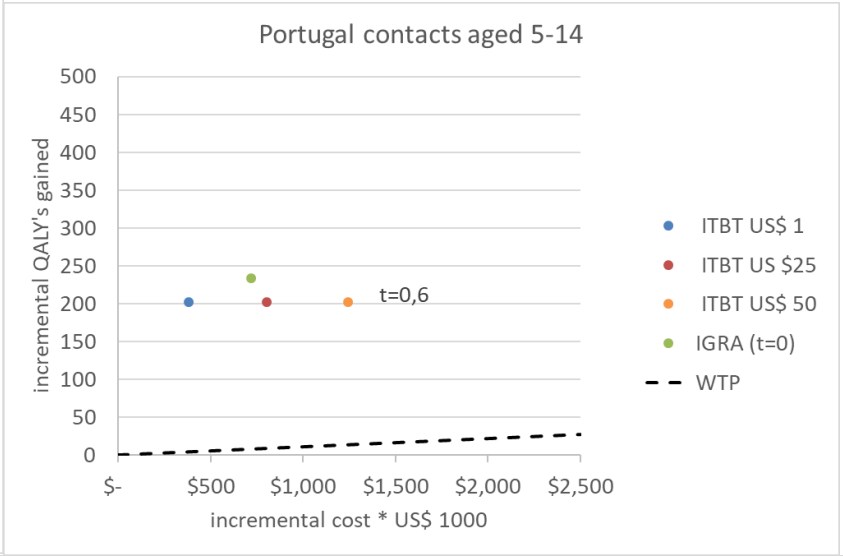
Results are cumulative incremental costs and QALYs gains over a 20-year period by doing ITB testing and treatment with 6H in a population of 10,000 contacts immediately after exposure, compared to the baseline of doing nothing. Each country has 4 graphs for 4 age groups. The vertical line (Y-axis) represents ICER=zero. The dashed line represents the willingness to pay threshold (WTP). Blue, red and yellow bullets on the same horizontal line are different costing options for the same frequency and time points of doing the ITB test. The alternative baseline is using IGRA screening for NL and PT or CRX screening for VN and SA (green bullet).

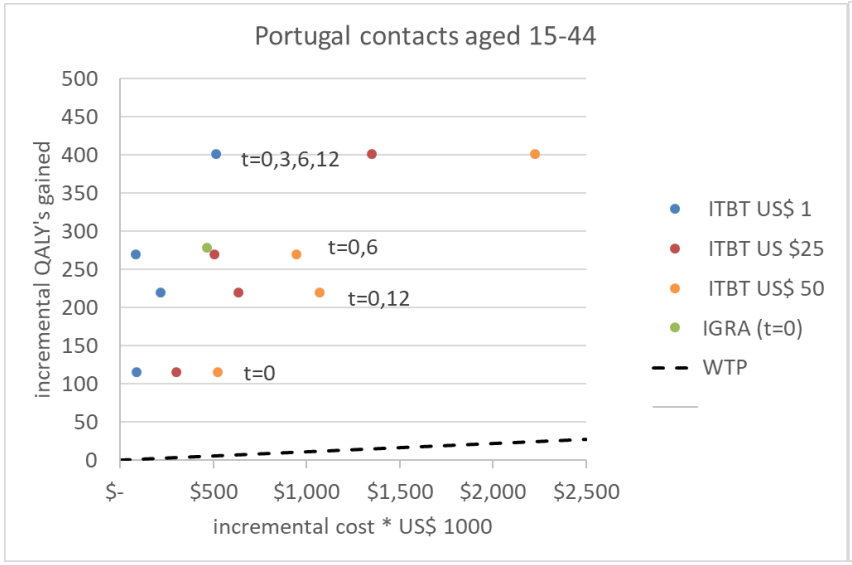
A. **Netherlands (only natives).**

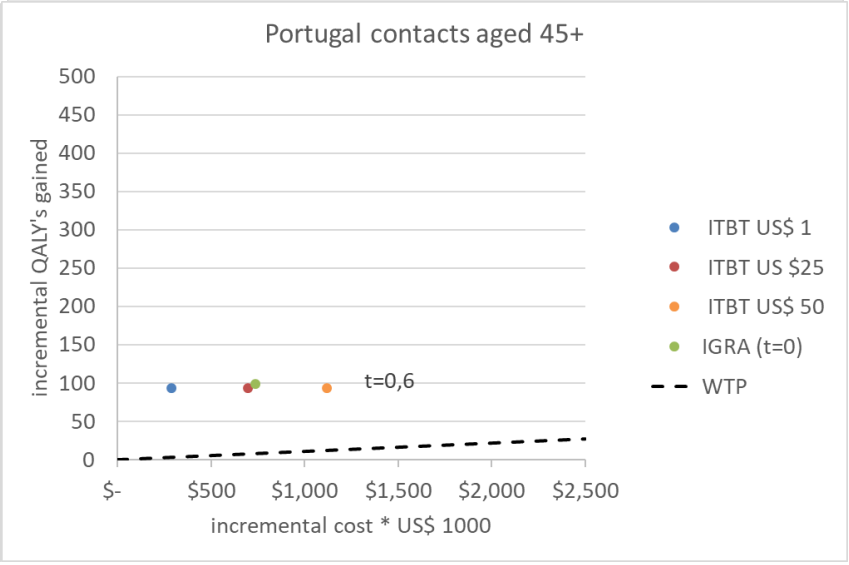


B. Portugal (only natives)

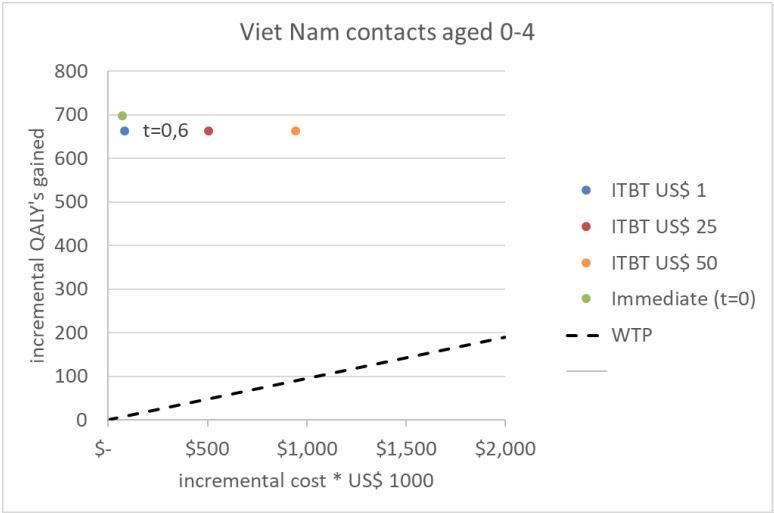


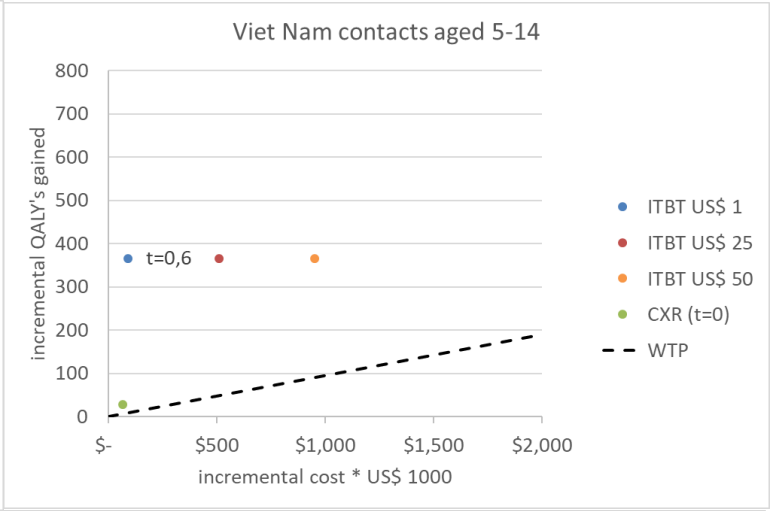


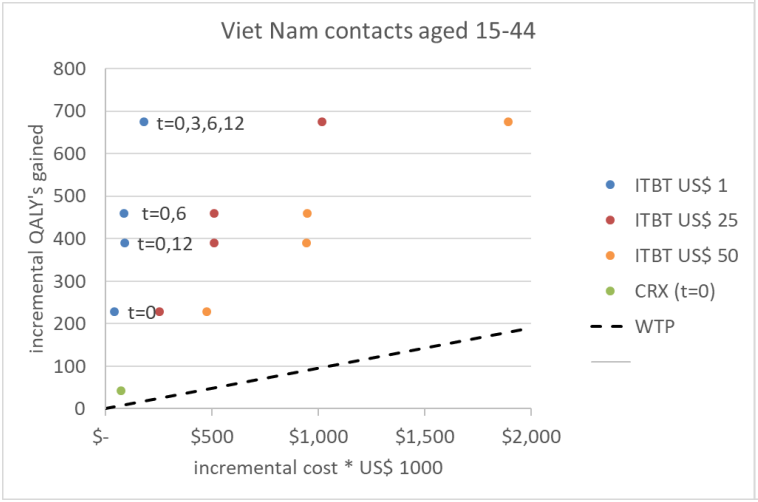


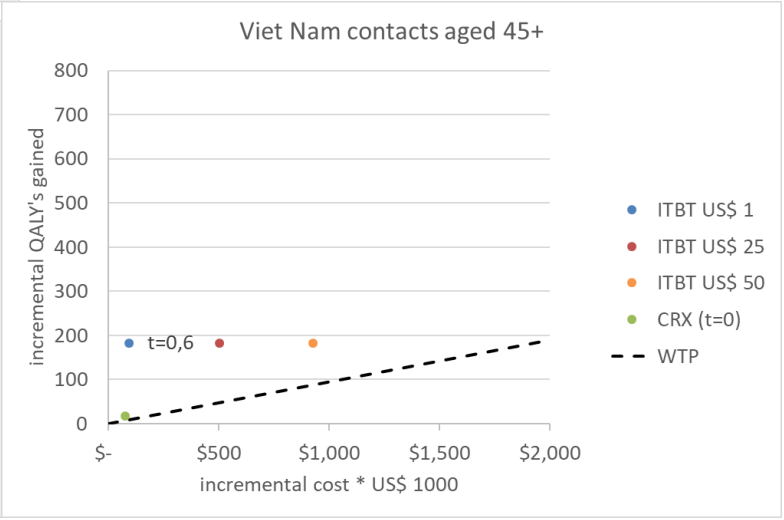


C. Viet Nam.


Viet Nam contacts aged 0-4
incremental QALY's gained
800
700
600
500
400
300
200
100
0
$-
$500
$1,000
$1,500
$2,000
incremental cost * US$ 1000
t=0,6
ITBT US$ 1
ITBT US$ 25
ITBT US$ 50
Immediate (t=0)
WTP


Viet Nam contacts aged 5-14
incremental QALY's gained
800
700
600
500
400
300
200
100
0
$-
$500
$1,000
$1,500
$2,000
incremental cost * US$ 1000
t=0,6
ITBT US$ 1
ITBT US$ 25
ITBT US$ 50
CXR (t=0)
WTP


Viet Nam contacts aged 15-44
incremental QALY's gained
800
700
600
500
400
300
200
100
0
$-
$500
$1,000
$1,500
$2,000
incremental cost * US$ 1000
t=0,3,6,12
t=0,6
t=0,12
t=0
ITBT US$ 1
ITBT US$ 25
ITBT US$ 50
CRX (t=0)
WTP


Viet Nam contacts aged 45+
incremental QALY's gained
800
700
600
500
400
300
200
100
0
$-
$500
$1,000
$1,500
$2,000
incremental cost * US$ 1000
t=0,6
ITBT US$ 1
ITBT US$ 25
ITBT US$ 50
CRX (t=0)
WTP

D. South Africa

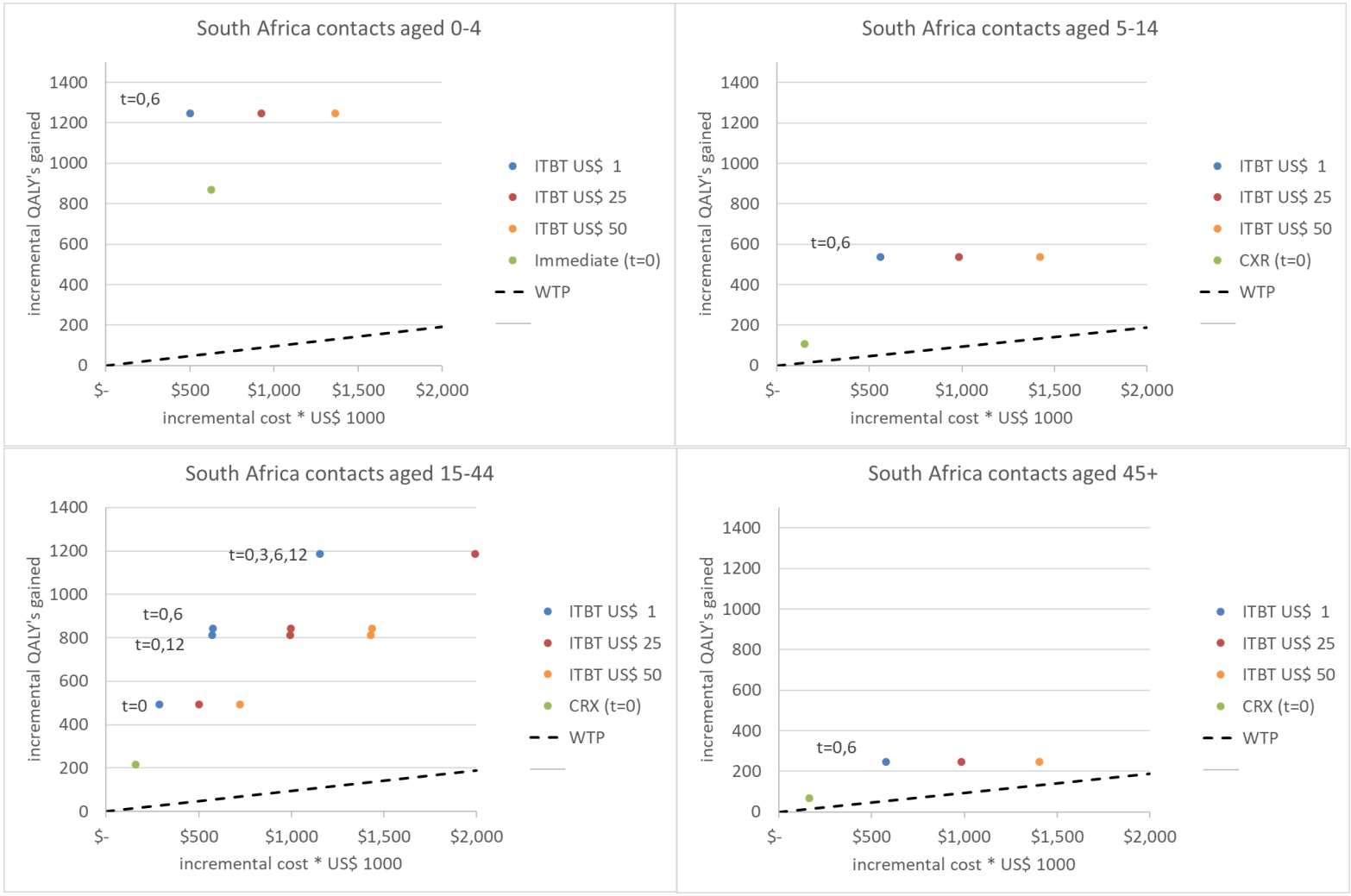


Figure 9. Maximum costs of ITB testing for contacts for baseline scenario

Figure represents maximum costs of ITB test for contacts screened at 0 and 6 months after diagnosis of index case, to make the ITB testing cost effective (exactly at the WTP threshold). All outcomes are based on using 6H as treatment and are compared to the baseline of doing nothing. NL and PT concern only natives.

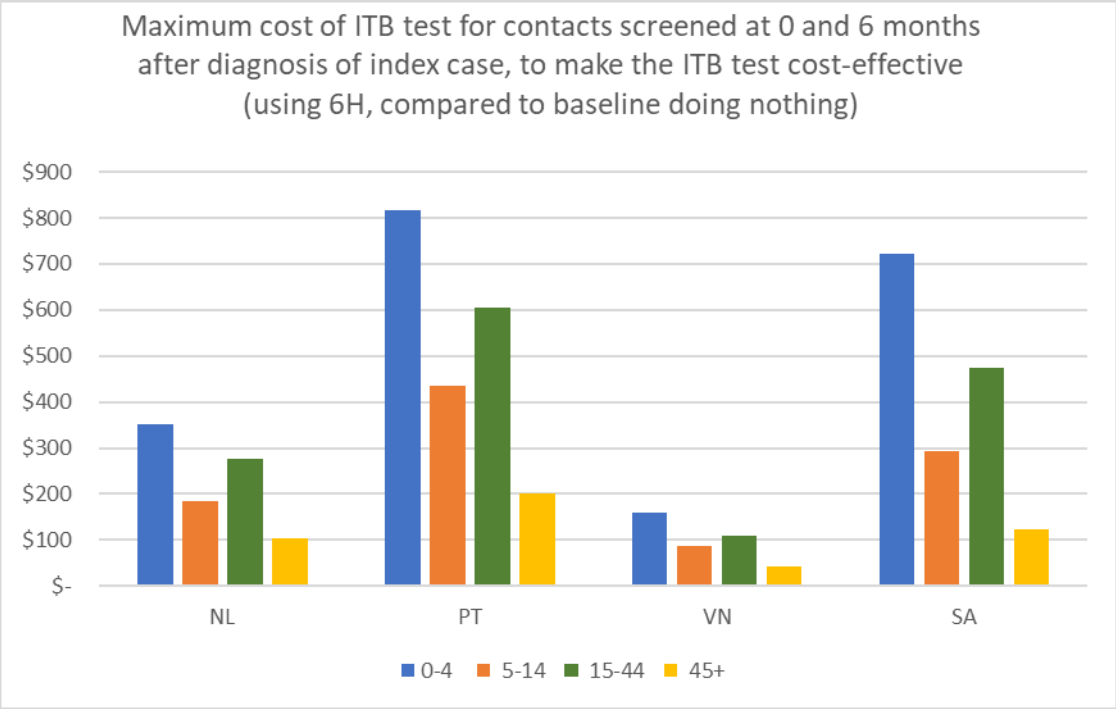


Table 9a. Summary of ITB test costs thresholds for cost-effectiveness for different scenarios for contacts.

Explanation of table: The costs represent the costs of the ITB test to make the ITB testing (i.e. test itself plus staff cost)cost-effective (i.e. exactly at the willingness to pay threshold (WTP)). Baseline scenario = use of incipient TB test at time t = 0 and 6 months compared to doing nothing, in adults aged 15-44, using 6H as treatment for those with a positive ITB test, assuming 90% screening coverage and 70% for a combination of treatment start and treatment completion, and assuming 0.5 secondary cases prevented. Alternatives scenarios are given in the rows.

	NL	PT	VN	SA
Contacts baseline scenario				
age groups				
0-4	$ 350	$ 816	$ 160	$ 723
5-14	$ 185	$ 436	$ 86	$ 292
15-44	$ 278	$ 605	$ 109	$ 475
45+	$ 103	$ 202	$ 42	$ 122
For age group 15-44:				
Alternative treatments				
6H (baseline)	$ 278	$ 605	$ 109	$ 475
3HR	$ 296	$ 635	$ 114	$ 491
2HRZE/4HR	$ 321	$ 677	$ 122	$ 548
Different performance 6H				
coverage 90% completed 70% (baseline)	$ 278	$ 605	$ 109	$ 475
coverage 95%, completed 95%	$ 354	$ 730	$ 131	$ 535
coverage 50%, completed 50%	$ 219	$ 516	$ 94	$ 442
Different assumptions on secondary cases prevented				
0	$ 165	$ 387	$ 71	$ 305
0.19	$ 208	$ 470	$ 86	$ 370
0.5 (baseline)	$ 278	$ 605	$ 109	$ 475
1	$ 391	$ 823	$ 148	$ 645

6.3.2. Alternative treatments

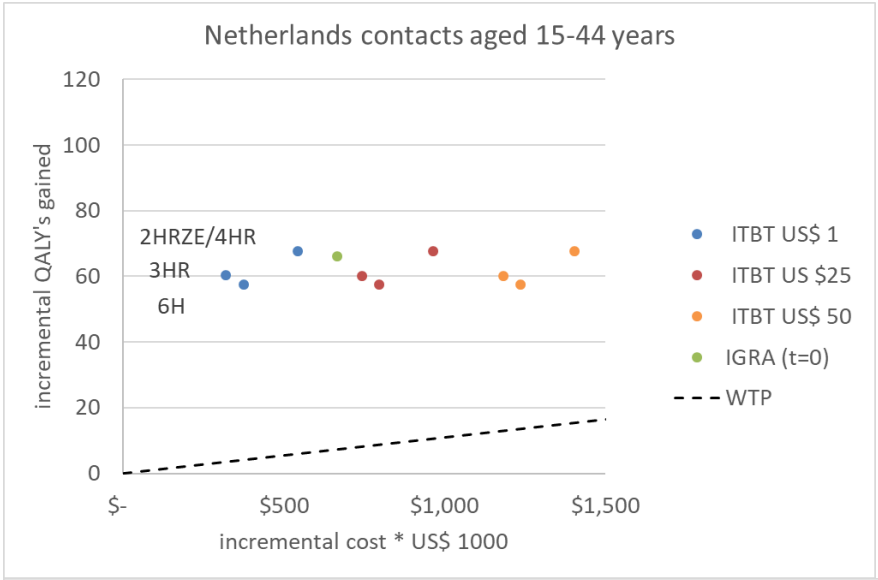
Figure 10 shows the effect of alternative treatments for the baseline scenario for all 4 countries. More QALYs are gained by using full treatment, but this option is also more costly. ITB testing will never be cost-saving but all treatment options are cost-effective; even at high test cost (Table 9). 3HR is slightly preferable over 6H since it is both cheaper and more QALYs are gained due to assumed higher treatment success (75% vs. 70%).

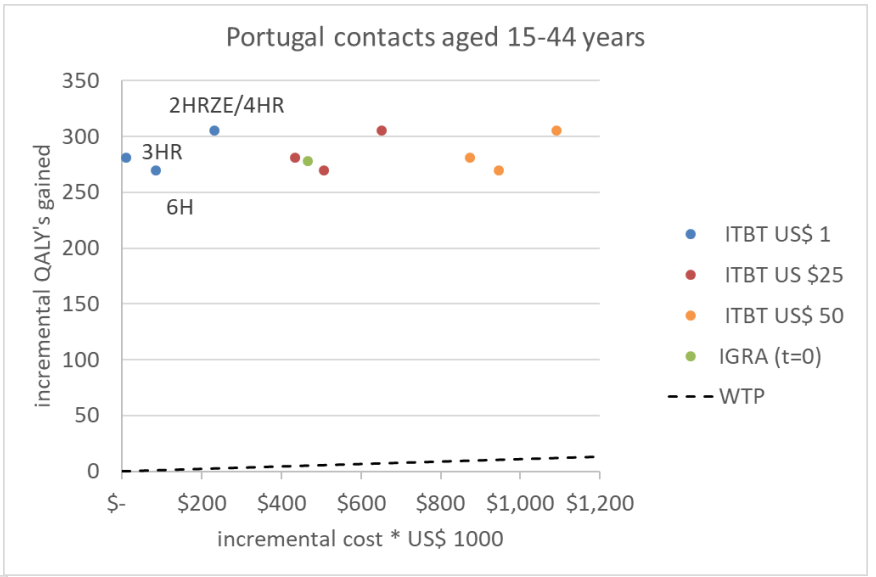
6.3.3. Alternative assumptions on prevention of secondary cases

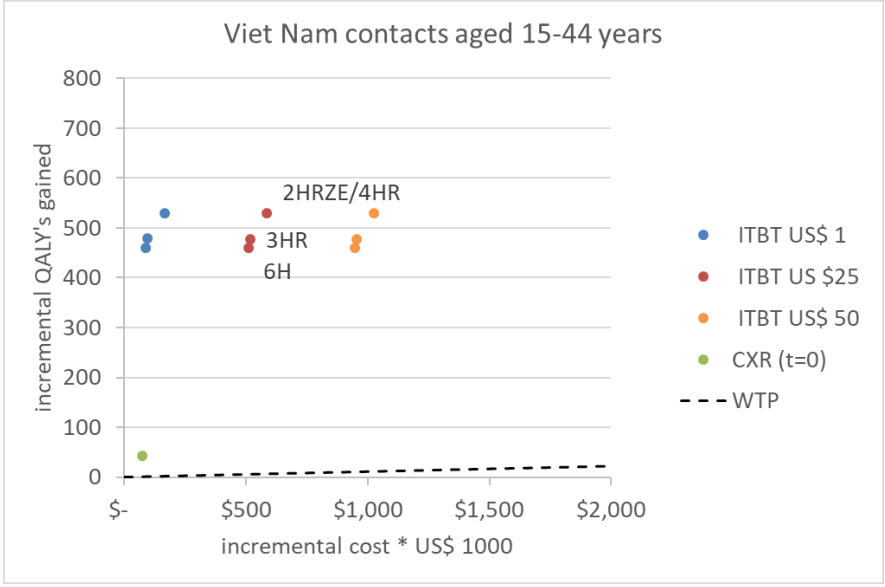
In our baseline we assumed 0.5 prevented secondary cases per index case prevented. When assuming prevention of 1 secondary cases, the incremental QALYs gained logically are 33.3% (2 vs. 1.5 cases) higher for all situations but the effect on cost is somewhat smaller (Figure 11). The latter is due to the fact that the investments remain the same, whereas only the averted future costs of TB treatments, hospitalizations and contact investigations are increased. Testing can be even cost-saving in Portugal when the ITB test costs are around US$10 and when assuming 1 secondary case prevented per source case, but it will never lead to cost-saving in NL, SA and VN (Table 9a).

Figure 10. Incremental costs and QALYs gained of a cohort of 10,000 contacts aged 15-44 in the 4 countries using different treatment options

Next page. Explanation see Figure 8. Blue, red and yellow DOTS on the same horizontal line represent different costing options for the same treatment scenario. A positive IGRA is treated with 6H.NL and PT only natives.


Netherlands contacts aged 15-44 years
incremental QALY's gained
120
100
80
60
40
20
0
2HRZE/4HR
3HR
6H
$-
$500
$1,000
$1,500
incremental cost * US$ 1000
ITBT US$ 1
ITBT US $25
ITBT US$ 50
IGRA (t=0)
WTP


Portugal contacts aged 15-44 years
incremental QALY's gained
350
300
250
200
150
100
50
0
2HRZE/4HR
3HR
6H
$-
$200
$400
$600
$800
$1,000
$1,200
incremental cost * US$ 1000
ITBT US$ 1
ITBT US $25
ITBT US$ 50
IGRA (t=0)
WTP


Viet Nam contacts aged 15-44 years
incremental QALY's gained
800
700
600
500
400
300
200
100
0
2HRZE/4HR
3HR
6H
$-
$500
$1,000
$1,500
$2,000
incremental cost * US$ 1000
ITBT US$ 1
ITBT US $25
ITBT US$ 50
CXR (t=0)
WTP

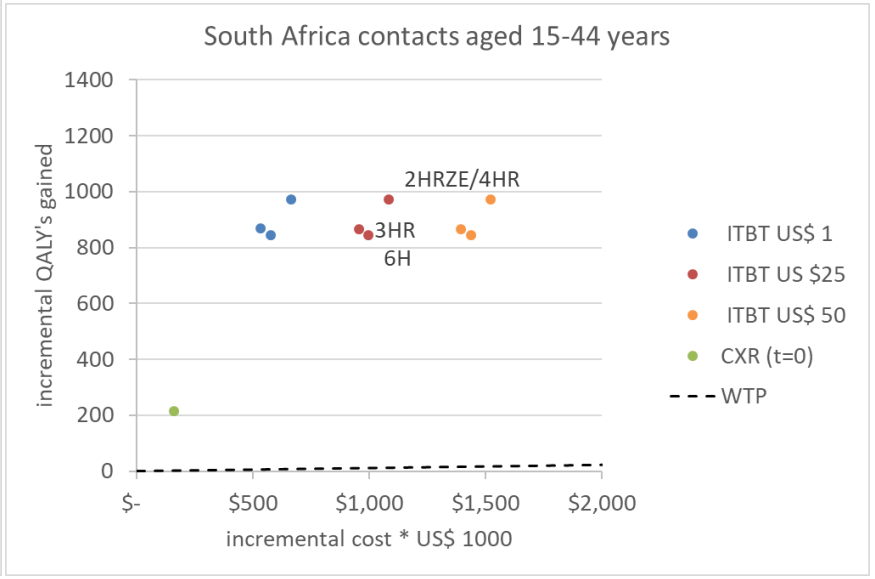
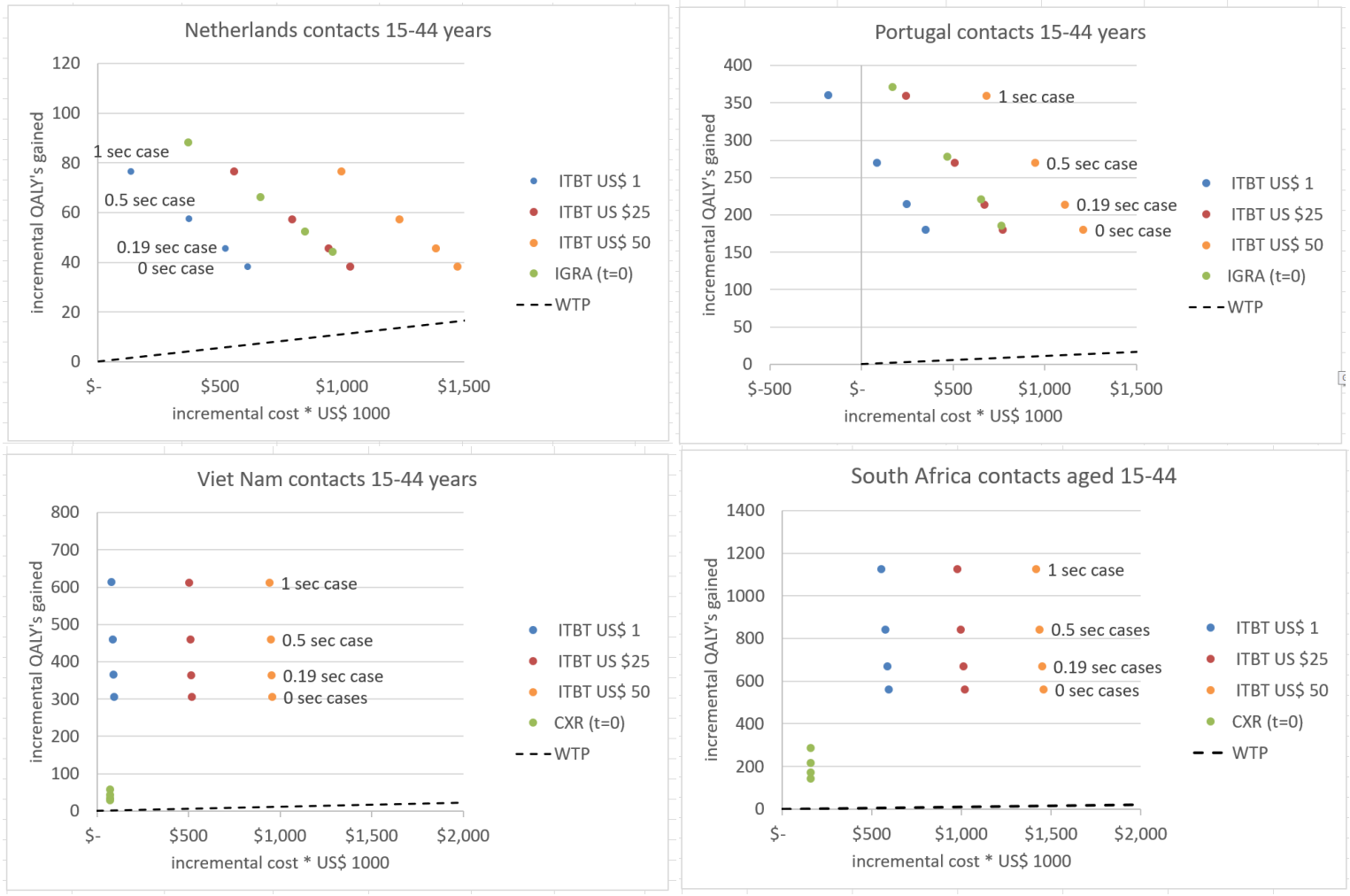

South Africa contacts aged 15-44 years
incremental QALY's gained
1400
1200
1000
800
600
400
200
0
2HRZE/4HR
3HR
6H
$-
$500
$1,000
$1,500
$2,000
incremental cost * US$ 1000
ITBT US$ 1
ITBT US $25
ITBT US$ 50
CXR (t=0)
WTP

Figure 11. Incremental costs and QALYs gained of a cohort of 10,000 contacts aged 15-44 in the 4 countries using different scenarios for prevented secondary cases

Explanation see Figure 8. Sec cases = prevented secondary cases for each index case prevented. Blue, red and yellow DOTS on the same horizontal line represent different costing options for the same secondary case scenario. NL and PT concern only natives.



6.4. Results of screening HIV infected persons and other immunocompromised persons

6.4.1 Using basic assumptions

HIV infected persons and other immunocompromised persons are presented together, since they have in common an increased risk of activation (relative risk, RR). The size of the increase is often unknown since it depends on for example stage of disease and treatment status. Testing adult immunocompromised persons with relative risk of activation (RR) = 4 aged 15-44 is our main scenario for adults, and RR=2 for children (for references see Methods).

Testing and treating for ITB of HIV patients and other immunocompromised persons born in very low incidence settings such as the Netherlands is not cost-effective, but it can be cost-effective in medium and high incidence countries, as well as for migrants from high-incidence countries (Figure 12). For HIV patients (and other immunocompromised with RR=4), screening every 3 years for ITB results in roughly the same health impact as the WHO recommended strategy of one time using IGRA and CXR combined for NL, PT, VN; the costs are comparable if an ITB test is in the order of magnitude of 10 US$. Annual screening yields more QALYs but is also more expensive.

In the Netherlands all options for natives are never cost saving AND more expensive than the WTP threshold; and testing for ITB only once is (therefore) the least unfavourable option. In Table 9b we can see that even when the RR = 10, testing this group will not lead a cost-effective result, simply because too few people have LTBI that can activate. For immunocompromised migrants in the Netherlands, and persons born in moderately endemic countries (e.g. Portugal) ITB testing is borderline cost-effective. For VN and SA, testing immunocompromised persons with is highly cost-effective.

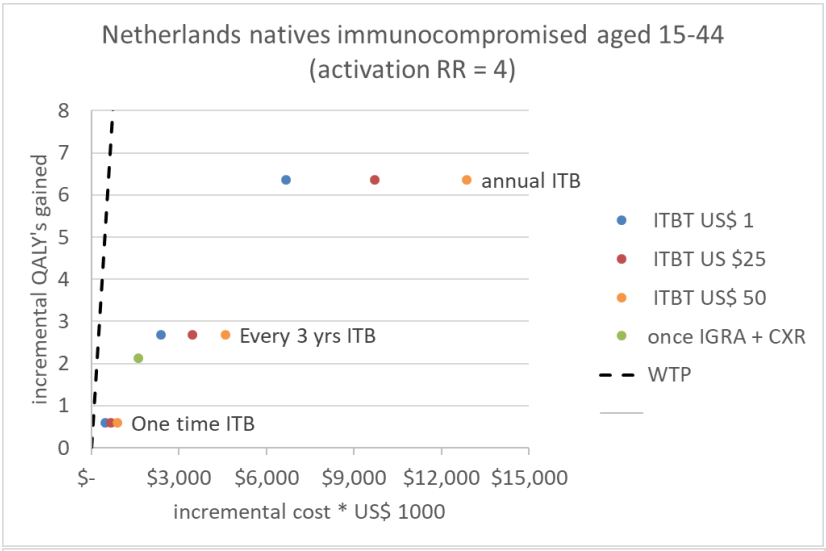
It should be noted that the alternative baseline of WHO policy CXR + IGRA for South Africa leads to the perverse outcome that it seems to have (slightly) more QALY loss than doing nothing. This is due to the assumption in the model that these persons return to susceptible where they are subject to re-infection (at a rate similar to naïve individuals) and thereby may have a higher risk to get TB again than those staying in remote LTBI (where re-infection is assumed to be subject to some degree of immunity). In real life this process may not occur as such.

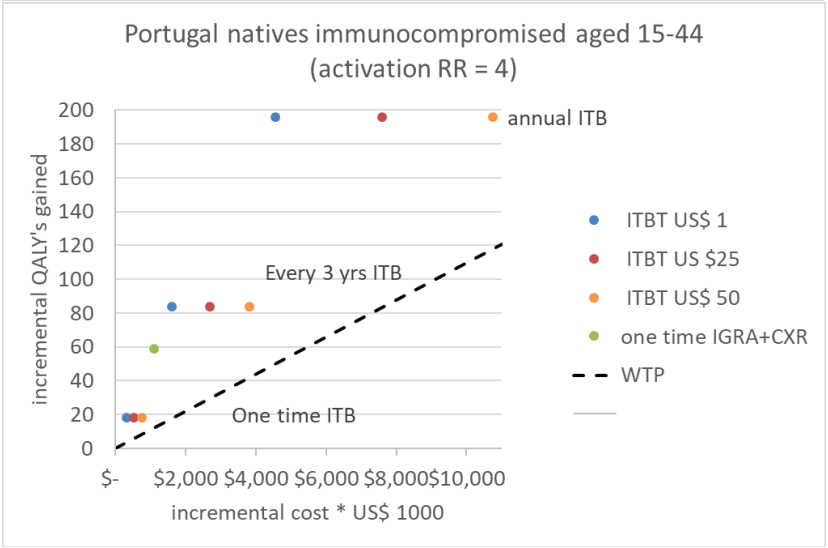
The maximum test-costs that can be charged by manufacturers to arrive at cost-effective outcomes can be several hundred US$ for screening HIV patients in SA, but are much less so for HIV infected persons in NL(migrants US$67-101), PT (US$26-47) and VN(US$42-54) (Table 9b).

We show an illustrative example on alternative age groups with relative risk of activation equal to 2 in the lower age groups (0-4 and 5-14) and RR = 4 in the higher age groups (15-44 and 45+) for South Africa (Figure 13). These results show that incremental QALYs gained for the younger age groups are less than for the 15-44 year age group, but still higher than the 45+ age group.

Figure 12. Incremental costs and QALYs gained of a cohort of 10,000 immunocompromised persons aged 15-44 in the 4 countries using different testing frequencies.

Next page. Explanation: see Figure 8 above. NL and PT concern only natives! Risk of activation (RR) = 4; blue, red and yellow dots on a horizontal line represent the same testing frequency at different costing options. Illustrative example of migrants in the Netherlands in the end.





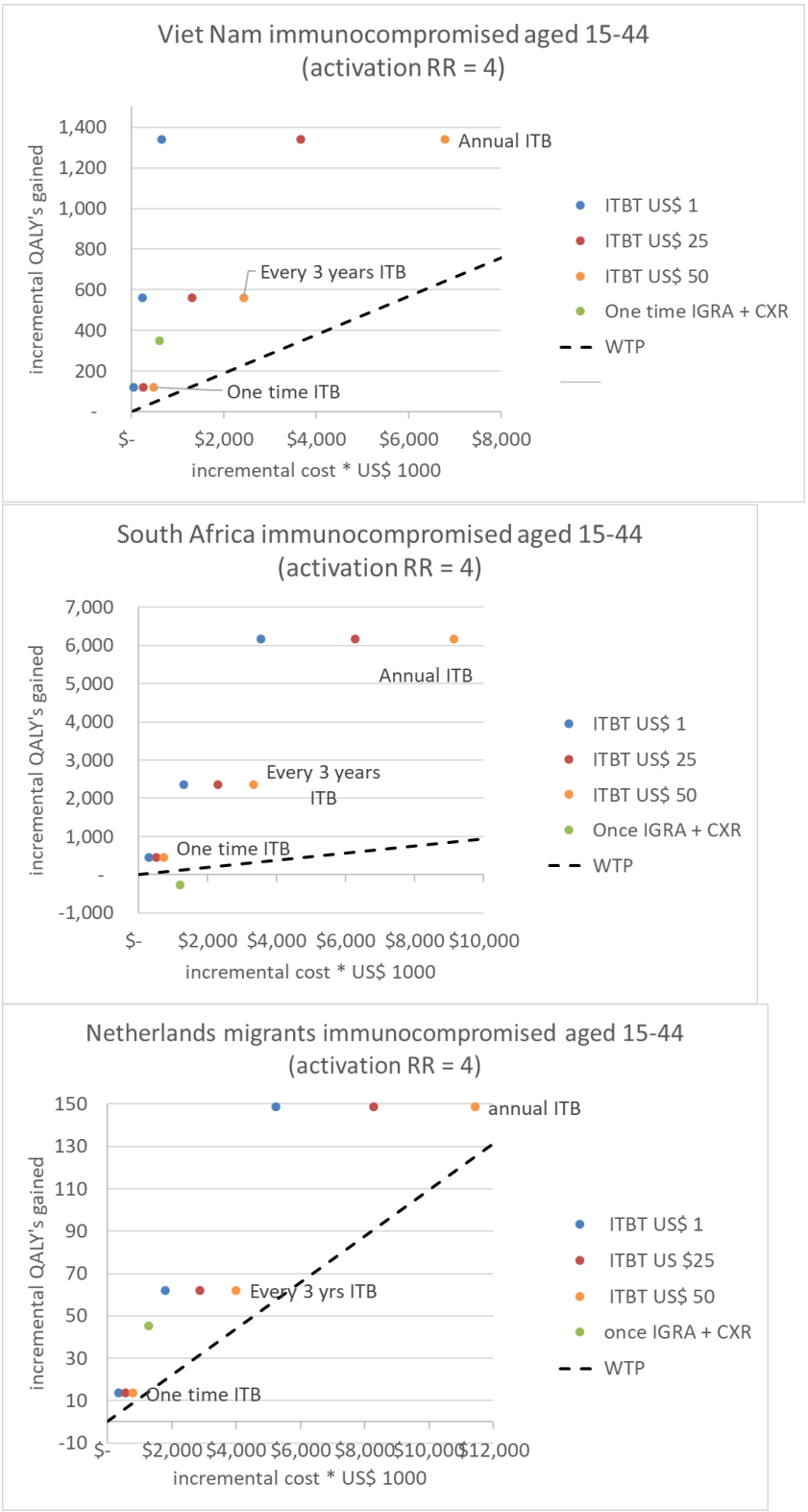
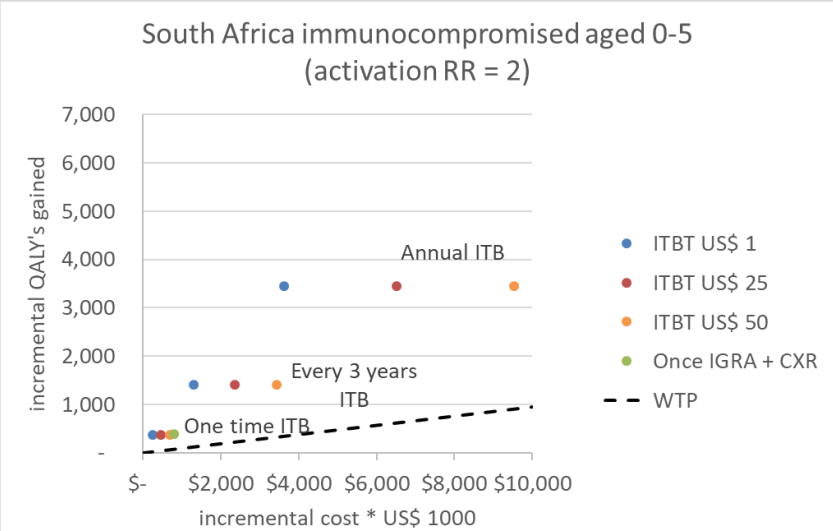
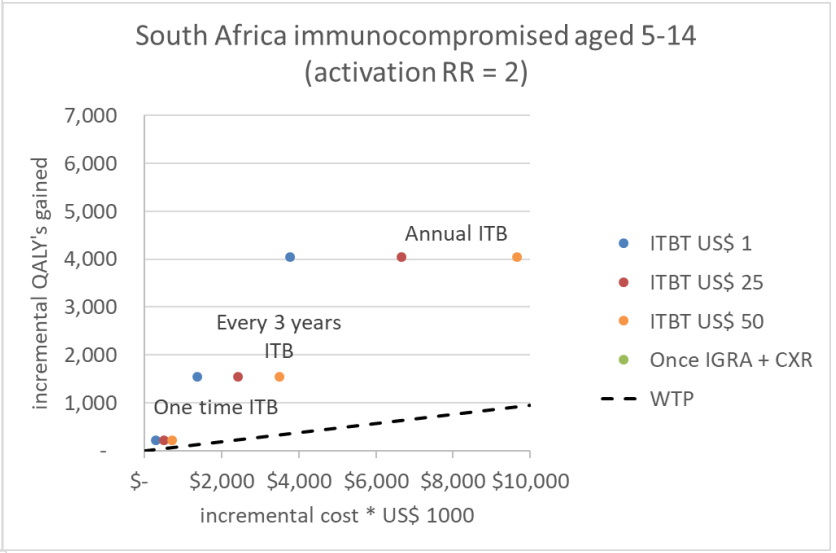
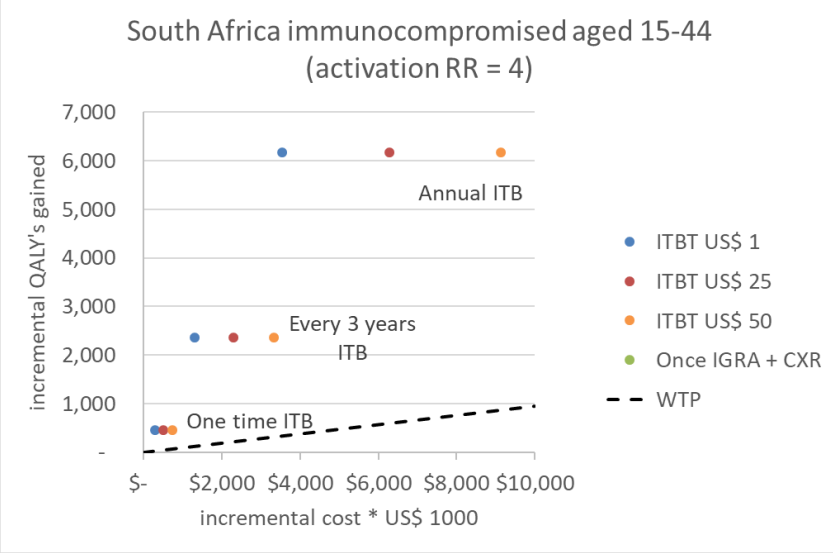


Figure 13. Incremental costs and QALYs gained of a cohort of 10,000 immunocompromised persons for all 4 age groups in South Africa using different testing frequencies.

Next page. Explanation: see Figure 8 above. Risk of activation (RR) = 2 for 0-4 and 5-14 and RR = 4 for 15-44 and 45+; blue, red and yellow dots on a horizontal line represent the same testing frequency at different costing options. Age group 15-44 is same as in Figure 12 and added for comparison.


South Africa immunocompromised aged 0-5
(activation RR = 2)
incremental QALY's gained
7,000
6,000
5,000
4,000
3,000
2,000
1,000
-
Annual ITB
Every 3 years
ITB
One time ITB
$-
$2,000
$4,000
$6,000
$8,000
$10,000
incremental cost * US$ 1000
ITBT US$ 1
ITBT US$ 25
ITBT US$ 50
Once IGRA + CXR
WTP


South Africa immunocompromised aged 5-14
(activation RR = 2)
incremental QALY's gained
7,000
6,000
5,000
4,000
3,000
2,000
1,000
-
Annual ITB
Every 3 years
ITB
One time ITB
$-
$2,000
$4,000
$6,000
$8,000
$10,000
incremental cost * US$ 1000
ITBT US$ 1
ITBT US$ 25
ITBT US$ 50
Once IGRA + CXR
WTP


South Africa immunocompromised aged 15-44
(activation RR = 4)
incremental QALY's gained
7,000
6,000
5,000
4,000
3,000
2,000
1,000
-
Annual ITB
Every 3 years
ITB
One time ITB
$-
$2,000
$4,000
$6,000
$8,000
$10,000
incremental cost * US$ 1000
ITBT US$ 1
ITBT US$ 25
ITBT US$ 50
Once IGRA + CXR
WTP

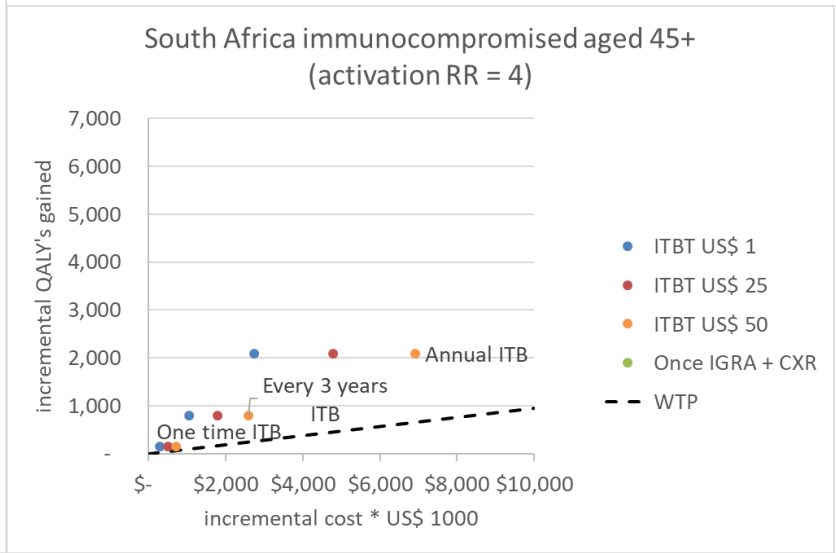

South Africa immunocompromised aged 45+
(activation RR = 4)
incremental QALY's gained
7,000
6,000
5,000
4,000
3,000
2,000
1,000
-
Annual ITB
Every 3 years
ITB
One time ITB
$-
$2,000
$4,000
$6,000
$8,000
$10,000
incremental cost * US$ 1000
ITBT US$ 1
ITBT US$ 25
ITBT US$ 50
Once IGRA + CXR
WTP

Table 9b. Summary of ITB testing costs thresholds for cost-effectiveness for different scenarios for immunocompromised.

Explanation of table: see table 9a

Regarding immunocompromised patients we used different assumptions for relative risk (RR) of activation from LTBI to ITB. For immunocompromised in NL & PT only 1 age group is given since the analysis shows that in this age group even in persons with RR=10 screening for ITB at zero costs for the screening is more expensive than the WTP threshold. In other age groups the outcomes will even be less favourable. The terminology 'natives' is only relevant for NL and PT.

Empty cells: we did not calculate all scenarios, when similar scenarios in that country were not cost-effective.

Negative numbers indicate the testing is not cost-effective.

	NL	PT	VN	SA
Immunocompromised aged 0-4				
RR=2				
One time ITB				$ 405
Every 3 years ITB				$ 316
Annual ITB				$ 274
Immunocompromised aged 5-14				
RR=2				
One time ITB				$ 219
Every 3 years ITB				$ 346
Annual ITB				$ 324
Immunocompromised aged 15-44 NL&PT natives; VN&SA general population				
RR=2				
One time ITB	$ -48	$ 13	$ 31	$ 356
Every 3 years ITB	$ -49	$ 6	$ 27	$ 318
Annual ITB	$ -49	$ -1	$ 22	$ 290
RR=4				
One time ITB	$ -45	$ 47	$ 54	$ 515
Every 3 years ITB	$ -46	$ 39	$ 50	$ 576
Annual ITB	$ -47	$ 26	$ 42	$ 540
RR=10				
One time ITB	$ -39	$ 127	$ 110	$ 989
Every 3 years ITB	$ -41	$ 104	$ 97	$ 1,174
Annual ITB	$ -43	$ 81	$ 82	$ 1,094
Immunocompromised aged 45+				

	NL	PT	VN	SA
RR=4				
One time ITB				$ 154
Every 3 years ITB				$ 234
Annual ITB				$ 228
Immunocompromised aged 15-44 RR = 4 NL&PT natives; VN&SA general population				

Different assumptions about secondary cases prevented				
Secondary cases prevented 0				
One time ITB	$ -48	$ 18	$ 34	$ 331
Every 3 years ITB	$ -48	$ 13	$ 32	$ 372
Annual ITB	$ -49	$ 4	$ 27	$ 348
Secondary cases prevented 1				
One time ITB	$ -43	$ 76	$ 74	$ 698
Every 3 years ITB	$ -44	$ 66	$ 69	$ 779
Annual ITB	$ -45	$ 49	$ 58	$ 731
Immunocompromised migrants aged 15-44				
RR=2				
One time ITB	$ 38			
Every 3 years ITB	$ 27			
Annual ITB	$ 15			
RR=4 (baseline)				
One time ITB	$ 101			
Every 3 years ITB	$ 87			
Annual ITB	$ 67			
RR=10				
One time ITB	$ 254			
Every 3 years ITB	$ 208			
Annual ITB	$ 169			
Immunocompromised migrants aged 15-44 RR = 4				
Secondary cases prevented 0				
One time ITB	$ 48			
Every 3 years ITB	$ 39			
Annual ITB	$ 26			
Secondary cases prevented 1				
One time ITB	$ 154			
Every 3 years ITB	$ 135			
Annual ITB	$ 108			

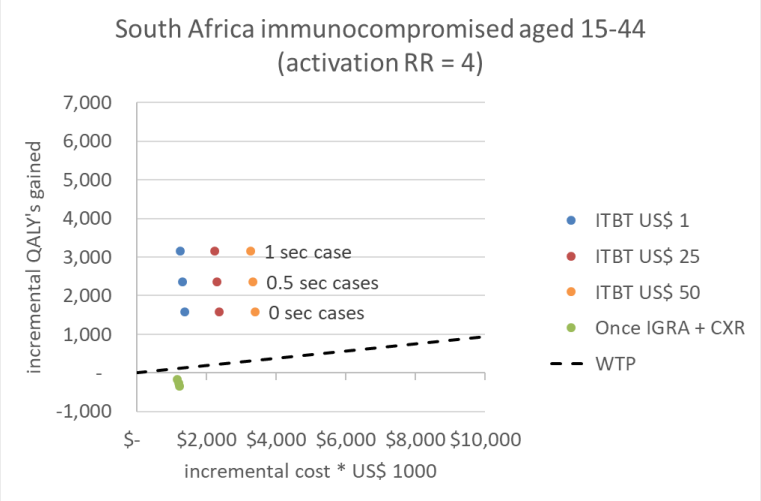
6.4.2. Alternative assumptions on prevention of secondary cases

Even when assuming 1 secondary case prevented for each averted primary TB case, testing natives is not cost-effective in the Netherlands, but can be cost effective in migrants, and also in Portugal, Viet Nam and South Africa (See Table 9b and illustrative example of South Africa in Figure 14). For example for Viet Nam and every 3 years ITB, when we assume 1

secondary cases are prevented rather than 0.5, the maximum cost of an ITB test to be cost-effective would increase from US$50 to US$69. Again, countries may use a different threshold for considering strategies cost effective, and cost effective strategies still require (often substantial) investments and should be affordable.

Figure 14. Incremental costs and QALYs gained of a cohort of 10,000 immunocompromised persons aged 15-44 in in South Africa using different assumptions on prevention of secondary cases.

Explanation see Figure 11. Assume ITB test every 3 years.



6.5. Other model outcomes and extrapolation to country level

We also calculated a number of other outcomes for the cohort of 10,000, and compared to baseline scenario of doing nothing, and compared to WHO policy (Table 11). We also extrapolated the cohort model results for a cohort of 10,000 to countrywide data and used some crude numbers for these as presented in Table 10. This table shows a crude estimate of the number of tests needed at country level for the estimated number of contacts and HIV infected persons. These data should be interpreted with caution, since all contacts and HIV infected persons were assumed to be of the same age; and there are many other limitations as indicated by the footnotes.

Table 10. Rough estimate of number of tests needed for contacts and HIV infected persons

	NL	PT	VN	SA	source
Household size average	2.17	2.5	3.7	3.3	NL&PT: EUROSTAT; VN: www.gso.gov.vn; SA: www.STATSSA.gov.za
All contacts of WHO estimated pts*	2,127	6,000	473,600	1,498,200	
Annual number of new HIV infections	<500	N/A, estimate 957**	12,000	290,000	UNAIDS, global AIDS monitoring 2015 (http://aidsinfo.unaids.org/)

* Multiplied household size by total number of estimated TB patients. Assume HH size of TB pts is 1 person more than average household size, and subtract index patient (so +1 and -1).
** based on proportion prevalence/incidence in NL

6.5.1. Other outcomes on screening contacts

Our model shows that in the Netherlands by screening household contacts only 21 TB cases and no deaths will be averted annually, when compared to doing nothing. When compared to IGRA, 21 more TB cases will occur, since IGRA is more often positive than ITB test, and therefore more preventive treatment is given. When an ITB test costs 50 US$, the cost per TB case averted is at least US$ 15,000 and 27 persons need to be screened to find one person with ITB.

In South Africa, over 33,000 TB cases and over 6,000 deaths can be averted annually when compared to doing nothing, and even more when comparing to CXR. The number of persons needed to screen is 7, and the cost per case averted when a test costs 50 US$ is also over €10,000.

6.5.1. Other outcomes on screening HIV infected persons

The extrapolation of a cohort of immunocompromised persons to countrywide data can only be done for HIV infected persons, since limited data are available on epidemiology of other immunocompromised diseases.

In the Netherlands, among natives, screening HIV infected persons once for ITB hardly prevents any TB case and no deaths, and the cost are enormous. This can be fully explained by the small probability of having acquired latent TB infection and thus being at risk of developing active TB, together with the fact that most active TB cases will be treated after self-reporting relatively rapidly. However in South Africa, over 7000 cases and 700 deaths can be averted by screening newly HIV infected persons once, compared to IGRA & CXR. The cost per case prevented when a test costs 50 US$ is for contacts over 9000 US$, and results in no cost for HIV infected persons.

Table 11. Other model outputs for cohort of 10,000 persons aged 15-44 and extrapolated to country level for selected scenarios.

	For cohort of 10,000					For actual country situation						
	N test needed	ITB persons #	screen detected TB patients	Self-reported TB averted ## ^	N deaths averted	N test needed	ITB persons #	screen detected TB patients	Self-reported TB averted ## ^	N deaths averted	NNS to detect 1 ITB**	cost/TB case averted if a test costs US$ 50 *^^
Netherlands-natives												
contacts, baseline scenario												
compared to doing nothing	17991	317	15	96	1	3827	67	3	21	0	27	$ 15,225
compared to IGRA				-21	0				-5	0		$ 16,278
HIV infected natives, baseline scenario RR=4, screen newly infected persons once												
compared to doing nothing	8998	41	0	1	0	450	2	0	0	0	216	$ 1,174,981
compared to IGRA+CXR				-3	0				0	0		$384,572
Portugal-natives												
contacts, baseline scenario												
compared to doing nothing	17991	423	30	140	6	10794	254	18	84	4	20	$ 8,623
compared to IGRA				-14	-1				-9	-1		$ 12,367
HIV infected persons , baseline scenario RR=4, screen newly infected persons once												
compared to doing nothing	8998	66	2	10	1	861	6	0	1	0	133	$ 91,981
compared to IGRA+CXR				-29	2				-3	0		$ 13,115
Viet Nam												
contacts, baseline scenario												
compared to doing nothing	17989	641	39	171	11	851,975	30,362	1,833	8,090	507	13	$ 7,176
compared to CXR				156	10				7,368	463		$ 6,571
HIV infected persons RR=4, baseline scenario; screen newly infected persons once												

	For cohort of 10,000					For actual country situation						
	N test needed	ITB persons #	screen detected TB patients	Self-reported TB averted ## ^	N deaths averted	N test needed	ITB persons #	screen detected TB patients	Self-reported TB averted ## ^	N deaths averted	NNS to detect 1 ITB**	cost/TB case averted if a test costs US$ 50 *^^
compared to doing nothing	8998	180	10	47	3	10,798	217	11	56	4	47	$12,914
compared to IGRA+CXR				-111	11				-134	-10		$ 1,128
South Africa												
contacts aged 15-44, baseline scenario												
compared to doing nothing	17974	1261	90	225	23	2,692,863	188,851	13,536	33,695	6,317	7	$ 10,668
compared to CXR				167	17				24,961	4,883		$ 9,647
HIV infected persons RR=4, baseline scenario; screen newly infected persons once												
compared to doing nothing	8995	617	55	117	12	260,858	17,887	1,594	3,403	340	13	$ 11,619
compared to IGRA+CXR				259	107				7,520	771		$ -1,756

persons starting ITB or LTBI treatment (already corrected for coverage and starting treatment but not necessarily completed treatment)(convenient value chosen: 85% of persons with positive test)

persons starting TB treatment (already corrected for coverage and starting treatment but not necessarily completed treatment). Some may be false positive.

*equals health care cost divided by TB cases

** equals persons divided by TB cases and for contacts correct for 2 tests per contact

^ Averted cases often occur in the first few years; therefore this number seems low;

^^ Not corrected for discounting; therefore annual cases averted per country would need correction of about 9%

7. Discussion and conclusion

7.1 Summary of main results

The model fitted reasonably well to age specific TB incidence and LTBI prevalence data in all 4 countries. Testing and treating for ITB among close contacts is cost effective in all 4 countries and for all 4 age groups. In contacts in NL and PT, the health impact of the WHO recommended strategy of one-time testing with IGRA is comparable to two to three times ITB testing, and overall costs are similar if an ITB test can be done for US$ 25. In VN and SA, ITB testing strongly outperforms the use of CXR for contacts, by resulting in a much higher health impact.

Testing and treating for ITB of HIV patients and other immunocompromised persons in very low incidence settings such as the Netherlands is never cost-effective, but it can be cost-effective in medium and high incidence countries, as well as for migrants from high-incidence countries. For HIV patients, screening every 3 years for ITB results in roughly the same health impact as the WHO recommended strategy of one time using IGRA and CXR combined for NL, PT, VN; the costs are comparable if an ITB test costs in the order of magnitude of US$ 10.

The maximum test-costs that can be charged by manufacturers to arrive at cost-effective outcomes can be one hundred to several hundred US$ for screening contacts in all countries, as well as HIV patients in SA, but much less so for HIV infected migrants in NL, and all HIV infected persons in PT and VN.

7.2. Factors that have most effect on model results

Cost-effectiveness outcomes were dependent on assumptions of TB-associated life years lost and how many prevented secondary cases were assumed, and to a lesser extent on the timing of ITB testing (6 month time-interval performed a bit better than 3 and 12 for close contacts) and LTBI therapy used (with 3HR slightly profitable relative to 6H).
Life years lost are responsible for a significant proportion of the overall QALY loss. This proportion is highest for young age and long duration till treatment. In our study death usually accounts for over 90% of overall QALY loss. It varies from 69% for 45+ in NL to 98% for the 0-4 group in SA. Thus, our assumptions regarding remaining life expectancy are essential for the overall outcome concerning cost-effectiveness, much more so than the GBD-based burden of disease (i.e. 0.331) when having active TB.

7.3. Strengths and weaknesses

Several aspects of this model are as strong as or stronger than in other models:

- This model allows for different sensitivity and specificity of diagnostic tests for different stages of disease.

- The model was fitted to countrywide data on all age groups, and matches reasonably well to the data by age group. Most differences can be explained by expected under-notification (for children).
- Previously published costing data have been used where possible.
- An innovative correction for age specific mortality for TB patients was done, since it was found that assumed mortality has strongest influence on ICER (see **section 7.2**). Since hardly any data are available to support this, more work is needed on TB-related mortality estimates.
- We estimated also the costs of implementing screening. Although we used a simple approach of 2 consultation visits (similar to IGRA screening), this gives a more realistic estimate than only including the cost of the test itself.
- We did not only include PTB but also (averted) EPTB patients.

This modelling work basically was a quick pilot exercise and therefore modelling and estimates are based on easily available data. Some details can be improved in future modelling work, for example:

a. On modelling

- The model assumes equilibrium (constant) in TB transmission before intervention rather than commonly observed decreasing trends in incidence. This is a more important factor for the outcomes of immunocompromised patients than for contacts, as the outcomes for the latter are mainly determined by the short period of extreme exposure.
- No separate HIV infected and HIV uninfected population groups were assumed, apart from the relative risk to activate after infection, while several other characteristics may differ between these groups, such as progression from ITB to active TB duration of disease till diagnosis, and sensitivity to LTBI diagnostics. E.g. among HIV infected diagnosis of TB is often made faster than among HIV uninfected persons, due to increased suspicion by the diagnosing health care worker. Further, for HIV infected persons without active TB in high incidence TB settings, current guidelines are to provide 36 months of preventive therapy, while we only modelled preventive therapy for 6 months.
- We used WHO estimated TB incidence, and extrapolated the proportion of cases by age groups, location (PTB/EPTB) and hospitalization from notified data since these are only publicly available for notified TB. WHO may have estimates for PTB/EPTB and age group and future models may use these.
- On EPTB there is very little information available. The natural history for PTB and EPTB could very well be rather different, whereas we basically assumed the same rates, durations and proportions. For example the sensitivity of symptom screening for EPTB may very well be lower than the 90% reported for PTB and assumed in the model for all TB. Adjustments for EPTB will have marginal effects on most of the results. This problem has most influence on NL and PT results since the (reported) proportion of EPTB is much higher than in VN and SA.
- In high incidence countries no detailed information was available for patients who are smear-negative, so we only had information for part of the PTB patients.
- Among contacts of MDR cases current preventive therapy is less effective and therefore usually not prescribed. A more advanced model may use lower treatment effectiveness for a subgroup of TB patients (MDR patients). New preventive therapies are being developed that may be more effective.

- For contacts different definitions were used. In order to calculate costs of contact tracing, we used the *actual number of contacts* included in NL (14) and PT (9); since costing approach was based on the previous version of this model for ECDC (20). However for extrapolating the results of cohorts of 10,000 contacts to country values, we used household contacts (based on average household size), in order to harmonize this approach between all 4 countries. And further, the proportion IGRA positive among contacts in the model (pre-set 12% for NL) was based on *close contacts*, which is probably more than household contacts, but less than average number of contacts investigated in NL and PT.
- The model estimates a much higher proportion TST positive than published studies show. This may be partly due to in reality also (as for IGRA) some degree of waning of the TST for those that move to susceptible after clearance of treatment, and partly due to the model assumption of homogenous mixing. Especially in South Africa, a substantial proportion of the population will not experience the same risk of TB as the majority population group. Future models may include sub-populations to allow for heterogeneous mixing, and may include a waning component for TST.
- Other assumptions on sensitivity and specificity of the ITB test can be used.

Screening of contacts can be further optimized by selecting other time points, in particular one to a couple of months after exposure, so not immediately. Preliminary analyses indicate that this may substantially increase health impact and reduce costs, as recently infected persons have more time to develop ITB, which will be picked up with the new ITB test. However, waiting too long will make them move to active TB, with associated health risks and high cost of treatment and hospitalization.

b. On costing

- For costing we used slightly different approaches between countries, due to availability of data. The advantage is that costs can be compared within countries to other publications about that same country. The disadvantage is that it is challenging to compare costs between countries.
- The implementation costs of ITB test are unknown. We now assumed 2 consultation visits, but there may be more costs involved.
- Societal and patient perspectives were not included.
- We assumed averted costs of contact tracing for every averted TB case (primary and secondary), whereas for contacts and immunocompromised patients this may not be always needed.
- The WTP threshold of 2x GDP is arbitrarily chosen to define cost-effectiveness. This is probably realistic for NL & PT, but VN and SA may not be able to afford this. A value of 0.5 may be used alternatively.

General considerations before using the results in practice:

- We included screening costs for the ITB test, based on 2 consultation visits. In practice implementing and sustaining such new screening system may cost more.
- We assumed that persons with a positive ITB test can be treated as LTBI or as active TB. Both assumptions are based on assuming the person has drug-sensitive TB. This may not be suitable for settings with high proportion MDR TB patients.
- Coverage of screening was calculated for the general population; if persons with a higher risk on TB do not show up for screening, the yield will be less.

7.3. Other models

Other groups are developing similar models at the same time, such as London School of Hygiene and Tropical Medicine (LSHTM), Imperial College in UK and Institute for Disease Modelling (IDM) in USA. A comparison of model results would be very useful.

One other model developed by Dowdy showed that subclinical disease may limit the impact of current diagnostic strategies for TB (4).He concluded that active detection of undiagnosed prevalent cases may achieve greater population-level TB control than increasing passive case detection. Our results seem to agree with that insight.

7.4. Conclusions

Testing and treating for ITB among contacts is always cost-effective. For high incidence countries substantial QALYs are gained, at the expense of relatively minor investments. Testing immunocompromised is not cost-effective for people born in very low incidence countries, but for all other groups it can be borderline cost-effective (migrants from high-incidence countries and inhabitants of moderately endemic countries) to very cost-effective (high-incidence countries). Recommended costing of testing for ITB differs widely between countries, depending on the costing approach and control strategy considered.

8. Ownership of model

The NDWG of the Stop TB Partnership and FIND will be allowed to use model for its purposes, but not have sole ownership. Erasmus MC will be allowed to develop model further for other partners. When adapting the model, ECDC should be acknowledged for supporting an earlier version of the model.

9. Acknowledgements

Stop TB partnership: New Diagnostic Working Group (NDWG)

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- Member LTBI task force: Samuel Schumacher, FIND
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- South Africa: Lindiwe Mvusi, Laura Anderson (WHO)

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10. References

1. WHO, FIND. Consensus meeting report: development of a target product profile (TPP) and a framework for evaluation for a test for predicting progression from tuberculosis infection to active disease. 2017.
2. Cobelens F, Kik S, Esmail H, Cirillo DM, Lienhardt C, Matteelli A. From latent to patent: rethinking prediction of tuberculosis. The Lancet Respiratory medicine. 2017;5(4):243-4.
3. Esmail H, Barry CE, 3rd, Young DB, Wilkinson RJ. The ongoing challenge of latent tuberculosis. Philosophical transactions of the Royal Society of London Series B, Biological sciences. 2014;369(1645):20130437.
4. Dowdy DW, Basu S, Andrews JR. Is passive diagnosis enough? The impact of subclinical disease on diagnostic strategies for tuberculosis. American journal of respiratory and critical care medicine. 2013;187(5):543-51.
5. Zak DE, Penn-Nicholson A, Scriba TJ, Thompson E, Suliman S, Amon LM, et al. A blood RNA signature for tuberculosis disease risk: a prospective cohort study. Lancet (London, England). 2016;387(10035):2312-22.
6. WHO. Systematic screening for active tuberculosis: an operational guide Operational guide. WHO Geneva 2015. WHO/HTM/TB/2015.16. . 2015.
7. Alsdurf H, Hill PC, Matteelli A, Getahun H, Menzies D. The cascade of care in diagnosis and treatment of latent tuberculosis infection: a systematic review and meta-analysis. Lancet Infect Dis. 2016;16(11):1269-78.
8. Karumbi J, Garner P. Directly observed therapy for treating tuberculosis. The Cochrane database of systematic reviews. 2015(5):Cd003343.
9. MacPherson P, Houben RM, Glynn JR, Corbett EL, Kranzer K. Pre-treatment loss to follow-up in tuberculosis patients in low- and lower-middle-income countries and high-burden countries: a systematic review and meta-analysis. Bulletin of the World Health Organization. 2014;92(2):126-38.
10. Sharma SK, Sharma A, Kadhiravan T, Tharyan P. Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB. The Cochrane database of systematic reviews. 2013(7):Cd007545.
11. Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. The Cochrane database of systematic reviews. 2010(1):Cd000171.
12. El-Sadr WM, Perlman DC, Denning E, Matts JP, Cohn DL. A review of efficacy studies of 6-month short-course therapy for tuberculosis among patients infected with human immunodeficiency virus: differences in study outcomes. Clin Infect Dis. 2001;32(4):623-32.
13. WHO. Guidelines on the management of latent tuberculosis infection. Geneva; World Health Organization. 2015.
14. WHO. Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries. 2012.
15. WHO. Systematic screening for active tuberculosis: principles and recommendations. WHO/HTM/TB/2013.04. 2013.
16. WHO. Latent tuberculosis infection: Updated and consolidated guidelines for programmatic management. 2018.
17. Getahun H, Matteelli A, Abubakar I, Aziz MA, Baddeley A, Barreira D, et al. Management of latent Mycobacterium tuberculosis infection: WHO guidelines for low tuberculosis burden countries. Eur Respir J. 2015;46(6):1563-76.
18. WHO. Recommendation on 36 months isoniazid preventive therapy to adults and adolescents living with HIV in resource-constrained and high TB- and HIV-prevalence settings. 2015 Update. 2015.

19. ECDC. Mathematical modelling of programmatic screening strategies for latent tuberculosis infection in countries with low tuberculosis incidence. Stockholm: European Centre for Disease Prevention and Control; 2018.
20. ECDC. Cost-effectiveness analysis of programmatic screening strategies for latent tuberculosis infection in the EU/EEA. Stockholm: European Centre for Disease Prevention and Control; 2018.
21. Andrews JR, Noubary F, Walensky RP, Cerda R, Losina E, Horsburgh CR. Risk of progression to active tuberculosis following reinfection with Mycobacterium tuberculosis. Clin Infect Dis. 2012;54(6):784-91.
22. Vynnycky E, Fine PE. Lifetime risks, incubation period, and serial interval of tuberculosis. Am J Epidemiol. 2000;152(3):247-63.
23. Sutherland I, Svandova E, Radhakrishna S. The development of clinical tuberculosis following infection with tubercle bacilli. 1. A theoretical model for the development of clinical tuberculosis following infection, linking from data on the risk of tuberculous infection and the incidence of clinical tuberculosis in the Netherlands. Tubercle. 1982;63(4):255-68.
24. Wang L, Turner MO, Elwood RK, Schulzer M, FitzGerald JM. A meta-analysis of the effect of Bacille Calmette Guerin vaccination on tuberculin skin test measurements. Thorax. 2002;57(9):804-9.
25. Diel R, Goletti D, Ferrara G, Bothamley G, Cirillo D, Kampmann B, et al. Interferon-gamma release assays for the diagnosis of latent Mycobacterium tuberculosis infection: a systematic review and meta-analysis. Eur Respir J. 2011;37(1):88-99.
26. Campbell JR, Krot J, Elwood K, Cook V, Marra F. A systematic review on TST and IGRA tests used for diagnosis of LTBI in immigrants. Mol Diagn Ther. 2015;19(1):9-24.
27. Diel R, Loddenkemper R, Nienhaus A. Evidence-Based Comparison of Commercial Interferon-gamma Release Assays for Detecting Active TB. Chest. 2010;137(4):952-68.
28. Oxlade O, Schwartzman K, Menzies D. Interferon-gamma release assays and TB screening in high-income countries: a cost-effectiveness analysis. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2007;11(1):16-26.
29. Pareek M, Watson JP, Ormerod LP, Kon OM, Woltmann G, White PJ, et al. Screening of immigrants in the UK for imported latent tuberculosis: a multicentre cohort study and cost-effectiveness analysis. Lancet Infect Dis. 2011;11(6):435-44.
30. Mori T, Harada N, Higuchi K, Sekiya Y, Uchimura K, Shimao T. Waning of the specific interferon-gamma response after years of tuberculosis infection. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2007;11(9):1021-5.
31. Heo EY, Chun EJ, Lee CH, Kim YW, Han SK, Shim YS, et al. Radiographic improvement and its predictors in patients with pulmonary tuberculosis. Int J Infect Dis. 2009;13(6):e371-6.
32. Menon B, Nima G, Dogra V, Jha S. Evaluation of the radiological sequelae after treatment completion in new cases of pulmonary, pleural, and mediastinal tuberculosis. Lung India. 2015;32(3):241-5.
33. van 't Hoog AH, Langendam MW, Mitchell E, Cobelens FG, Sinclair D, Leeflang MMG, et al. A systematic review of the sensitivity and specificity of symptom- and chest-radiography screening for active pulmonary tuberculosis in HIV-negative persons and persons with unknown HIV status. Geneva: WHO; 2013.
34. Schwartzman K, Menzies D. Tuberculosis screening of immigrants to low-prevalence countries. A cost-effectiveness analysis. American journal of respiratory and critical care medicine. 2000;161(3 Pt 1):780-9.
35. Erkens C, Slump E, Kamphorst M, Keizer S, van Gerven PJ, Bwire R, et al. Coverage and yield of entry and follow-up screening for tuberculosis among new immigrants. Eur Respir J. 2008;32(1):153-61.
36. van Rest J, Erkens C, de Vries G. Evaluatie tuberculosescreening immigranten in Nederland, 2005-2010. 2012.

37. Burman WJ, Reves RR. Review of false-positive cultures for Mycobacterium tuberculosis and recommendations for avoiding unnecessary treatment. Clin Infect Dis. 2000;31(6):1390-5.
38. de Boer AS, Blommerde B, de Haas PE, Sebek MM, Lambregts-van Weezenbeek KS, Dessens M, et al. False-positive mycobacterium tuberculosis cultures in 44 laboratories in The Netherlands (1993 to 2000): incidence, risk factors, and consequences. J Clin Microbiol. 2002;40(11):4004-9.
39. Jasmer RM, Roemer M, Hamilton J, Bunter J, Braden CR, Shinnick TM, et al. A prospective, multicenter study of laboratory cross-contamination of Mycobacterium tuberculosis cultures. Emerg Infect Dis. 2002;8(11):1260-3.
40. WHO. Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children. Policy update. Geneva: WHO; 2013.
41. Kik SV, Rangaka MX. Predictive utility of the tuberculin skin test and interferon-gamma release assay among individuals who are not prescribed tuberculosis preventive therapy. Summary report for the WHO LTBI guideline committee (unpublished). Geneva: WHO; 2014.
42. Auguste P, Tsertsvadze A, Pink J, Court R, McCarthy N, Sutcliffe P, et al. Comparing interferon-gamma release assays with tuberculin skin test for identifying latent tuberculosis infection that progresses to active tuberculosis: systematic review and meta-analysis. BMC Infect Dis. 2017;17(1):200.
43. Santin M, Munoz L, Rigau D. Interferon-gamma release assays for the diagnosis of tuberculosis and tuberculosis infection in HIV-infected adults: a systematic review and meta-analysis. PLoS One. 2012;7(3):e32482.
44. Huo ZY, Peng L. Accuracy of the interferon-gamma release assay for the diagnosis of active tuberculosis among HIV-seropositive individuals: a systematic review and meta-analysis. BMC Infect Dis. 2016;16:350.
45. Cattamanchi A, Smith R, Steingart KR, Metcalfe JZ, Date A, Coleman C, et al. Interferon-gamma release assays for the diagnosis of latent tuberculosis infection in HIV-infected individuals: a systematic review and meta-analysis. J Acquir Immune Defic Syndr. 2011;56(3):230-8.
46. Pieterman ED, Liqui Lung FG, Verbon A, Bax HI, Ang CW, Berkhout J, et al. A multicentre verification study of the QuantiFERON((R))-TB Gold Plus assay. Tuberculosis. 2018;108:136-42.
47. Barcellini L, Borroni E, Brown J, Brunetti E, Codecasa L, Cugnata F, et al. First independent evaluation of QuantiFERON-TB Plus performance. Eur Respir J. 2016;47(5):1587-90.
48. Telisinghe L, Amofa-Sekyi M, Maluzi K, Kaluba-Milimo D, Cheeba-Lengwe M, Chiwele K, et al. The sensitivity of the QuantiFERON((R))-TB Gold Plus assay in Zambian adults with active tuberculosis. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2017;21(6):690-6.
49. Tiemersma EW, van der Werf MJ, Borgdorff MW, Williams BG, Nagelkerke NJ. Natural history of tuberculosis: duration and fatality of untreated pulmonary tuberculosis in HIV negative patients: a systematic review. PLoS One. 2011;6(4):e17601.
50. Berg G. The prognosis of open pulmonary tuberculosis. A clinical statistical study. Acata Tuberc Scand. 1939;suppl IV:1-206.
51. Borgdorff MW, Sebek M, Geskus RB, Kremer K, Kalisvaart N, van Soolingen D. The incubation period distribution of tuberculosis estimated with a molecular epidemiological approach. Int J Epidemiol. 2011;40(4):964-70.
52. KNCVTuberculosisFoundation. tbc-online The Hague: KNCV Tuberculosis Foundation; 2017 [Available from: www.tbc-online.nl.
53. Menzies NA, Wolf E, Connors D, Bellerose M, Sbarra AN, Cohen T, et al. Progression from latent infection to active disease in dynamic tuberculosis transmission

models: a systematic review of the validity of modelling assumptions. Lancet Infect Dis. 2018.
54. Marais BJ, Gie RP, Schaaf HS, Hesseling AC, Obihara CC, Starke JJ, et al. The natural history of childhood intra-thoracic tuberculosis: a critical review of literature from the pre-chemotherapy era. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2004;8(4):392-402.
55. Vynnycky E, Fine PE. The natural history of tuberculosis: the implications of age-dependent risks of disease and the role of reinfection. Epidemiol Infect. 1997;119(2):183-201.
56. Marais BJ. Tuberculosis in children. J Paediatr Child Health. 2014;50(10):759-67.
57. Trauer JM, Moyo N, Tay EL, Dale K, Ragonnet R, McBryde ES, et al. Risk of Active Tuberculosis in the Five Years Following Infection . . . 15%? Chest. 2016;149(2):516-25.
58. Erkens CG, Slump E, Verhagen M, Schimmel H, Cobelens F, van den Hof S. Risk of developing tuberculosis disease among persons diagnosed with latent tuberculosis infection in the Netherlands. Eur Respir J. 2016;48(5):1420-8.
59. Nagelkerke N. Courtesans and Consumption: How sexually transmitted infections drive tuberculosis epidemics. Eburon Academic Publishers. 2012.
60. Groth-Petersen E, Knudsen J, Wilbek E. Epidemiological basis of tuberculosis eradication in an advanced country. Bulletin of the World Health Organization. 1959;21:5-49.
61. Shisana O, Rehle T, Simbayi LC, Zuma K, Jooste S, Zungu N, et al. South African National HIV Prevalence, Incidence and Behaviour Survey, 2012. Cape Town; 2014.
62. Mulder C, van Deutekom H, Huisman EM, Toumanian S, Koster BF, Meijer-Veldman W, et al. Role of the QuantiFERON(R)-TB Gold In-Tube assay in screening new immigrants for tuberculosis infection. Eur Respir J. 2012;40(6):1443-9.
63. Mulder C, Mulleners B, Borgdorff MW, van Leth F. Predictive value of the tuberculin skin test among newly arriving immigrants. PLoS One. 2013;8(3):e60130.
64. Finnie RK, Khoza LB, van den Borne B, Mabunda T, Abotchie P, Mullen PD. Factors associated with patient and health care system delay in diagnosis and treatment for TB in sub-Saharan African countries with high burdens of TB and HIV. Trop Med Int Health. 2011;16(4):394-411.
65. Sreeramareddy CT, Panduru KV, Menten J, Van den Ende J. Time delays in diagnosis of pulmonary tuberculosis: a systematic review of literature. BMC Infect Dis. 2009;9:91.
66. Verver S, Bwire R, Borgdorff MW. Screening for pulmonary tuberculosis among immigrants: estimated effect on severity of disease and duration of infectiousness. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2001;5(5):419-25.
67. UNDP. World Population Prospects: The 2017 Revision. 2017.
68. CBS. demography tables 2016 [Available from: www.cbs.nl.
69. Statistics Portugal. Demography tables 2016.
70. WHO. Global TB report 2016. 2016.
71. Slump E, Erkens CGM, van Hunen R, Schimmel HJ, van Soolingen D, Teirlinck AC, et al. Tuberculosis in the Netherlands. Surveillance report inclusief rapportage monitoring van interventies (TB in The Netherlands. Surveillance report including monitoring of interventions). Bilthoven: RIVM; 2016.
72. Gupta S, Abimbola T, Date A, Suthar AB, Bennett R, Sangrujee N, et al. Cost-effectiveness of the Three I's for HIV/TB and ART to prevent TB among people living with HIV. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2014;18(10):1159-65.
73. Sinanovic E, Ramma L, Vassall A, Azevedo V, Wilkinson L, Ndjeka N, et al. Impact of reduced hospitalisation on the cost of treatment for drug-resistant tuberculosis in South Africa. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2015;19(2):172-8.

74. Lawn SD, Harries AD, Williams BG, Chaisson RE, Losina E, De Cock KM, et al. Antiretroviral therapy and the control of HIV-associated tuberculosis. Will ART do it? The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2011;15(5):571-81.
75. Lawn SD, Kranzer K, Wood R. Antiretroviral therapy for control of the HIV-associated tuberculosis epidemic in resource-limited settings. Clin Chest Med. 2009;30(4):685-99, viii.
76. Lawn SD, Wood R, De Cock KM, Kranzer K, Lewis JJ, Churchyard GJ. Antiretrovirals and isoniazid preventive therapy in the prevention of HIV-associated tuberculosis in settings with limited health-care resources. Lancet Infect Dis. 2010;10(7):489-98.
77. Gupta A, Wood R, Kaplan R, Bekker LG, Lawn SD. Tuberculosis incidence rates during 8 years of follow-up of an antiretroviral treatment cohort in South Africa: comparison with rates in the community. PLoS One. 2012;7(3):e34156.
78. Bock P, Jennings K, Vermaak R, Cox H, Meintjes G, Fatti G, et al. Incidence of Tuberculosis Among HIV-Positive Individuals Initiating Antiretroviral Treatment at Higher CD4 Counts in the HPTN 071 (PopART) Trial in South Africa. J Acquir Immune Defic Syndr. 2018;77(1):93-101.
79. Dodd PJ, Prendergast AJ, Beecroft C, Kampmann B, Seddon JA. The impact of HIV and antiretroviral therapy on TB risk in children: a systematic review and meta-analysis. Thorax. 2017;72(6):559-75.
80. WHO. Cost effectiveness and strategic planning (WHO-CHOICE) 2017 [Available from: www.who.int/choice/en.
81. LoBue PA, Moser KS. Use of isoniazid for latent tuberculosis infection in a public health clinic. American journal of respiratory and critical care medicine. 2003;168(4):443-7.
82. Nolan CM, Goldberg SV, Buskin SE. Hepatotoxicity associated with isoniazid preventive therapy: a 7-year survey from a public health tuberculosis clinic. JAMA. 1999;281(11):1014-8.
83. OECD. The Organisation for Economic Cooperation and Development (OECD); 2017 [Available from: www.oecd.org.
84. Vogel F. What Is a Purchasing Power Parity? : World Bank; 2017 [Available from: https://siteresources.worldbank.org/ICPINT/Resources/270056-1255977254560/6483625-1338834270350/FVogel_WhatisPurchasingPowerParity.pdf.
85. Minh HV, Mai VQ, Nhung NV, Hoi LV, Giang KB, Chung LH, et al. Costs of providing tuberculosis diagnosis and treatment services in Viet Nam. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2017;21(9):1035-40.
86. Vassall A, Siapka M, Foster N, Cunnama L, Ramma L, Fielding K, et al. Cost-effectiveness of Xpert MTB/RIF for tuberculosis diagnosis in South Africa: a real-world cost analysis and economic evaluation. The Lancet Global health. 2017;5(7):e710-e9.
87. MSH. INTERNATIONAL MEDICAL PRODUCTS PRICE GUIDE: MSH; 2015 [Available from: https://www.msh.org/resources/international-medical-products-price-guide.
88. Cox H, Ramma L, Wilkinson L, Azevedo V, Sinanovic E. Cost per patient of treatment for rifampicin-resistant tuberculosis in a community-based programme in Khayelitsha, South Africa. Trop Med Int Health. 2015;20(10):1337-45.
89. Pooran A, Pieterson E, Davids M, Theron G, Dheda K. What is the cost of diagnosis and management of drug resistant tuberculosis in South Africa? PLoS One. 2013;8(1):e54587.
90. WHO. WHO methods and data sources for global burden of disease estimates 2000-2011. Geneva: World Health Organization. 2013.
91. Morrison J, Pai M, Hopewell PC. Tuberculosis and latent tuberculosis infection in close contacts of people with pulmonary tuberculosis in low-income and middle-income countries: a systematic review and meta-analysis. Lancet Infect Dis. 2008;8(6):359-68.
92. CBS. bevolking (population): Centraal bureau voor de statistiek; 2016 [Available from: www.statline.cbs.nl.

93. Houben RM, Lalli M, Sumner T, Hamilton M, Pedrazzoli D, Bonsu F, et al. TIME Impact - a new user-friendly tuberculosis (TB) model to inform TB policy decisions. BMC Med. 2016;14(1):56.
94. Hoa NB, Cobelens FG, Sy DN, Nhung NV, Borgdorff MW, Tiemersma EW. First national tuberculin survey in Viet Nam: characteristics and association with tuberculosis prevalence. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2013;17(6):738-44.
95. Marks GB, Nhung NV, Nguyen TA, Hoa NB, Khoa TH, Son NV, et al. Prevalence of latent tuberculous infection among adults in the general population of Ca Mau, Viet Nam. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2018;22(3):246-51.
96. Mahomed H, Ehrlich R, Hawkridge T, Hatherill M, Geiter L, Kafaar F, et al. Screening for TB in high school adolescents in a high burden setting in South Africa. Tuberculosis. 2013;93(3):357-62.
97. Andrews JR, Nemes E, Tameris M, Landry BS, Mahomed H, McClain JB, et al. Serial QuantiFERON testing and tuberculosis disease risk among young children: an observational cohort study. The Lancet Respiratory medicine. 2017;5(4):282-90.
98. Middelkoop K, Bekker LG, Liang H, Aquino LD, Sebastian E, Myer L, et al. Force of tuberculosis infection among adolescents in a high HIV and TB prevalence community: a cross-sectional observation study. BMC Infect Dis. 2011;11:156.
99. Middelkoop K, Bekker LG, Morrow C, Lee N, Wood R. Decreasing household contribution to TB transmission with age: a retrospective geographic analysis of young people in a South African township. BMC Infect Dis. 2014;14:221.
100. Lebina L, Abraham PM, Milovanovic M, Motlhaoleng K, Chaisson RE, Rakgokong M, et al. Latent tuberculous infection in schoolchildren and contact tracing in Matlosana, North West Province, South Africa. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2015;19(11):1290-2.
101. Ncayiyana JR, Bassett J, West N, Westreich D, Musenge E, Emch M, et al. Prevalence of latent tuberculosis infection and predictive factors in an urban informal settlement in Johannesburg, South Africa: a cross-sectional study. BMC Infect Dis. 2016;16(1):661.
102. Mulder C, van Deutekom H, Huisman EM, Meijer-Veldman W, Erkens CG, van Rest J, et al. Coverage and yield of tuberculosis contact investigations in the Netherlands. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2011;15(12):1630-7.
103. Duarte R, Neto M, Carvalho A, Barros H. Improving tuberculosis contact tracing: the role of evaluations in the home and workplace. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2012;16(1):55-9.
104. Fox GJ, Anh NT, Nhung NV, Loi NT, Hoa NB, Ngoc Anh LT, et al. Latent tuberculous infection in household contacts of multidrug-resistant and newly diagnosed tuberculosis. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2017;21(3):297-302.
105. Golla V, Snow K, Mandalakas AM, Schaaf HS, Du Preez K, Hesseling AC, et al. The impact of drug resistance on the risk of tuberculosis infection and disease in child household contacts: a cross sectional study. BMC Infect Dis. 2017;17(1):593.
106. Shah M, Kasambira TS, Adrian PV, Madhi SA, Martinson NA, Dorman SE. Longitudinal analysis of QuantiFERON-TB Gold In-Tube in children with adult household tuberculosis contact in South Africa: a prospective cohort study. PLoS One. 2011;6(10):e26787.
107. GGDGHOR. Prestatiecodelijst verzekerde TBC zorg 2016 (Coding of deliverables for insured TB care). Utrecht; 2016.

108. de Vries G, blok N, van den Hof S, Erkens C, Meijer W. Schatting kosten diagnostiek screening op LTBI en tuberculose en kosten behandeling.(Estimate of cost of diagnostics for screening on LTBI and tuberculosis and cost of treatment) 2016.
109. ZIN. Medicijnkosten (cost of Medication): Zorginstituut Nederland; [Available from: www.medicijnkosten.nl.
110. NZA. Tarieven en prestaties. Bijlage-1-bij-TB-CU-7078-02 (Tarrifs and deliverables): Nederlandse Zorgautoriteit; [Available from: www.nza.nl/regelgeving/tarieven.
111. De Vries G, Baltussen R. Kosten van tuberculose en tbc-bestrijding in Nederland.(Cost of TB control in the Netherlands). Tegen de tuberculose. 2013;109(1):3-7.
112. de Vries G, Schimmel H, Blok N. Kosten van tbc-bestrijding zijn gedaald (cost of TB control decreased). Tegen de tuberculose. 2016(1).
113. Hakkaart-van Roijen L, van der Linden N, Bouwmans C, Kanters T, Swan Tan S. Kostenhandleiding: Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg (Costing guidelines: Methodology of cost research and reference prices for economic evaluations in health care). 2015.

Annexes

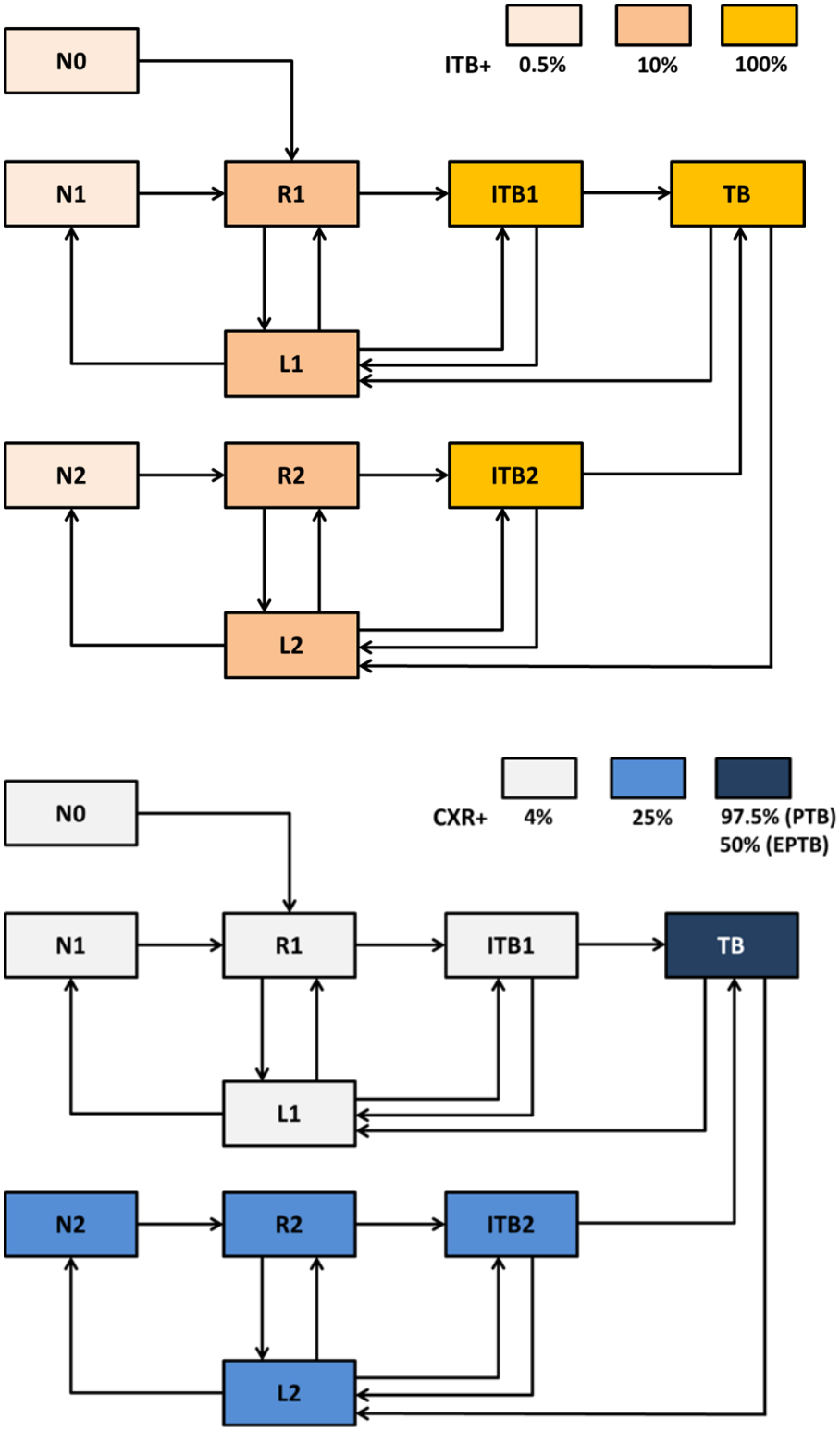
Annex 1. Abbreviations

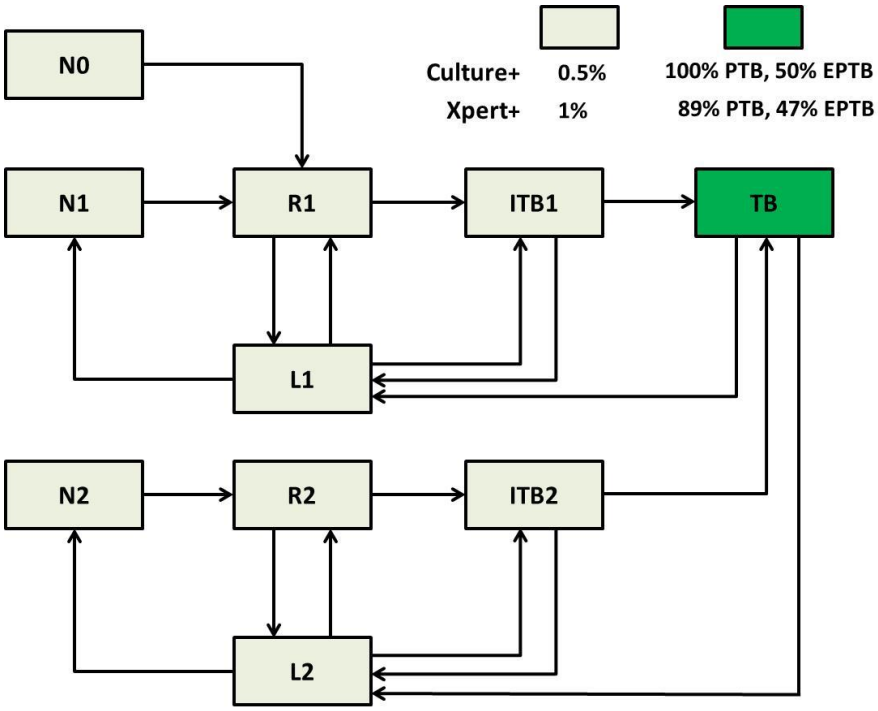
6H	6 months isoniazid
3HR	3 months isoniazid and rifampicin
2HRZE/4RH	2 months of isoniazid, rifampicin, pyrazinamide and etambutol, followed by 4 months of isoniazid and rifampicin
ART	Antiretroviral therapy
BCG	Bacilli Calmette-Guerin
C	Culture
CEA	Cost-effectiveness analysis
CXR	Chest X-ray
DOT	Direct observed treatment
DS	Drug-sensitive
ECDC	European Centre for Disease Control
EPTB	Extra-pulmonary tuberculosis
FOI	Force of infection
HIV	Human immunodeficiency virus
ICER	Incremental cost-effectiveness ratio
IGRA	Interferon gamma release assay
IPT	Isoniazid preventive therapy
ITB	Incipient tuberculosis
ITBT	Incipient tuberculosis test
LE	Life expectancy
LTBI	Latent tuberculosis infection
MDR	Multidrug-resistant
NL	Netherlands
PHS	Public Health Service
PPD	Purified protein derivative
PT	Portugal
PTB	Pulmonary tuberculosis
SA	South Africa
SS	Sputum smear
TB	Tuberculosis
TPP	Targeted product profile
TST	Tuberculin skin test
VN	Viet Nam
WHO	World Health Organization

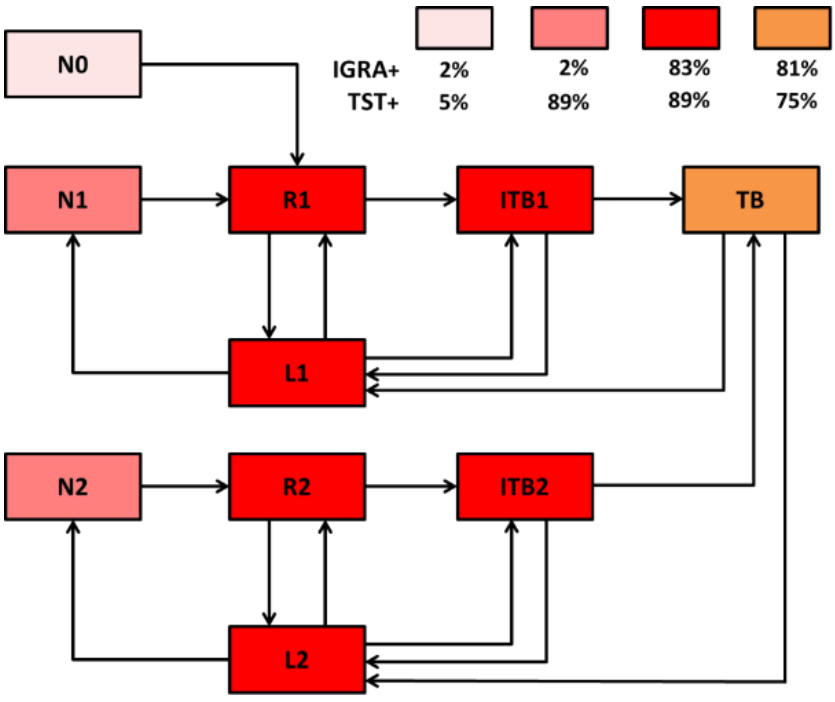
Annex 2. Diagnostic test assumptions.

Figure Annex 2. Proportions persons positive per disease stage with each diagnostic test: CXR, TST, IGRA, culture, GeneXpert, ITB test

N=no infection, R=recent, L =remote (long time ago), 1=no previous TB, 2 = with previous TB

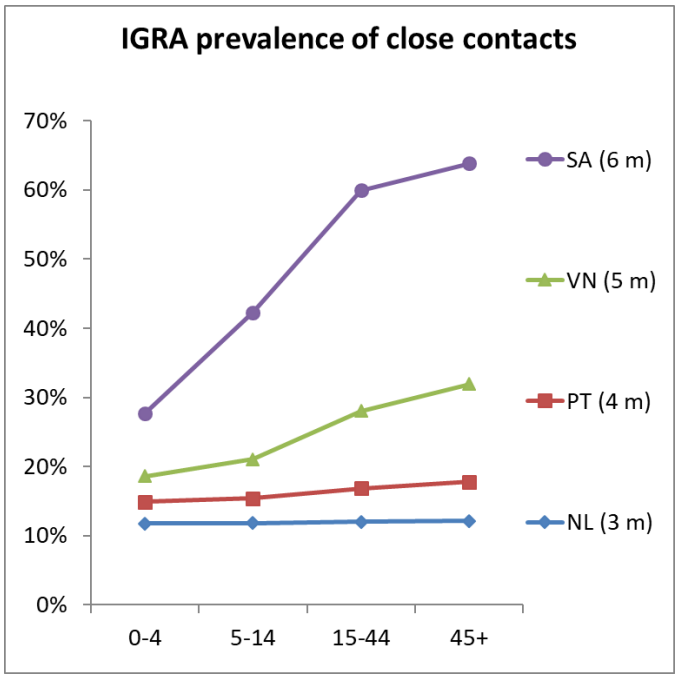



N0
N1
R1
ITB1
TB
L1
N2
R2
ITB2
L2
Culture+ 0.5%
Xpert+ 1%
100% PTB, 50% EPTB
89% PTB, 47% EPTB


N0
N1
R1
ITB1
TB
L1
N2
R2
ITB2
L2
IGRA+ 2% 2% 83% 81%
TST+ 5% 89% 89% 75%

Annex 3. Overview of activation and re-activation rates and transmission parameters

Figure A3.1. Prevalence IGRA positive among contacts by age



Only the 12% for 15-44 in NL was chosen based on literature(102).
Contacts have a FOI per month of 0.042788

Table A3.1. Model characteristics for the country-specific force of infection, hospitalization ratio and mortality

	Netherlands	Portugal	Viet Nam	South Africa
FOI per month				
Total population	0.000041	0.000163	0.001188	0.010075
Natives	0.000022	0.000206		
Migrants	0.000570	0.000809		
Proportion in hospitalization*				
Severe pathology TB	100.0%	100.0%	58.3%	52.5%
Self-reported TB	18.4%	15.3%	0.0%	0.0%
Proportion of people with severe pathology dying**				
0-44	12.5%	35.1%	52.1%	89.3%
45+	50.1%	87.9%	91.2%	98.2%
Assumed factor of 45+ vs. 0-44	4	2.5	1.75	1.1

FOI= force of infection.
*TB patients eventually move to self-reporting or to severe pathology; those 2 together may lead to hospitalization. In NL and PT hospitalizations are assumed to be a combination of all persons with severe pathology plus part of those self-reporting. In VN and SA hospitalizations are assumed to only occur among severe pathology cases. The given proportions lead to the observed hospitalization rates.

**Death is linked to severe pathology, even though in reality some patients may die at home, especially in VN and SA. The given proportions lead to the observed TB-death rates.

Annex 4. Details on costing

In **Table annex 4.0** the average duration of hospitalization is presented, that was used to calculate hospitalization cost. Other sub-annexes give details per country.

Table Annex 4.0. Average duration of hospitalization by country used for calculating cost

	NL	PT	VN	SA
Average duration DS TB	1.5 weeks	2.5 weeks	20 days	21 days
Average duration MDR TB	16 weeks	16 weeks	20 days	54 days

Annex 4.1. Netherlands

For the Netherlands costs were calculated in euros and converted to dollars for this report. An exchange rate of 1.11 was used for 2015. Although data were provided for a mix of 2015 and 2016, all costs were assumed to be for 2015. This tables is also published in (20).

Table Annex 4.1. Prices per item and the quantity provided under the different activities of tuberculosis control for the Netherlands in years 2015/2016

Activity	Price (EUR)	Quantity	Notes / references
Screening:			Tuberculin skin test and Chest X-ray;(107)
Tuberculin skin test	47.55	1	Interferon gamma release assay: average of costs charged by 25 public health service (PHS), often linked to different laboratories in the Netherlands (KNCV[3]). These usually included one visit to the PHS and we added another visit.
Interferon gamma release assay	91.41	1	
Chest X-ray	62.66	1	
Culture	52.05	1	Culture (108)
			For all the above consultation costs was included as applicable.
Latent tuberculosis infection treatment:			
3-month isoniazid plus rifampicin*	157.06	1	(109)
6-month isoniazid	69.40	1	

[3]Acknowledgements Ineke Spruijt, KNCV Tuberculosis Foundation

Activity	Price (EUR)	Quantity	Notes / references
Start consultation physician	54.26	1	(110)
Monthly physician consultation	27.13	2-5**	
Monthly nurse support	19.00	3-6**	
Chest X-ray	43.66	3	
Aspartate aminotransferase and alanine aminotransferase	4.02	2	
Tuberculosis treatment:			
2-month isoniazid, rifampicin, pyrazinamide and ethambutol + 4-month isoniazid and rifampicin (2HRZE + 4HR) (non multidrug-resistant TB)*	511.00	1	(109)
Treatment for multidrug-resistant TB*	17 369.95	1	
Start consultation	54.26	1	(110)
Monthly physician consultation	27.13	4	
Monthly nurse support	19.00	6	
Chest X-ray	43.66	5	
Microscopy	16.19	4	
Culture (for monitoring)	24.92	4	
Polymerase chain reaction	42.19	3	
Drug susceptibility testing	16.19	4	
Aspartate aminotransferase and alanine aminotransferase	4.02	4	
Hemoglobin	1.71	1	
Blood sedimentation rate of erythrocytes	1.67	1	
HIV	11.35	1	
Gamma-glutamyl transpeptidase	1.93	1	
Bilirubin	1.61	1	
Serum creatinine	1.77	1	
Thrombocyte	1.67	1	
Leucocyte	1.67	1	
Hepatits B antigen	12.85	1	
Contact tracing:			
Fixed, per contact investigation	2 150.00	1	

Activity	Price (EUR)	Quantity	Notes / references
Variable, per contact screened	135.57	14	Based on average 14 individuals investigated per contact investigation in the Netherlands
Directly observed treatment:			
For normal tuberculosis treatment	330.00	1	(108)
For multidrug/ extensively drug–resistant tuberculosis treatment	1 647.00	1	
Hospitalization:***			
For normal tuberculosis patient (per week)	4 228.00	1.5	(111) and update (112) (average hospitalization time was 1.9 weeks, when subtracting MDR TB patients 1.5 weeks). Updated with bedcosts from reference (113)
For multidrug/ extensively drug–resistant tuberculosis patient (per week)	2 532.00	15.6	

* Traded goods.

** Depends on number of months of treatment (3, 4, or 6). For physician consultation minus 1 (=start consultation).

Annex 4.2. Portugal

Validation of PPP conversions

Portugal was asked to provide unit costs of screening (CXR, IGRA, TST, and confirmation tests), treatment (TB, LTBI, directly observed treatment, side effects), and contact investigation. Unfortunately, Portugal only provided data to a limited extent. In addition, data that were provided proved hard to interpret, as it was sometimes unclear what the precise ingredients were in the provided cost-estimates (e.g. for costs of treatment could not be determine whether only the costs of drugs were provided, or also the costs of monitoring, consultations, etc.). Therefore, in favour of consistency, only the unit cost data obtained from the Netherlands was used, and correct data using PPP conversions was used for Portugal. After doing so, Portugal was requested to only comment on the used quantities in the PPP calculations, and to adjust where necessary. This resulted in the country-specific values of **Table 8** in the main report. As estimates were received from Portugal for at least some of the requested unit costs, a comparison between the PPP method and the data provided could be performed. The results are summarized in **Table Annex 4.2**, and the most significant discrepancies are discussed in the footnotes.

Table Annex 4.2. Validation of unit cost, purchasing power parity method compared to data provided by Portugal

	Expert	**PPP**
Screening		
CXR	EUR 43 [a]	EUR 47
IGRA	EUR 50	EUR 68
TST	EUR15	EUR 35
Treatment		
TB	EUR140 [b]	EUR 982
LTBI 3–month isoniazid and rifampicin	EUR91 [b]	EUR319
Directly observed treatment	unknown	EUR 246

CXR= chest X-ray, IGRA= interferon gamma release assay, LTBI=latent tuberculosis infection, N/A = not available, PPP= purchasing power parity; TST= tuberculin skin test; TB= tuberculosis.

[a] The costs of a CXR may be estimated including or excluding write-off and other costs; the PPP estimate was derived from the Dutch catalogued price.

[b] These values probably reflect only the costs for medication, not additional consultations /tests performed.

Amounts are rounded to whole EUR.

Annex 4.3. Viet Nam

Cost data

The quantities of the TB interventions (diagnostic and treatment procedure) for AFB+PTB (<15 years; ≥15 years), AFB-PTB (<15 years; ≥15 years), EPTB (<15 years; ≥15 years), MDR-TB in new TB cases (<15 years; ≥15 years), and MDR-TB in retreatment TB patients (<15 years; ≥15 years) were taken from the Standard TB diagnosis and treatment protocols published in the article *Costs of providing tuberculosis diagnosis and treatment services in Viet Nam(85)*. The prices for the TB interventions (diagnostic and treatment procedure) were taken from *Prices of medical examination services, Ministry of Health & Ministry of Finance, (Issued together with Joint Circular No. 37/2015 / TTLT-BYT-BTC dated 29 October 2015).* These prices apply from 01 July 2016 and include direct costs and staff costs. Officially these are valid from 1/7/2016 onwards, but we have assumed them here for 2015. The prices of TB interventions that could not be found in that document were provided to us by National TB Control Program (NTP) Vietnam and apply to the National Lung Hospital in Hanoi. The overhead costs were not available.

National, provincial and district level

The costs of the TB interventions (diagnostic and treatment procedure) for each type of TB patient were calculated for the TB interventions done at the national and district level. Provincial level was ignored, since procedures do not differ from the ones done at the National level, staff costs are negligibly different from national level, not all costs were available, and some diagnostic procedures are not available at all provincial hospitals. According to NTP Vietnam in Q3 and Q4 2016, 4% of all TB patients in Vietnam were diagnosed at the National level, 14% at Provincial level and 82% at the District level. The diagnostics of TB is usually done only at National and Provincial level, except for AFB+TB which is also diagnosed at district level. The Intensive phase of TB treatment is normally done at all three levels, whereas the continuation phase is done only at the District level.

For the calculations of the costs of the TB interventions per patient the diagnosis costs were used from the national level (except for AFB+TB from district level). The intensive and continuation phase costs for all types of patients were used from the district level.

In order to calculate an average price per patient the proportions of DS TB patients (AFB+, AFB-, EPTB) and MDR TB patients (new, retreatment) in Q1 and Q2 2016 were obtained from NTP Vietnam.

Limitations

It is assumed that all AFB+ PTB are diagnosed at district level, so the costs are underestimated, because patients can also be diagnosed at national or provincial level, where the costs are higher. For the other patients (EPTB, MDR-TB) the total costs are overestimated because for the diagnostic part only prices at the national level are used.

Screening in Vietnam is done for prisoners, PLHIV, methadone centres, and children contacts, but costs are unavailable.

For some of the procedures for TB diagnostics and treatment (copied from the Standard TB diagnosis and treatment protocols published in the paper by Minh et al 2017)it was unclear whether they were used for all patients or only a selection of patients (bronchoscopy and

gastric aspiration for TB diagnosis in children, frequency of use of solid and/or liquid culture, frequency of use of antibiotics culture 2nd line and Hain test). This information could also not be obtained from NTP Vietnam. Our calculations were done with an assumption that all procedures were done for all the patients. The price for the treatment drugs was the same for the children and adults. Therefore for some patients group the total costs are overestimated, but some costs were not taken in consideration, such as other non-TB drugs used. It is therefore expected that these under and overestimations will compensate each other.

The overhead costs were not available, so they are not included in the prices.

Annex 4.4. South Africa

The cost of treatment of DS TB cases was calculated by combining information from table 1 and S2 from Vassall(86)as in **Table Annex 4.4**:

Table annex 4.4. Calculation of cost of treatment of DS TB from Vassall(86)

treatment	N Persons in microscopy group	N persons in Xpert group	total	Calculated %	Cost*
cat1 (New cases)	245	224	469	91%	$171.12
cat2 (retreatment cases)	34	12	46	9%	$252.95
Total	279	236	515	100%	$178.43

*The paper gives cost in 2014. For this report all cost were converted to 2015 cost.

Annex 5. Full address details

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